JAMA | Review

Breast Cancer Treatment
A Review

Adrienne G. Waks, MD; Eric P. Winer, MD

IMPORTANCE Breast cancer will be diagnosed in 12% of women in the United States over the course of their lifetimes and more than 250 000 new cases of breast cancer were diagnosed in the United States in 2017. This review focuses on current approaches and evolving strategies for local and systemic therapy of breast cancer.

OBSERVATIONS Breast cancer is categorized into 3 major subtypes based on the presence or absence of molecular markers for estrogen or progesterone receptors and human epidermal growth factor 2 (*ERBB2*; formerly *HER2*): hormone receptor positive/*ERBB2* negative (70% of patients), *ERBB2* positive (15%-20%), and triple-negative (tumors lacking all 3 standard molecular markers; 15%). More than 90% of breast cancers are not metastatic at the time of diagnosis. For people presenting without metastatic disease, therapeutic goals are tumor eradication and preventing recurrence. Triple-negative breast cancer is more likely to recur than the other 2 subtypes, with 85% 5-year breast cancer–specific survival for stage I triple-negative tumors vs 94% to 99% for hormone receptor positive and *ERBB2* positive. Systemic therapy for nonmetastatic breast cancer is determined by subtype: patients with hormone receptor–positive tumors receive endocrine therapy, and a minority receive chemotherapy as well; patients with *ERBB2*-positive tumors receive *ERBB2*-targeted antibody or small-molecule inhibitor therapy combined with chemotherapy; and patients with triple-negative tumors receive chemotherapy alone. Local therapy for all patients with nonmetastatic breast cancer consists of surgical resection, with consideration of postoperative radiation if lumpectomy is performed. Increasingly, some systemic therapy is delivered before surgery. Tailoring postoperative treatment based on preoperative treatment response is under investigation. Metastatic breast cancer is treated according to subtype, with goals of prolonging life and palliating symptoms. Median overall survival for metastatic triple-negative breast cancer is approximately 1 year vs approximately 5 years for the other 2 subtypes.

CONCLUSIONS AND RELEVANCE Breast cancer consists of 3 major tumor subtypes categorized according to estrogen or progesterone receptor expression and *ERBB2* gene amplification. The 3 subtypes have distinct risk profiles and treatment strategies. Optimal therapy for each patient depends on tumor subtype, anatomic cancer stage, and patient preferences.

JAMA. 2019;321(3):288-300. doi:10.1001/jama.2018.19323

JAMA Patient Page page 316

Audio

CME Quiz at jamanetwork.com/learning

Author Affiliations: Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Eric P. Winer, MD, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215 (eric_winer@dfci.harvard.edu).

Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

Worldwide, breast cancer is the most common cancer in women, other than nonmelanoma skin cancer.[1] More than 250 000 new cases of breast cancer were diagnosed in the United States in 2017, and breast cancer will be diagnosed in 12% of all women in the United States over their lifetimes.[2] This review summarizes evidence-based approaches to the systemic and local treatment of the 3 major breast cancer subtypes: hormone receptor positive/*ERBB2* negative (HR+/*ERBB2*−), *ERBB2* positive (*ERBB2*+), and triple-negative.

Methods

We searched PubMed for English-language articles related to the treatment of breast cancer, with a focus on large randomized clinical trials or meta-analyses and guidelines of major professional societies. The indices of major medical and oncology journals were comprehensively reviewed for articles published from January 1, 2013, to November 11, 2018, on the topic of breast cancer treatment. Articles agreed on by both authors to define modern practice were included, with priority given to prospective randomized trials and large meta-analyses that represent the first and/or the most important evidence establishing current standard of care in breast cancer.

Clinical Presentation

In the modern era of widespread screening mammography, more than half of breast cancers in the United States are diagnosed on screening mammogram, and approximately one-third

Table 1. Prevalence, Prognosis, and Therapeutic Options for the 3 Breast Cancer Subtypes

	Hormone Receptor (HR) +/*ERBB2*−	*ERBB2*+ (HR+ or HR−)	Triple-Negative
Pathological definition	≥1% Of tumor cells stain positive for estrogen receptor or progesterone receptor proteins	Tumor cells stain strongly (3+) for ERBB2 protein or *ERBB2* gene is amplified in tumor cells. Approximately half of *ERBB2*+ tumors are also HR+	Tumor does not meet any pathologic criteria for positivity of estrogen receptor, progesterone receptor, or *ERBB2*
Molecular pathogenesis	Estrogen receptor α (a steroid hormone receptor) activates oncogenic growth pathways	The oncogene *ERBB2*, encoding ERBB2 receptor tyrosine kinase from the epidermal growth factor receptor family, is overactive	Unknown (likely various)
Percentage of breast cancer cases, %[12]	70	15-20	15
Prognosis			
Stage I (5-y breast cancer-specific survival), %[13,a]	≥99	≥94	≥85
Metastatic (median overall survival)[14-16,b]	4-5 y	5 y	10-13 mo
Typical systemic therapies for nonmetastatic disease (agents, route, and duration)	• Endocrine therapy (all patients): • Tamoxifen, letrozole, anastrozole, or exemestane • Oral therapy • 5-10 y • Chemotherapy (some patients): • Adriamycin/cyclophosphamide (AC) • Adriamycin/cyclophosphamide/ paclitaxel (AC-T) • Docetaxel/cyclophosphamide (TC) • Intravenous therapy • 12-20 wk	• Chemotherapy plus ERBB2-targeted therapy (all patients): • Paclitaxel/trastuzumab (TH) • Adriamycin/cyclophosphamide/ paclitaxel/trastuzumab ± pertuzumab (AC-TH±P) • Docetaxel/carboplatin/trastuzumab ± pertuzumab (TCH±P) • Intravenous therapy • 12-20 wk of chemotherapy; 1 y of ERBB2-targeted therapy • Endocrine therapy (if also hormone receptor positive) • Tamoxifen, letrozole, anastrozole, or exemestane • Oral therapy • 5-10 y	• Chemotherapy (all patients): • AC • AC-T • TC • Intravenous therapy • 12-20 wk

[a] Prognosis estimated from nearly 44 000 patients with breast cancer enrolled in the California Cancer Registry (2005-2008); stage I breast cancer defined by the American Joint Committee on Cancer staging manual anatomic staging table, 8th edition. 95% CIs for stage I 5-year breast cancer–specific survival estimates are as follows: 98%-100% for HR+/*ERBB2*−, 83%-100% for *ERBB2*+, and 75%-98% for triple-negative.

[b] Prognosis listed is from time of diagnosis of metastatic breast cancer.

are diagnosed as a palpable breast mass.[3] Palpable axillary mass, nipple discharge, nipple inversion, breast asymmetry, breast skin erythema, and breast skin thickening (peau d'orange) are less common presentations of breast cancer.[4] Sixty-two percent of breast cancers in the United States are confined to the breast at diagnosis, while an additional 31% have spread to regional lymph nodes. Only 6% of breast cancers are metastatic at the time of diagnosis, defined as involvement of sites distant from the breast and its regional lymph nodes.[2]

Diagnosis and Pathophysiology

Breast cancer is a histologic diagnosis made according to standardized pathologic criteria. The most common breast cancer histology is invasive ductal carcinoma (50%-75% of patients), followed by invasive lobular carcinoma (5%-15% of patients), with mixed ductal/lobular carcinomas and other rarer histologies making up the remainder of patients.[5]

Two main molecular targets in breast cancer pathogenesis have been identified. One is estrogen receptor alpha (ERα), which is expressed in approximately 70% of invasive breast cancers. ERα is a steroid hormone receptor and a transcription factor that, when activated by estrogen, activates oncogenic growth pathways in breast cancer cells. Expression of the closely related steroid hormone progesterone receptor (PR) is also a marker of ERα signaling.[6] Tumors with expression of either estrogen receptor (ER) or PR in at least 1% of tumor cells are categorized as HR+.[7] The use of endocrine agents to downregulate ER signaling is the primary systemic therapy for ER-positive or PR-positive breast cancers.

The second main molecular target is epidermal growth factor 2 (*ERBB2*, formerly *HER2* or *HER2/neu*), a transmembrane receptor tyrosine kinase in the epidermal growth factor receptor family that is amplified or overexpressed in approximately 20% of breast cancers, and is associated with poor prognosis in the absence of systemic therapy.[8] Tumors with amplification or overexpression of the gene *ERBB2* are *ERBB2*+.[9] Patients with *ERBB2*-amplified or -overexpressing breast cancer benefit from *ERBB2*-targeted therapy, including anti-*ERBB2* antibodies (such as trastuzumab and pertuzumab) and small-molecule tyrosine kinase inhibitors (such as lapatinib and neratinib).

Triple-negative breast cancer, which makes up approximately 15% of all breast tumors,[10] is characterized by the lack of expression of molecular targets ER, PR, or *ERBB2*. Triple-negative tumors have a high risk of distant relapse in the first 3 to 5 years following diagnosis.[11] The specific molecular pathophysiology of triple-negative breast cancer remains poorly understood.

Distinct prevalences, prognoses, and systemic therapy options characterize the 3 breast cancer subtypes: HR+, *ERBB2*+, or triple-negative (**Table 1**). Triple-negative breast tumors are more likely to occur in women who are younger, black, or Hispanic,[11] whereas HR+ tumors are more likely in older women. Breast cancer

is staged I-IV, where IV denotes distant metastatic disease. Stage I breast cancers, defined anatomically as a breast tumor smaller than 2 cm and no lymph node involvement, have 5-year breast cancer–specific survival of at least 99%, at least 94%, and at least 85% for HR+, *ERBB2*+, and triple-negative subtypes, respectively. Stage IV breast cancers have median overall survival of approximately 5 years for HR+ or *ERBB2*+ subtypes and 1 year for triple-negative.[13-16]

Principles of Therapy

For nonmetastatic breast cancer, the main goals of therapy are eradicating tumor from the breast and regional lymph nodes and preventing metastatic recurrence. Local therapy for nonmetastatic breast cancer consists of surgical resection and sampling or removal of axillary lymph nodes, with consideration of postoperative radiation. Systemic therapy may be preoperative (neoadjuvant), postoperative (adjuvant), or both. Breast cancer subtype guides the standard systemic therapy administered (Table 1), which consists of endocrine therapy for all HR+ tumors (with some patients requiring chemotherapy as well), trastuzumab-based ERBB2-directed antibody therapy plus chemotherapy for all *ERBB2*+ tumors (with endocrine therapy given in addition, if concurrent HR positivity), and chemotherapy alone for triple-negative breast cancer.

For metastatic breast cancer, therapeutic goals are prolonging life and symptom palliation. Currently, metastatic breast cancer remains incurable in virtually all affected patients. The same basic categories of systemic therapy are used in metastatic breast cancer as in neoadjuvant/adjuvant approaches outlined here. Local therapy modalities (surgery and radiation) are typically used for palliation only in metastatic disease.

Systemic Therapy for Nonmetastatic Breast Cancer

HR+/*ERBB2*– Subtype

Endocrine therapy, which counteracts estrogen-promoted tumor growth, is the primary systemic therapy for HR+/*ERBB2*– breast cancer. Standard endocrine therapy consists of oral antiestrogen medication taken daily for 5 years, and options differ according to menopausal status. Tamoxifen is a selective estrogen receptor modulator that competitively inhibits estrogen's binding to ER and is effective in both pre- and postmenopausal women. Aromatase inhibitors (anastrozole, exemestane, and letrozole) decrease circulating estrogen levels by inhibiting conversion of androgens to estrogen[6] and are effective only in postmenopausal women (including those who are postmenopausal because of medical ovarian suppression or oophorectomy). Typical adverse effects of endocrine therapy are listed in **Table 2**.

Five years of tamoxifen for patients with HR+ breast cancer reduces the breast cancer recurrence rate by approximately 50% in the first 5 years after diagnosis compared with no endocrine therapy.[17] The absolute benefit of tamoxifen is proportional to the risk associated with a given tumor. For example, a woman with an anatomic stage III HR+ breast cancer may have a 50% 5-year risk of recurrence without systemic therapy reduced to 25% with a 5-year course of tamoxifen. A woman with anatomic stage I HR+ breast cancer and a 10% 5-year risk of recurrence without systemic therapy has her recurrence risk reduced to 5% with a 5-year course of tamoxifen. Compared with 5 years of tamoxifen, 5 years of aromatase inhibitor in a postmenopausal woman is somewhat more effective. In a meta-analysis of 31 920 women, tamoxifen was associated with a 10-year breast cancer recurrence risk of 22.7% vs 19.1% for aromatase inhibitors. A "switch" strategy (initial 2-3 years of tamoxifen, followed by aromatase inhibitor for completion of a 5-year course of endocrine therapy) is equivalent to 5 years of aromatase inhibitor use for breast cancer mortality, and is a viable strategy for women who wish to mitigate toxicities from both classes of endocrine therapy.[18] Because absolute benefit is related to risk, in low-risk patients, the added benefit of aromatase inhibitors over tamoxifen is small, and treatment decisions should be guided by adverse effects. Even in higher-risk women, intolerance of an aromatase inhibitor should lead to substitution of tamoxifen.

When treating a premenopausal woman with endocrine therapy, the first decision is whether to treat with ovarian suppression using gonadotropin-releasing hormone agonists, such as leuprolide acetate and goserelin, or oophorectomy to induce menopause; the second decision, if inducing menopause, is whether to treat with tamoxifen or aromatase inhibitor. These approaches have been compared in 2 large clinical trials (combined N = 5738).[19,20] A small but significant improvement in 8-year overall survival was observed with ovarian suppression plus tamoxifen compared with tamoxifen alone (93.3% vs 91.5%, respectively; $P = .01$). Ovarian suppression plus aromatase inhibitor is not associated with better survival compared with ovarian suppression plus tamoxifen; however, the former combination shows a modest improvement in 8-year freedom from distant recurrence compared with ovarian suppression plus tamoxifen (91.8% vs 89.7%, respectively; $P = .02$).[20] Overall, adding ovarian suppression to either tamoxifen or aromatase inhibitor is indicated in premenopausal women with higher-risk disease, with aromatase inhibitors favored for those at the highest risk.

Patients with HR+ breast cancer are at risk of recurrent disease even multiple decades after primary diagnosis.[21] Therefore, studies have evaluated extending both tamoxifen and aromatase inhibitors beyond the typical 5-year duration. Two randomized trials compared 5 vs 10 years of tamoxifen, and showed a small but significant improvement (2.8% absolute improvement) in breast cancer mortality with a 10-year course of therapy. As expected, higher rates of endometrial cancer and thromboembolic disease were observed with longer therapy (Table 2).[22,23] A separate trial evaluated 5 vs 10 years of aromatase inhibitor use, and found a small reduction in distant recurrences with longer therapy. There was no significant improvement in overall survival with extended-duration aromatase inhibitor therapy, whereas new-onset osteoporosis and fracture (known adverse effects of aromatase inhibitors) were both significantly more common.[24] Therefore, extending endocrine therapy provides small benefits but adds toxicity and thus warrants consideration in high-risk patients.

Clinicians must decide when to add chemotherapy to endocrine therapy for patients with HR+/*ERBB2*– breast cancer. Clinicopathologic features, such as anatomic stage and tumor grade, are important but imperfect components of risk and chemosensitivity assessment.[21,25,26] Multiple RNA-based genomic risk scores have been developed to estimate prognosis and predict chemotherapy benefit. Published prospective evidence regarding the value of

Table 2. Important Toxicities of Common Treatments for Nonmetastatic Breast Cancer

Agent/Regimen	Mechanisms	Common Toxicities (>10%)[a]	Uncommon Toxicities (≤10%)[a]
Endocrine Therapy			
Tamoxifen	• Selective estrogen receptor modulator • Competitively inhibits binding of estrogen to estrogen receptor	• Hot flashes (42.9%)[100]	• Uterine cancer (0%- 2.7% increase compared with no-tamoxifen control; risk increases with age)[17,18] • Thromboembolic disease (2.5% increase compared with letrozole control)[100]
Aromatase inhibitor (letrozole, anastrozole, or exemestane)	• Inhibit conversion of androgens to estrogen	• Hot flashes (37.7%)[100] • Arthralgias or myalgias (commonly joint stiffness/discomfort) (34.7%; 3.3% grade 3 and above)[100]	• Osteoporosis-related bone fracture (2.7% increase compared with tamoxifen control; risk increases with age)[18]
Cytotoxic Chemotherapy			
Docetaxel/ cyclophosphamide	• Docetaxel: disrupts mitosis by inhibiting microtubule function • Cyclophosphamide: alkylating agent, disrupts DNA replication	• Asthenia (>75%; 3% grade 3 and above)[101] • Edema (34%)[101] • Myalgias (33%)[101] • Myelosuppression (anemia: 5%-6%, neutropenia: 62%, thrombocytopenia: 1%)[101,b]	• Febrile neutropenia (8%)[43]
Adriamycin/ cyclophosphamide (AC)	• Adriamycin: disrupts DNA replication through multiple mechanisms • Cyclophosphamide: alkylating agent, disrupts DNA replication	• Asthenia (>75%; 4% grade 3 and above)[101] • Nausea (82%)[101] • Myelosuppression (anemia: 8%, neutropenia: 58%, thrombocytopenia: 1%)[101,b]	• Leukemia, adriamycin-related (0.2%)[34] • Cardiac mortality, eg, adriamycin-related (rate ratio 1.61 compared with no anthracycline; risk increases with age and cardiac risk factors)[34] • Febrile neutropenia (2.5%)[101,b]
Adriamycin/ cyclophosphamide/ paclitaxel (AC-T)	As above for AC plus: • Paclitaxel: disrupts mitosis by inhibiting microtubule function	As above for AC plus: • Sensory neuropathy (15% grade 1) • 3%-4% grade 2 and above[37,43]	As above for AC, with slightly higher risk of febrile neutropenia: • Febrile neutropenia (3%-4%)[43]
Cytotoxic Chemotherapy + ERBB2-Directed Therapy			
Adriamycin/ cyclophosphamide/ paclitaxel/ trastuzumab	As above for AC-T plus: • Trastuzumab: antibody targeting *ERBB2*	As above for AC-T	• Class III-IV congestive heart failure (1.3%-3.1% increase compared with no-trastuzumab control)[48,49]
Docetaxel/ carboplatin/ trastuzumab	• Docetaxel: disrupts mitosis by inhibiting microtubule function • Carboplatin: cross-links DNA and disrupts DNA replication • Trastuzumab: antibody targeting *ERBB2*	• Asthenia (all grades not listed; 7.2% grade 3 and above)[49] • Sensory neuropathy (36% any grade)[49] • Myelosuppression (anemia ≥ grade 3: 5.8%, neutropenia ≥ grade 3: 65.9%, thrombocytopenia ≥ grade 3: 6.1%)[49]	• Febrile neutropenia (9.6%)[49] • Class III-IV congestive heart failure (0.4%)[49]

[a] Grading refers to Common Terminology Criteria for Adverse Events, where toxicity is graded on a scale of 1 (least severe) to 5 (most severe). This is not an exhaustive list of toxicities but rather a list of the most common or the most serious toxicities encountered in clinical practice.

[b] Trials in which no patients received growth factor support to increase neutrophil counts.

these assays is summarized in **Table 3**. Two signatures, the 21-gene recurrence score and the 70-gene assay, are recommended by the American Society of Clinical Oncology to guide decisions on administering adjuvant chemotherapy for patients with HR+/*ERBB2*− node-negative breast cancer, based on high-quality evidence.[30,31] More limited evidence suggests that these genomic assays are similarly associated with determination of chemotherapy benefit and prognosis in node-positive HR+/*ERBB2*− breast cancer (Table 3).[26,29,32] However, because the data are preliminary and could evolve, the use of genomic risk scores as an indicator of chemotherapy benefit in node-positive disease is not universally accepted.[30,31,33]

Chemotherapy Regimen Selection for *ERBB2*− Subtypes

Despite the associated short- and long-term risks, chemotherapy remains an essential treatment for preventing recurrence in many patients with stage I-III breast cancer. It is the only systemic therapy with demonstrated efficacy in triple-negative breast cancer and an important adjunct to endocrine therapy or ERBB2-directed therapy in patients with HR+/*ERBB2*− or *ERBB2*+ breast cancer, respectively. A meta-analysis of approximately 100 000 women enrolled in randomized trials of chemotherapy for early breast cancer demonstrated that a high-dose anthracycline-containing chemotherapy regimen (compared with no chemotherapy) significantly reduced 10-year breast cancer mortality by approximately one-third (risk ratio, 0.64 [standard error, 0.09]), with most survival benefit occurring in the first 5 years after diagnosis. As with adjuvant endocrine therapy for HR+ tumors, higher-risk tumors are associated with greater absolute benefit from chemotherapy.[34]

Many different neoadjuvant and adjuvant chemotherapy regimens may be considered in early breast cancer. Major prospective trials leading to the establishment of standard modern regimens are shown in **Figure 1**. Overall, the regimens docetaxel/cyclophosphamide, adriamycin/cyclophosphamide, and cyclophosphamide/methotrexate/5-fluorouracil are all reasonable choices in lower-risk patients where chemotherapy benefits are smaller and toxicities are especially important considerations. Chemotherapy regimens containing both anthracycline (eg, adriamycin) and taxane (such as adriamycin/cyclophosphamide followed by taxane) achieve the greatest risk reduction and remain the appropriate choice in high-risk patients. Specifically, the use of anthracycline appears most important in patients with more lymph node involvement and with triple-negative disease.[43] Chemotherapy toxicities are listed in Table 2. In patients who receive a complete course of neoadjuvant

Table 3. Summary From Prospective Evaluations of Genomic Risk Scores for Chemotherapy Decision Making in Nonmetastatic Breast Cancer[a]

	21-Gene Assay							70-Gene Assay	
	TAILORx[25,27]	TAILORx[27]	TAILORx[27]	TAILORx[27]	WGSG PlanB[26]	RxPONDER[28]	RxPONDER[28]	MINDACT[29]	MINDACT[29]
Total patients, No.	1619	6711	6711	1389	348	TBD	TBD	1550	1550
Score category[b]	Low (≤10)	Intermediate (11-25)	Intermediate (11-25)	High (≥26)	Low (≤11)	Low-intermediate (≤25)	High (≥26)	Clinical high risk/ MammaPrint low risk	Clinical high risk/ MammaPrint low risk
Long-term outcome	96.8% 9-y Distant recurrence-free interval (±0.7 SE)	94.5% 9-y Distant recurrence-free interval (±0.5 SE)[c]	95.0% 9-y Distant recurrence-free interval (±0.5 SE)[c]	86.8% 9-y Distant recurrence-free interval (±1.7 SE)	98.4% 3-y Disease-free survival (95% CI, 97.0%-99.8%)	Not yet reported	Not yet reported	94.4% 5-y Distant recurrence-free survival (95% CI, 92.3%-95.9%)	95.9% 5-y Distant recurrence-free survival (95% CI, 94.0%-97.2%)
Chemotherapy receipt of included patients	No	No (by randomization)	Yes (by randomization)	Yes	No	Randomized[d]	Yes	No (by randomization)	Yes (by randomization)
Nodal status of included patients	N0	N0	N0	N0	N0-N1	N1	N1	N0-N1	N0-N1

Abbreviations: HR, hormone receptor; MINDACT, Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy; N1, 1-3 positive lymph nodes; RxPONDER, Rx for Positive Node, Endocrine Responsive Breast Cancer; TAILORx, Trial Assigning Individualized Options for Treatment; TBD, to be determined; WGSG, West German Study Group.

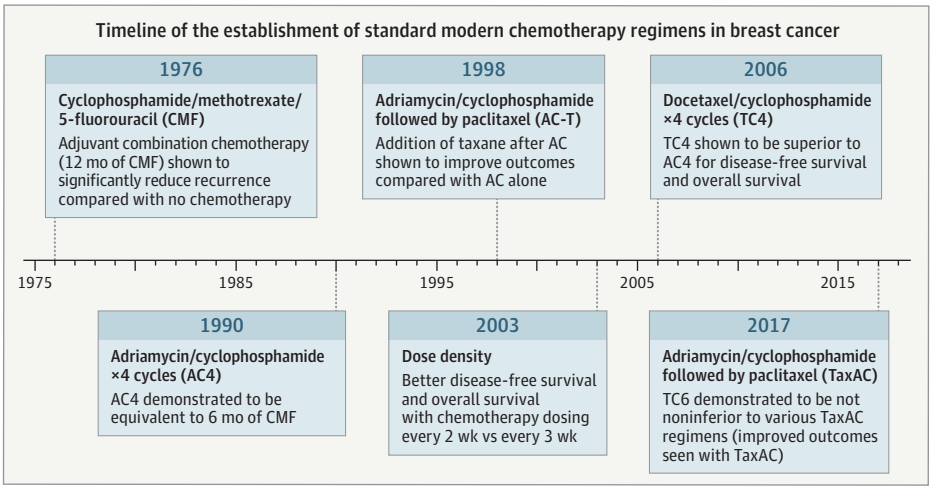
[a] In these prospective studies, genomic biomarkers were used to stratify patients into low risk, intermediate risk, or high risk. None of the low-risk patients received chemotherapy, while all of the high-risk patients received chemotherapy. Those who were at intermediate risk were randomized to chemotherapy or no chemotherapy. Of note, all patients were HR+/*ERBB2*− except in the MINDACT study, where 9.5% of patients had other breast cancer subtypes. All HR+ patients received adjuvant endocrine therapy.

[b] Scale from 0 to 100, with 0 being the best prognosis and 100 being the worst prognosis.

[c] In TAILORx, there was no significant benefit for chemotherapy with scores ≤25 in the overall treatment population. However, there was some suggestion of chemotherapy benefit for women ≤50 years old with scores 21-25, possibly caused by chemotherapy-mediated ovarian suppression, which should be discussed with patients.

[d] Chemotherapy vs no chemotherapy.

Figure 1. The Development of Modern Neoadjuvant/Adjuvant Chemotherapy Regimens in Breast Cancer



Years indicated are the year of initial presentation/publication of the relevant evidence, though additional significant references are included as well (1976[35]; 1990[34,36]; 1998[34,37-39]; 2003[40,41]; 2006[42]; 2017[43]). TaxAC indicates various anthracycline-plus-taxane–containing regimens.

chemotherapy with anthracycline and taxane, it remains unclear when to give additional treatment if there is residual disease found at surgery. A recent trial suggested that capecitabine could lower recurrence rates and improve survival for patients with residual disease following neoadjuvant chemotherapy,[44] but many unanswered questions remain about this approach.

Triple-Negative Subtype

Given the relatively unfavorable prognosis (Table 1), chemotherapy is generally administered to all patients with triple-negative breast tumors larger than 5 mm, even with negative axillary nodes. Chemotherapeutic agents are the only agents approved by the Food and Drug Administration (FDA) for treating nonmetastatic triple-negative disease. Because deficient DNA damage repair is a biological hallmark of some triple-negative tumors,[10] investigation of the DNA-crosslinking platinum chemotherapies has been of interest in triple-negative disease. Two trials have randomized patients with triple-negative breast cancer to receive neoadjuvant chemotherapy with or without carboplatin, and both demonstrated a significant improvement in pathologic complete response (pCR)

at surgery with the addition of carboplatin (from 41% to 54% in one trial and from 37% to 53% in the other). However, only 1 of the trials demonstrated a significant improvement in disease-free survival in the carboplatin-containing group, and in this case, the other components of the chemotherapy regimen were not consistent with standard therapy and did not include an alkylating agent.[45,46] Therefore, the role of platinum salts in the treatment of patients with stage I-III triple-negative breast cancer remains uncertain.

For triple-negative tumors treated with neoadjuvant chemotherapy, pCR (all tumor gone from the breast and lymph nodes) at surgery is a highly favorable prognostic biomarker. In a meta-analysis of patients treated with neoadjuvant chemotherapy, prognosis was improved in patients with triple-negative breast cancer (N = 1157) who achieved pCR compared with those who did not (hazard ratio, 0.24 for event-free survival with pCR).[47] New treatment approaches for patients with triple-negative disease who do not achieve pCR are needed, and platinum chemotherapy is one strategy being evaluated in several clinical trials. To date, the only evidence-based adjuvant escalation strategy available in this setting is single-agent capecitabine, as discussed here.[44]

ERBB2+ Subtype

The development of ERBB2-targeted therapy has been one of the greatest advances in breast cancer treatment. Trastuzumab, a monoclonal antibody targeting the extracellular domain of ERBB2, first entered clinical trials in the 1990s. Four randomized adjuvant trials demonstrated that the addition of 1 year of trastuzumab to standard adjuvant chemotherapy markedly improved disease-free survival and overall survival for patients with *ERBB2*+ breast cancer, with disease-free survival hazard ratios of 0.48 to 0.75 favoring trastuzumab-containing regimens.[8,48,49] While several different chemotherapy regimens combined with trastuzumab were studied across these trials, the 2 guideline-preferred neoadjuvant/adjuvant accompanying chemotherapy regimens in stages II and III *ERBB2*+ breast cancer in the United States are adriamycin/cyclophosphamide-paclitaxel and docetaxel/carboplatin (see notable toxicities in Table 2).[50] The 1-year duration of neoadjuvant/adjuvant trastuzumab comes from prospective comparisons showing 2 years is no better than 1, whereas therapy for less than 1 year is inferior to 1 year in most, but not all, studies.[51-53] Even 9 weeks of adjuvant trastuzumab is superior to none for patients with *ERBB2*+ breast cancer.[54]

Following the significant effectiveness of trastuzumab for preventing recurrences and death from *ERBB2*+ breast cancer, subsequent investigations have focused on (1) decreasing the number of accompanying chemotherapy agents in lower-risk patients and (2) adding novel agents in higher-risk patients. In a single-group trial, 406 patients with tumors that were mostly less than 2 cm and node-negative were treated with adjuvant paclitaxel for 12 weeks and the standard 1 year of adjuvant trastuzumab. The 7-year recurrence-free interval was 97.5%, with 5 local-regional recurrences and 4 distant recurrences at 7-year follow-up.[55] Given the excellent long-term outcomes and reduced toxicity of single-agent accompanying chemotherapy, paclitaxel/trastuzumab is now the standard of care for patients with small, node-negative *ERBB2*+ tumors.

In patients with higher-risk *ERBB2*+ breast cancer, the agents pertuzumab and neratinib further lower the risk of recurrence below what is observed with standard trastuzumab-containing regimens. Pertuzumab is a monoclonal antibody targeting the ERBB2 dimerization domain. In a phase 3 randomized trial of 4804 patients with stage I-III *ERBB2*+ breast cancer, pertuzumab led to a small but statistically significant improvement in 3-year invasive disease-free survival (94.1% with pertuzumab vs 93.2% with placebo; hazard ratio, 0.81 [95% CI, 0.66-1.00]; $P = .045$). In subgroup analyses, risk reduction with pertuzumab was observed in node-positive and HR− patients but was not observed in node-negative and HR+ subgroups, though the trial did not have statistical power to evaluate these individual subgroups and follow-up was relatively short.[56] At this time, treatment regimens incorporating pertuzumab are reasonable to use in high-risk patients defined by tumor size and nodal status, while the added toxicity and cost in lower-risk patients is difficult to justify.

Neratinib is an oral small-molecule tyrosine kinase inhibitor of multiple HER family members, including ERBB2. A randomized phase 3 trial of 2840 patients compared 1 year of adjuvant daily neratinib vs placebo following completion of neoadjuvant/adjuvant chemotherapy plus trastuzumab for *ERBB2*+ breast cancer. Invasive disease-free survival at 5 years favored neratinib (90.2% with neratinib vs 87.7% with placebo; hazard ratio, 0.73 [95% CI, 0.57-0.92]; $P = .008$). In contrast to the pertuzumab adjuvant trial, this invasive disease-free survival advantage was observed only in the HR+ subgroup and not in HR− patients, though reasons for this are unclear.[57] At present, there is no direct evidence to support using adjuvant neratinib in a pertuzumab-treated patient, or vice versa, as the major trials of each agent did not include use of the other. Finally, to date, neither agent has shown overall survival benefit when administered as adjuvant therapy.

Local Therapy for Nonmetastatic Breast Cancer

Surgery

Surgical treatment of breast cancer has evolved significantly in past decades, with advances aimed at minimizing the long-term cosmetic and functional sequelae of local therapy. Based on decades of research, the standard approaches are either a total mastectomy or an excision plus radiation, assuming that clear margins can be achieved. These 2 approaches have been shown consistently to be equivalent with regard to relapse-free and overall survival.[58] Contraindications to conservative surgery include (1) the presence of diffuse suspicious microcalcifications on breast imaging; (2) positive pathologic margins after lumpectomy; (3) disease that cannot be addressed by excision of a single breast tissue region with satisfactory cosmetic result, except in highly select patients; (4) certain collagen-vascular diseases, such as scleroderma; and (5) prior radiotherapy to the involved breast.[50]

Surgical management of axillary lymph nodes must be considered separately from surgical therapy of the breast. Lymph node removal serves both a diagnostic purpose (determining the anatomic extent of the breast cancer) and a therapeutic purpose (removal of cancerous cells). Surgical decision-making is based on whether axillary lymph node involvement is evident at diagnosis and whether neoadjuvant systemic therapy is administered. Axillary lymph node dissection (ALND), which remains standard of care in any patient with clinically evident axillary involvement at diagnosis who undergoes surgery as initial treatment,[50] was the universal approach to the axilla until clinical trials demonstrated that in women

with clinically node-negative (cN0) breast cancer, there was no significant difference in regional recurrence or survival outcomes between women who underwent full ALND vs women who underwent sentinel lymph node (SLN) biopsy, with conversion to ALND only if the SLN was positive.[59] Of note, "false-negative" SLN biopsy in the setting of cN0 disease and surgery as initial treatment has typically been as high as 5% to 10%, suggesting that leaving some axillary disease in place does not compromise long-term outcomes.[60]

Subsequent trials have demonstrated that ALND is not necessary even in all patients with a positive SLN. The landmark American College of Surgeons Oncology Group (ACOSOG) Z0011 trial enrolled 891 patients with cN0 breast tumors ≤5 cm in diameter and 1 to 2 positive SLNs (excluding patients with gross extranodal extension), all of whom underwent lumpectomy and breast radiation. Patients were randomized to ALND or SLN biopsy, with no difference in regional or distant recurrence-free survival or overall survival.[61] The AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) trial followed a similar design except that a subset of patients underwent mastectomy, and patients with positive SLNs were randomized to ALND or axillary radiation. As in ACOSOG Z0011, the non-ALND option was equivalent to ALND for long-term outcomes.[62] In both trials, lymphedema was significantly more prevalent in the group undergoing ALND (23% vs 11% in non-ALND patients).[61,62] Thus, in cN0 patients undergoing conservative surgery with tumor size ≤5 cm and only 1 to 2 positive SLNs prior to systemic therapy, SLN biopsy alone is sufficient axillary treatment for most, with the option of adding axillary radiation in selected patients.

The surgical treatment of patients who receive neoadjuvant systemic therapy is evolving. Multiple prospective randomized trials, and a recent meta-analysis, demonstrate that neoadjuvant chemotherapy increased patients' eligibility for breast-conserving therapy, without compromising long-term outcomes.[63,64] Some evidence suggested that among clinically node-positive (cN1) patients who convert to cN0 after neoadjuvant therapy, the false-negative rate of SLN biopsy was similar to that in patients undergoing upfront surgery,[65] as long as care was taken to maximize SLN identification (eg, use of dual SLN mapping methodology, consideration for placing a clip in the biopsy-proven node and retrieval of the clipped node at the time of SLN dissection, and retrieval of at least 3 SLNs). Therefore, current clinical practice and guidelines generally support the use of SLN biopsy in this setting (cN1 converted to cN0), with omission of ALND in patients who are SLN negative by stringent criteria.[65] However, optimal treatment of lymph node disease after neoadjuvant therapy is an area of active investigation.

Radiation Therapy

Radiation therapy in breast cancer may be delivered to the whole breast or a portion of the breast (after lumpectomy), the chest wall (after mastectomy), and the regional lymph nodes. Postlumpectomy whole-breast radiation is a standard component of breast-conserving therapy.[58] A meta-analysis of 10 801 patients showed that administration of radiation following lumpectomy was associated with reductions in breast cancer recurrences (locoregional or distant) by approximately half (from 35.0% to 19.3%) and in breast cancer deaths by one-sixth (from 25.2% to 21.4%) at 10 and 15 years, respectively. As with adjuvant systemic therapies, the proportional benefit of radiation was approximately constant regardless of overall breast cancer risk. Thus, the absolute benefits were larger in patients with higher-risk disease, and conversely, the mortality benefit confidence interval included zero in patients with the lowest-risk node-negative tumors.[66]

Prospective trials have examined the efficacy of a shorter course of radiation after lumpectomy and how to identify patients who can benefit from escalated dosing. While the historical standard dose and schedule of postlumpectomy radiation was 50 Gy over 25 fractions, more recent evidence has shown that a hypofractionated schedule (approximately 42.5 Gy over 16 fractions) is as effective for local recurrence risk reduction and equally if not more effective for cosmesis.[67,68] Therefore, a hypofractionated schedule for whole-breast radiation is now "preferred" per current guidelines.[50] Postlumpectomy radiation to the partial breast, as opposed to the whole breast, is an approach that has been studied predominantly in lower-risk patients 50 years of age and older. Though some trials suggested that partial breast radiation was associated with a slightly higher local recurrence risk and slightly worse cosmesis, emerging data contradict this, and consensus guidelines support nonintraoperative partial breast radiation in low-risk patients.[50,69,70] Administering a boost of radiation specifically to the tumor bed improves local control but not overall survival and should be considered in higher-risk patients.[50,71] Further, prospective randomized trials have shown that in women 65 years and older or 70 years and older with low-risk HR+/*ERBB2*− breast cancer, postlumpectomy whole-breast radiation has no significant effect on distant recurrence or overall survival (though omitting radiation leads to a small increased risk of locoregional events).[72,73] Whole-breast radiation should be discussed on an individualized basis with older women who fit this profile.

Postmastectomy radiation is radiation to the chest wall, sometimes with incorporation of a boost to the mastectomy scar and/or regional nodal radiation. A meta-analysis (N = 8135) of randomized trials of radiation following mastectomy with ALND showed that in patients with negative lymph nodes, receipt of postmastectomy radiation was not associated with recurrence or survival outcomes. However, in patients with positive lymph nodes, receipt of postmastectomy radiation was associated with improved locoregional and overall recurrence risk and breast cancer mortality. Of note, the trials included in this meta-analysis were conducted from 1964 to 1986, and it is likely that postmastectomy radiation benefits are substantially smaller with modern systemic therapy regimens.[74] The addition of regional nodal radiation (covering the axillary, paraclavicular, and/or internal mammary nodes) either following lumpectomy or following mastectomy was associated with significantly improved disease-free survival, was not associated with overall survival, and was associated with an increase in radiation toxicities such as pneumonitis and lymphedema. The benefits of regional nodal radiation were observed in women who had undergone ALND.[75,76] Given the lack of overall survival benefit, nodal radiation is not universally administered even in node-positive patients, but should be considered for patients with higher nodal disease burden or high-risk biology.

Systemic Therapy for Metastatic Breast Cancer

More than 150 000 women in the United States are living with a diagnosis of metastatic breast cancer. Nearly 41 000 deaths from

Figure 2. Standard Approach to Therapy of Metastatic Breast Cancer

Breast cancer receptor subtype	Therapeutic approach		Notes
Hormone receptor positive (HR+) and *ERBB2*-	Serial endocrine therapy-based regimens until disease is endocrine resistant, then transition to single-agent chemotherapy		In general, premenopausal women with HR+ metastatic breast cancer should undergo treatment to achieve medical or surgical menopause.
	Initial line(s) of therapy	Later lines of therapy	
	Aromatase inhibitor plus CDK4/6 inhibitor[a] Median progression-free survival = 24.8 mo Overall response rate = 53%-59% In some patients, CDK4/6 inhibitor may be reserved for second line	Hormonal and/or targeted therapy Fulvestrant ± everolimus Exemestane + everolimus Tamoxifen Abemaciclib[b] (if ≥1 line prior hormonal therapy and ≥1 line prior chemotherapy) Olaparib or talazoparib (if germline *BRCA1/2* mutation) If resistant to multiple lines of hormonal therapy, transition to single-agent chemotherapy.	
ERBB2+	ERBB2-targeted agent combined with chemotherapy, or combined with endocrine therapy if HR+		*ERBB2+* brain metastases are common (eventually occurring in up to 50% of patients with metastatic disease) and may be treated with both local (radiation, surgery) and systemic therapies.[f]
	Initial line(s) of therapy	Later lines of therapy	
	Taxane[c] + trastuzumab + pertuzumab[d] Median progression-free survival = 18.5 mo Overall response rate = 80% Selected patients with HR+/*ERBB2+* disease can receive endocrine therapy plus *ERBB2*-targeted therapy Ado-trastuzumab emtansine[e] Median progression-free survival = 9.6 mo Overall response rate = 47%	ERBB2-targeted agent plus chemotherapy or endocrine therapy if HR+ Trastuzumab + chemotherapy Trastuzumab + endocrine therapy Lapatinib + capecitabine	
Triple-negative	Single-agent chemotherapy		There is no single recommended first-line chemotherapy regimen.
	Initial line(s) of therapy	Later lines of therapy	
	Single-agent chemotherapy[g] Taxane Median progression-free survival = 4.5 mo Overall response rate = 36% Platinum Median progression-free survival = 3.1 mo Overall response rate = 31% Anthracycline	Single-agent chemotherapy[h] Capecitabine Eribulin Vinorelbine Gemcitabine Olaparib or talazoparib (if germline *BRCA1/2* mutation)	

This approach to treatment represents the authors' institution, has not been evaluated in a randomized trial, and may not reflect all reasonable approaches to treatment. For patients with metastatic disease recurrence, the approach should be tailored based on therapies received in the neoadjuvant/adjuvant setting. In all patients, treatment should be tailored based on individual tolerability. Major phase 3 trials supporting initial line(s) of therapy are referenced. Available clinical trials should also be considered at all points. Local treatment modalities (surgery and radiation) may be indicated to palliate localized symptoms. Denosumab or bisphosphonate should be added in patients with bony metastases. A comprehensive list of recommended therapies for each breast cancer subtype can be found in National Comprehensive Cancer Network Guidelines: Breast Cancer. Adapted in part from the National Comprehensive Cancer Network Guidelines: Breast Cancer, Version 3.2018.[50] CDK indicates cyclin-dependent kinase.

[a] Fulvestrant is preferable if the patient had recent progression while taking an aromatase inhibitor. PALOMA-2[78]; MONARCH 3[79]; and MONALEESA-2 trials.[80]

[b] There are no data to support abemaciclib after progression with prior CDK4/6 inhibitor use.

[c] If taxane contraindicated, can substitute vinorelbine.

[d] CLEOPATRA trial.[81]

[e] EMILIA trial.[82]

[f] Kabraji et al.[83]

[g] TNT trial.[84]

[h] Other agents not administered in initial lines are also acceptable options.

breast cancer occur annually, virtually all due to metastatic disease.[2,77] Median overall survival for metastatic breast cancer by subtype is shown in Table 1. Tumor- and patient-level factors are prognostically important: visceral metastases, brain metastases, and multiple metastatic sites all confer worse prognosis, whereas a better performance status, younger age at diagnosis, bone-only metastatic disease, and longer disease-free interval between initial diagnosis and development of metastatic recurrence all confer improved prognosis.

An overview of the approach to systemic therapy of metastatic disease by breast cancer subtype, including standard regimens used early in treatment course (ie, early lines) plus agents for consideration later in treatment course (ie, later lines), is shown in **Figure 2**. A few general principles are paramount. In metastatic HR+/*ERBB2*− breast cancer, early treatment should be endocrine therapy based, typically with incorporation of a cyclin-dependent kinase (CDK) 4/6 inhibitor, such as abemaciclib, palbociclib, or ribociclib, in the first or second line. After resistance develops to the available hormonal options, patients transition to treatment with chemotherapy. Multiple prospective randomized trials have demonstrated equivalent overall survival for sequential single-agent vs combination chemotherapy in metastatic breast cancer, with less toxicity and improved patient quality of life on single agents. Thus, the standard of care is single-agent sequential chemotherapy.[85,86] The same is true for metastatic triple-negative breast cancer, where cytotoxic chemotherapy is the only

Table 4. New Metastatic Breast Cancer Drug Approvals by the US Food and Drug Administration in the Past 6 Years (2013-Present)

Drug Name	Drug Class	Drug Mechanism	MBC Indication[a]	Notable Toxicities[b]
Hormone Receptor+/*ERBB2*−				
Abemaciclib[79,88,89]	CDK4/6 inhibitor	Inhibit progression through the cell cycle	With aromatase inhibitor; as first-line endocrine therapy	• Myelosuppression (anemia: 29%, neutropenia: 46%, thrombocytopenia: 16%) • Transaminase elevation (12%-13%) • Diarrhea (86%; 13% grade 3 and above) • Fatigue (40%)
			With fulvestrant; ≥1 prior line of endocrine therapy for MBC	
			≥1 Prior line of endocrine therapy and ≥1 prior line of chemotherapy for MBC	
Palbociclib[78,102]	CDK4/6 inhibitor		With aromatase inhibitor; as first-line endocrine therapy	• Myelosuppression (anemia: 24%, neutropenia: 80%, thrombocytopenia: 16%) • Fatigue (37%)
			With fulvestrant; ≥1 prior line of endocrine therapy for MBC	
Ribociclib[80,103]	CDK4/6 inhibitor		With aromatase inhibitor; as first-line endocrine therapy	• Myelosuppression (anemia: 19%, neutropenia: 74%, thrombocytopenia: <15%) • Transaminase elevation (15%-16%) • Fatigue (37%)
			With fulvestrant; as first-line endocrine therapy or after ≥1 prior line of endocrine therapy for MBC	
***ERBB2*−**				
Olaparib[92]	PARP inhibitor	Interfere with normal cellular DNA damage repair	Patients with deleterious germline *BRCA* mutation; ≥1 prior line of chemotherapy (and ≥1 prior line of endocrine therapy if HR+) for MBC	• Myelosuppression (anemia: 40%, neutropenia: 27%, thrombocytopenia: <15%) • Fatigue (29%) • Nausea (58%)
Talazoparib[104]	PARP inhibitor		Patients with deleterious germline *BRCA* mutation	• Myelosuppression (anemia: 53%, neutropenia: 35%, thrombocytopenia: 27%) • Fatigue (50%) • Nausea (49%)
***ERBB2*+**				
Trastuzumab-emtansine[82]	ERBB2-targeted antibody-drug conjugate	Delivery of cytotoxic chemotherapy specifically to *ERBB2*+ tumor cells	Following prior therap y with trastuzumab and taxane	• Thrombocytopenia (28%) • Transaminase elevation (17%-22%) • Fatigue (35%) • Nausea (39%)

Abbreviations: CDK, cyclin-dependent kinase; MBC, metastatic breast cancer; PARP, poly-ADP ribose polymerase.

[a] Indications for use are summaries only and further details are available in original trial publications as referenced.

[b] Notable toxicities are those that are common and/or clinically relevant in standard clinical practice. Grading refers to Common Terminology Criteria for Adverse Events, where toxicity is graded on a scale of 1 (least severe) to 5 (most severe).

therapeutic option available in patients without germline *BRCA1/2* mutations (where targeted inhibitors of poly[adenosine diphosphate-ribose] polymerase [PARP] enzymes are approved). In *ERBB2*+ metastatic breast cancer, standard first-line therapy consists of a taxane plus trastuzumab and pertuzumab, and the antibody-drug conjugate trastuzumab emtansine is frequently used as second-line therapy. Subsequent treatment generally combines a new chemotherapy agent (or endocrine therapy, if HR+) with an ERBB2-targeted agent, as the continuation of ERBB2-directed therapy even after progression with prior anti-ERBB2 therapy has been shown to improve outcomes.[87]

Table 4 summarizes drugs newly approved for metastatic breast cancer by the FDA in the past 6 years. More effective therapy for patients with metastatic triple-negative breast cancer is needed. Recent data indicate that novel antibody-drug conjugates have promising activity in pretreated metastatic triple-negative breast cancer, and late-phase clinical trials are ongoing.[14] A recent phase 3 trial (N = 902) of nab-paclitaxel plus either the programmed death-ligand 1 (PD-LI) inhibitor atezolizumab or placebo demonstrated improved progression-free survival for the chemotherapy and immunotherapy combination.[90] This study will likely lead to a new standard approach for at least some patients with triple-negative metastatic disease. Last, brain metastases are diagnosed in approximately 10% to 20% of patients with metastatic breast cancer, and their treatment remains a therapeutic challenge.[91] Women with *ERBB2*+ and triple-negative disease are at highest risk of developing brain metastases. Poor permeability of many systemic therapies because of the blood-brain barrier, distinct features of the brain microenviroment, and genomic differences in brain vs non-brain metastatic lesions may have previously limited progress.[83]

Role of Genomics in Treatment Decisions

Germline mutations in *BRCA1* or *BRCA2* are the only DNA alterations with an associated targeted therapy that has demonstrated clinical efficacy in breast cancer. Approximately 5% of patients with breast cancer carry germline mutations in *BRCA1* or *BRCA2*, tumor suppressor genes that function in DNA damage repair. Inhibition of PARP enzymes has been shown to specifically target BRCA-deficient cells, in part by synthetic lethality.[92] In 2018, the FDA approved the PARP inhibitors olaparib and talazoparib for treating patients with refractory metastatic breast cancer with deleterious germline mutations in *BRCA1/2* (Table 4). The presence of mismatch repair deficiency or high microsatellite instability are now FDA-approved indications to use the checkpoint inhibitor immunotherapy pembrolizumab (anti–programmed cell death-1 [PD-1] antibody) in any refractory malignancy, though only a minority (1%-2%) of breast tumors have these alterations.[93]

Otherwise, outside of a clinical trial, tumor DNA sequencing does not determine treatment decisions in breast cancer. Somatic activating mutations in *ERBB2* and the estrogen receptor gene *ESR1* are observed in some patients with breast cancer, and evolving clinical evidence suggests that both mutations may predict response and resistance to standard therapies: *ERBB2*-activating mutations confer possible sensitivity to neratinib, and *ESR1* mutations appear to confer resistance to aromatase inhibitors, with largely retained sensitivity to fulvestrant.[94-96] Prospective trials of patients selected for specific mutations are ongoing; at present, neither mutation has treatment implications outside of a clinical trial.

Disparities in Breast Cancer

A substantial proportion of breast cancer deaths is due to health disparities. Breast cancer mortality rates are 41% higher in black Americans than in white Americans,[97] and this disparity has increased steadily since the 1990s.[98] A study of 563 497 black and white American women with breast cancer in the National Cancer Data Base demonstrated that black women were more likely to be uninsured or have Medicaid insurance (22.7% vs 8.4%), present with HR− tumors (35.2% vs 19.3%), and present with larger tumors (16.4% vs 9.8%). The top 4 factors contributing to breast cancer mortality differences between black and white women were, in order of decreasing importance, insurance status, tumor characteristics (such as size and receptor status), comorbidities, and breast cancer treatment (such as receipt of surgery, radiation, or chemotherapy).[97] Independent of race/ethnicity, lower socioeconomic status contributes to poorer outcomes.[99] A commitment to studying and eradicating disparities is necessary in the breast cancer community as a whole.

Limitations

This review has several limitations. First, aspects of breast cancer treatment may be institution specific and some of the practice patterns described here reflect the authors' own institution. Second, the practices described are based on drugs approved and available in the United States, and differ internationally. Third, the diagnostic and prognostic statistics provided relate to populations of women in the United States undergoing screening mammography, and may not be applicable to unscreened or international populations.

Conclusions

Breast cancer consists of 3 major tumor subtypes categorized according to estrogen or progesterone receptor expression and *ERBB2* gene amplification. The 3 subtypes have distinct risk profiles and treatment strategies. Optimal therapy for each patient depends on tumor subtype, anatomic cancer stage, and patient preferences.

ARTICLE INFORMATION

Accepted for Publication: December 10, 2018.

Author Contributions: Drs Waks and Winer had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Both authors.
Acquisition, analysis, or interpretation of data: Waks.
Drafting of the manuscript: Both authors.
Critical revision of the manuscript for important intellectual content: Both authors.
Administrative, technical, or material support: Both authors.
Supervision: Both authors.

Conflict of Interest Disclosures: Dr Winer reported personal fees from Genentech, Roche, Lilly, Tessaro, GlaxoSmithKline, Leap Pharmaceuticals, Carrick Therapeutics, and Jounce Pharmaceuticals and stock options from Verastem outside the submitted work. No other disclosures were reported.

Additional Contributions: We gratefully acknowledge Jennifer Bellon, MD (Dana-Farber Cancer Institute, Boston, Massachusetts), and Tari King, MD (Brigham and Women's Hospital, Boston, Massachusetts), for their assistance in reviewing portions of this manuscript. They did not receive compensation for their contributions.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492

2. National Institutes of Health; National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: female breast cancer. https://seer.cancer.gov/statfacts/html/breast.html. Accessed January 23, 2018.

3. Caughran J, Braun TM, Breslin TM, et al. The effect of the 2009 USPSTF breast cancer screening recommendations on breast cancer in Michigan: a longitudinal study. *Breast J*. 2018;24(5):730-737. doi:10.1111/tbj.13034

4. Morrow M. Physical examination of the breast. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. *Diseases of the Breast*. Philadelphia, PA: Wolters Kluwer Health; 2014:chap 3.

5. Dillon D, Guidi AJ, Schnitt SJ. Pathology of invasive breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. *Diseases of the Breast*. 5th ed. Philadelphia, PA: Wolters Kluwer Health; 2014.

6. Joshi H, Press MF. Molecular oncology of breast cancer. In: Bland KI, Copeland EM, Klimberg VS, Gradishar WJ, eds. *The Breast*. Philadelphia, PA: Elsevier; 2018:22. doi:10.1016/B978-0-323-35955-9.00022-2

7. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(16):2784-2795. doi:10.1200/JCO.2009.25.6529

8. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1659-1672. doi:10.1056/NEJMoa052306

9. Wolff AC, Hammond ME, Hicks DG, et al; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997-4013. doi:10.1200/JCO.2013.50.9984

10. Denkert C, Liedtke C, Tutt A, von Minckwitz G. Molecular alterations in triple-negative breast cancer-the road to new treatment strategies. *Lancet*. 2017;389(10087):2430-2442. doi:10.1016/S0140-6736(16)32454-0

11. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *N Engl J Med*. 2010;363(20):1938-1948. doi:10.1056/NEJMra1001389

12. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*. 2014;106(5):dju055. doi:10.1093/jnci/dju055

13. Chavez-MacGregor M, Mittendorf EA, Clarke CA, Lichtensztajn DY, Hunt KK, Giordano SH. Incorporating tumor characteristics to the American Joint Committee on Cancer Breast Cancer Staging System. *Oncologist*. 2017;22(11):1292-1300. doi:10.1634/theoncologist.2017-0116

14. Bardia A, Mayer IA, Diamond JR, et al. Efficacy and Safety of anti-trop-2 antibody drug conjugate sacituzumab govitecan (IMMU-132) in heavily pretreated patients with metastatic triple-negative breast cancer. *J Clin Oncol*. 2017;35(19):2141-2148. doi:10.1200/JCO.2016.70.8297

15. Swain SM, Baselga J, Kim SB, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-734. doi:10.1056/NEJMoa1413513

16. Robertson JFR, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg versus anastrazole as first-line treatment for advanced breast cancer: overall survival from the phase II 'first' study. In: San Antonio Breast Cancer Symposium; December 9-13, 2014; San Antonio, TX. Abstract S6-04.

17. Davies C, Godwin J, Gray R, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378(9793):771-784. doi:10.1016/S0140-6736(11)60993-8

18. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386(10001):1341-1352. doi:10.1016/S0140-6736(15)61074-1

19. Pagani O, Regan MM, Walley BA, et al; TEXT and SOFT Investigators; International Breast Cancer Study Group. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2014;371(2):107-118. doi:10.1056/NEJMoa1404037

20. Francis PA, Pagani O, Fleming GF, et al; SOFT and TEXT Investigators and the International Breast Cancer Study Group. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med*. 2018;379(2):122-137. doi:10.1056/NEJMoa1803164

21. Pan H, Gray R, Braybrooke J, et al; EBCTCG. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med*. 2017;377(19):1836-1846. doi:10.1056/NEJMoa1701830

22. Davies C, Pan H, Godwin J, et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381(9869):805-816. doi:10.1016/S0140-6736(12)61963-1

23. Gray RG, Rea D, Handley D, Bowden SJ, Perry P. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. *J Clin Oncol*. 2013;31(18 suppl). doi:10.1200/jco.2013.31.18_suppl.5

24. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med*. 2016;375(3):209-219. doi:10.1056/NEJMoa1604700

25. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med*. 2015;373(21):2005-2014. doi:10.1056/NEJMoa1510764

26. Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: first prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. *J Clin Oncol*. 2016;34(20):2341-2349. doi:10.1200/JCO.2015.63.5383

27. 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(2):111-121. doi:10.1056/NEJMoa1804710

28. Jasem J, Fisher CM, Amini A, et al. The 21-gene recurrence score assay for node-positive, early-stage breast cancer and impact of RxPONDER Trial on chemotherapy decision-making: have clinicians already decided? *J Natl Compr Canc Netw*. 2017;15(4):494-503. doi:10.6004/jnccn.2017.0049

29. Cardoso F, van't Veer LJ, Bogaerts J, et al; MINDACT Investigators. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729. doi:10.1056/NEJMoa1602253

30. Harris LN, Ismaila N, McShane LM, et al; American Society of Clinical Oncology. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34(10):1134-1150. doi:10.1200/JCO.2015.65.2289

31. Krop I, Ismaila N, Andre F, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol*. 2017;35(24):2838-2847. doi:10.1200/JCO.2017.74.0472

32. Albain KS, Barlow WE, Shak S, et al; Breast Cancer Intergroup of North America. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol*. 2010;11(1):55-65. doi:10.1016/S1470-2045(09)70314-6

33. Duffy MJ, Harbeck N, Nap M, et al. Clinical use of biomarkers in breast cancer: updated guidelines from the European Group on Tumor Markers (EGTM). *Eur J Cancer*. 2017;75:284-298. doi:10.1016/j.ejca.2017.01.017

34. Peto R, Davies C, Godwin J, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379(9814):432-444. doi:10.1016/S0140-6736(11)61625-5

35. Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med*. 1976;294(8):405-410. doi:10.1056/NEJM197602192940801

36. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol*. 1990;8(9):1483-1496. doi:10.1200/JCO.1990.8.9.1483

37. Henderson IC, Berry DA, Demetri GD, et al. Improved disease-free and overall survival from the addition of sequential paclitaxel but not from the escalation of doxorubicin dose level in the adjuvant chemotherapy of patients with node-positive primary breast cancer. In: American Society of Clinical Oncology Annual Meeting; May 16-19, 1998; Los Angeles, CA. Abstract 101a.

38. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med*. 2008;358(16):1663-1671. doi:10.1056/NEJMoa0707056

39. Martín M, Seguí MA, Antón A, et al; GEICAM 9805 Investigators. Adjuvant docetaxel for high-risk, node-negative breast cancer. *N Engl J Med*. 2010;363(23):2200-2210. doi:10.1056/NEJMoa0910320

40. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol*. 2003;21(8):1431-1439. doi:10.1200/JCO.2003.09.081

41. Gray R, Bradley R, Braybrooke J, et al. Increasing the dose intensity of adjuvant chemotherapy: an EBCTCG meta-analysis. In: San Antonio Breast Cancer Symposium; December 5-7, 2017; San Antonio, TX. Abstract GS1-01.

42. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol*. 2009;27(8):1177-1183. doi:10.1200/JCO.2008.18.4028

43. 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(23):2647-2655. doi:10.1200/JCO.2016.71.4147

44. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376(22):2147-2159. doi:10.1056/NEJMoa1612645

45. von Minckwitz G, Loibl S, Schneeweiss A, et al. Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto). In: San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract S2-04.

46. Sikov WM, Berry DA, Perou CM, et al. Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/− carboplatin and/or bevacizumab in triple-negative breast cancer: outcomes from CALGB 40603 (Alliance). In: San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract S2-05.

47. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164-172. doi:10.1016/S0140-6736(13)62422-8

48. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1673-1684. doi:10.1056/NEJMoa052122

49. Slamon D, Eiermann W, Robert N, et al; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365(14):1273-1283. doi:10.1056/NEJMoa0910383

50. Breast Cancer. National Comprehensive Cancer Network: National Clinical Practice Guidelines in Oncology. Version 3. 2018. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

51. Pivot X, Romieu G, Debled M, et al; PHARE trial investigators. 6 Months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(8):741-748. doi:10.1016/S1470-2045(13)70225-0

52. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al; Herceptin Adjuvant (HERA) Trial Study Team. 11 Years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017;389(10075):1195-1205. doi:10.1016/S0140-6736(16)32616-2

53. Earl HM, Hiller L, Vallier A-L, et al. PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results. *J Clin Oncol*. 2018;36(15_suppl). doi:10.1200/JCO.2018.36.15_suppl.506

54. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al; FinHer Study Investigators. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006;354(8):809-820. doi:10.1056/NEJMoa053028

55. Tolaney SM, Barry WT, Guo H, et al. Seven-year follow-up of adjuvant paclitaxel and trastuzumab (APT trial) for node-negative, HER2+ breast cancer. *J Clin Oncol*. 2017;35(15 suppl). doi:10.1200/JCO.2017.35.15_suppl.511

56. von Minckwitz G, Procter M, de Azambuja E, et al; APHINITY Steering Committee and Investigators. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(2):122-131. doi:10.1056/NEJMoa1703643

57. Martin M, Holmes FA, Ejlertsen B, et al; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1688-1700. doi:10.1016/S1470-2045(17)30717-9

58. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233-1241. doi:10.1056/NEJMoa022152

59. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11(10):927-933. doi:10.1016/S1470-2045(10)70207-2

60. Krag DN, Anderson SJ, Julian TB, et al; National Surgical Adjuvant Breast and Bowel Project. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *Lancet Oncol*. 2007;8(10):881-888. doi:10.1016/S1470-2045(07)70278-4

61. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305(6):569-575. doi:10.1001/jama.2011.90

62. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15(12):1303-1310. doi:10.1016/S1470-2045(14)70460-7

63. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol*. 2018;19(1):27-39. doi:10.1016/S1470-2045(17)30777-5

64. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol*. 2008;26(5):778-785. doi:10.1200/JCO.2007.15.0235

65. Pilewskie M, Morrow M. Axillary nodal management following neoadjuvant chemotherapy: a review. *JAMA Oncol*. 2017;3(4):549-555. doi:10.1001/jamaoncol.2016.4163

66. Darby S, McGale P, Correa C, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707-1716. doi:10.1016/S0140-6736(11)61629-2

67. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med*. 2010;362(6):513-520. doi:10.1056/NEJMoa0906260

68. Haviland JS, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol*. 2013;14(11):1086-1094. doi:10.1016/S1470-2045(13)70386-3

69. Coles CE, Griffin CL, Kirby AM, et al; IMPORT Trialists. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet*. 2017;390(10099):1048-1060. doi:10.1016/S0140-6736(17)31145-5

70. Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol*. 2017;7(2):73-79. doi:10.1016/j.prro.2016.09.007

71. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol*. 2007;25(22):3259-3265. doi:10.1200/JCO.2007.11.4991

72. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol*. 2013;31(19):2382-2387. doi:10.1200/JCO.2012.45.2615

73. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015;16(3):266-273. doi:10.1016/S1470-2045(14)71221-5

74. McGale P, Taylor C, Correa C, et al; EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014;383(9935):2127-2135. doi:10.1016/S0140-6736(14)60488-8

75. Whelan TJ, Olivotto IA, Parulekar WR, et al; MA.20 Study Investigators. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med*. 2015;373(4):307-316. doi:10.1056/NEJMoa1415340

76. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med*. 2015;373(4):317-327. doi:10.1056/NEJMoa1415369

77. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the number of women

living with metastatic breast cancer in the United States. *Cancer Epidemiol Biomarkers Prev*. 2017;26 (6):809-815. doi:10.1158/1055-9965.EPI-16-0889

78. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925-1936. doi:10.1056/NEJMoa1607303

79. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32): 3638-3646. doi:10.1200/JCO.2017.75.6155

80. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for hr-positive, advanced breast cancer. *N Engl J Med*. 2016;375 (18):1738-1748. doi:10.1056/NEJMoa1609709

81. Baselga J, Cortés J, Kim SB, et al; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109-119. doi:10.1056/NEJMoa1113216

82. Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367 (19):1783-1791. doi:10.1056/NEJMoa1209124

83. Kabraji S, Ni J, Lin NU, Xie S, Winer EP, Zhao JJ. Drug resistance in HER2-positive breast cancer brain metastases: blame the barrier or the brain? *Clin Cancer Res*. 2018;24(8):1795-1804. doi:10.1158/1078-0432.CCR-17-3351

84. Tutt A, Ellis P, Kilburn L, et al. The TNT trial: a randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer. In: San Antonio Breast Cancer Symposium; December 9-13, 2014. Abstract S3-01.

85. Cardoso F, Bedard PL, Winer EP, et al; ESO-MBC Task Force. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. *J Natl Cancer Inst*. 2009;101(17): 1174-1181. doi:10.1093/jnci/djp235

86. Joensuu H, Holli K, Heikkinen M, et al. Combination chemotherapy versus single-agent therapy as first- and second-line treatment in metastatic breast cancer: a prospective randomized trial. *J Clin Oncol*. 1998;16(12):3720-3730. doi:10.1200/JCO.1998.16.12.3720

87. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German breast group 26/breast international group 03-05 study. *J Clin Oncol*. 2009;27(12):1999-2006. doi:10.1200/JCO.2008.19.6618

88. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884. doi:10.1200/JCO.2017.73.7585

89. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory $HR^+/HER2^-$ metastatic breast cancer. *Clin Cancer Res*. 2017;23(17):5218-5224. doi:10.1158/1078-0432.CCR-17-0754

90. Schmid P, Adams S, Rugo HS, et al; IMpassion130 Trial Investigators. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108-2121. doi:10.1056/NEJMoa1809615

91. Bowman KM, Kumthekar P. Medical management of brain metastases and leptomeningeal disease in patients with breast carcinoma. *Future Oncol*. 2018;14(4):391-407. doi:10.2217/fon-2017-0255

92. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377(6):523-533. doi:10.1056/NEJMoa1706450

93. Cortes-Ciriano I, Lee S, Park WY, Kim TM, Park PJ. A molecular portrait of microsatellite instability across multiple cancers. *Nat Commun*. 2017;8:15180. doi:10.1038/ncomms15180

94. Ben-Baruch NE, Bose R, Kavuri SM, Ma CX, Ellis MJ. HER2-mutated breast cancer responds to treatment with single-agent neratinib, a second-generation HER2/EGFR tyrosine kinase inhibitor. *J Natl Compr Canc Netw*. 2015;13(9):1061-1064. doi:10.6004/jnccn.2015.0131

95. Bose R, Kavuri SM, Searleman AC, et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov*. 2013;3(2):224-237. doi:10.1158/2159-8290.CD-12-0349

96. Fribbens C, O'Leary B, Kilburn L, et al. Plasma ESR1 mutations and the treatment of estrogen receptor-positive advanced breast cancer. *J Clin Oncol*. 2016;34(25):2961-2968. doi:10.1200/JCO.2016.67.3061

97. Jemal A, Robbins AS, Lin CC, et al. Factors that contributed to black-white disparities in survival among nonelderly women with breast cancer between 2004 and 2013. *J Clin Oncol*. 2018;36(1): 14-24. doi:10.1200/JCO.2017.73.7932

98. Hunt BR, Whitman S, Hurlbert MS. Increasing black:white disparities in breast cancer mortality in the 50 largest cities in the United States. *Cancer Epidemiol*. 2014;38(2):118-123. doi:10.1016/j.canep.2013.09.009

99. Shariff-Marco S, Yang J, John EM, et al. Intersection of race/ethnicity and socioeconomic status in mortality after breast cancer. *J Community Health*. 2015;40(6):1287-1299. doi:10.1007/s10900-015-0052-y

100. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al; BIG 1-98 Collaborative Group. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med*. 2009;361 (8):766-776. doi:10.1056/NEJMoa0810818

101. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol*. 2006;24(34):5381-5387. doi:10.1200/JCO.2006.06.5391

102. Turner NC, Ro J, André F, et al; PALOMA3 Study Group. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2015;373(3):209-219. doi:10.1056/NEJMoa1505270

103. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol*. 2018;36(24): 2465-2472. doi:10.1200/JCO.2018.78.9909

104. 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 (8):753-763. doi:10.1056/NEJMoa1802905