Oncology Oral, Breast Cancer Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
abemaciclib (Verzenio®)[1]	Eli Lilly	▪ In combination with an aromatase inhibitor (AI) as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer ▪ In combination with fulvestrant for the treatment of women with hormone receptor HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy ▪ Monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting
alpelisib (Piqray®)[2]	Novartis	▪ In combination with fulvestrant for the treatment of men and postmenopausal women with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen; patients should be selected for therapy based on the presence of one or more PIK3CA mutations in tumor tissue or plasma specimens*
anastrozole (Arimidex®)[3]	generic, Ani	▪ Adjuvant treatment of postmenopausal women with HR-positive early breast cancer ▪ First-line treatment of postmenopausal women with HR-positive or receptor unknown locally advanced or metastatic breast cancer ▪ Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy; patients with estrogen receptor (ER)-negative disease and patients who did not respond to previous tamoxifen therapy rarely respond to anastrozole
capecitabine (Xeloda®)[4]	generic, Genentech	▪ In combination with docetaxel after failure of prior anthracycline-containing therapy for metastatic breast cancer ▪ As monotherapy for metastatic breast cancer in patients who are resistant to both paclitaxel and an anthracycline-containing regimen ▪ Adjuvant treatment of colon cancer (Dukes' C) ▪ First-line monotherapy for metastatic colorectal cancer when treatment with fluoropyrimidine therapy alone is preferred
cyclophosphamide[5]	generic	▪ Lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma ▪ Other malignant diseases: multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma ▪ Nephrotic syndrome: biopsy proven minimal change nephrotic syndrome in pediatric patients who failed to adequately respond to or are unable to tolerate adrenocorticosteroid therapy†
exemestane (Aromasin®)[6]	generic, Pfizer	▪ Adjuvant treatment of postmenopausal women with ER-positive early breast cancer who have received 2 to 3 years of tamoxifen and are switched to exemestane for completion of a total of 5 consecutive years of adjuvant hormonal therapy ▪ Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy

ER=estrogen receptor; HR=hormone receptor; HER2=human epidermal growth factor receptor 2

* As detected by an FDA-approved test: http://www.fda.gov/CompanionDiagnostics; if a mutation is not detected in a plasma specimen then the tumor tissue should be tested

† Limitation of use for cyclophosphamide: the safety and effectiveness for the treatment of nephrotic syndrome in adults or other renal disease has not been established

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FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
fulvestrant (Faslodex®)[7]	generic, AstraZeneca	▪ Treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy ▪ Treatment of HR-positive advanced breast cancer in postmenopausal women whose disease has progressed following endocrine therapy ▪ Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women, in combination with ribociclib, as initial endocrine-based therapy or following disease progression on endocrine therapy ▪ Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy
lapatinib (Tykerb®)[8]	Novartis	▪ In combination with capecitabine (Xeloda), for the treatment of patients with advanced or metastatic breast cancer whose tumors over express HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab (Herceptin)[‡] ▪ In combination with letrozole (Femara), for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that over expresses the HER2 receptor for whom hormonal therapy is indicated[§]
letrozole (Femara®)[9]	generic, Novartis	▪ Adjuvant treatment of postmenopausal women with HR-positive early breast cancer ▪ Extended adjuvant treatment of early breast cancer in postmenopausal women who have received prior adjuvant tamoxifen therapy ▪ First- and second-line treatment of postmenopausal women HR-positive or unknown advanced breast cancer
neratinib (Nerlynx®)[10]	Puma	▪ Extended adjuvant treatment of adults with early stage HER-2 overexpressed/amplified breast cancer following adjuvant trastuzumab therapy ▪ In combination with capecitabine, treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2 based regimens in the metastatic setting
palbociclib (Ibrance®)[11]	Pfizer	▪ Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an AI as initial endocrine-based therapy for men or postmenopausal women ▪ Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with fulvestrant (Faslodex) in patients with disease progression following endocrine therapy
ribociclib (Kisqali®)[12]	Novartis	▪ Treatment of pre/perimenopausal or postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy, in combination with an AI ▪ Treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer as initial endocrine-based therapy or following disease progression on endocrine therapy, in combination with fulvestrant (Faslodex)
ribociclib/letrozole (Kisqali Femara Co-Pack®)[13]	Novartis	▪ Treatment of pre-, peri-, or postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer as initial endocrine-based therapy

ER=estrogen receptor; HR=hormone receptor; HER2=human epidermal growth factor receptor 2

[‡] A limitation of use for lapatinib in combination with capecitabine: should be reserved for patients who experienced disease progression on trastuzumab (Herceptin).

§ Lapatinib in combination with an aromatase inhibitor (AI) has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

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FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indications
talazoparib (Talzenna®)[14]	Pfizer	▪ Treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (*BRCA*)-mutated (*gBRCAm*) HER2-negative locally advanced or metastatic breast cancer‖
tamoxifen citrate tablets[15]	generic	▪ Adjuvant therapy for breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation to decrease the incidence of contralateral breast cancer ▪ Treatment of metastatic breast cancer in men and pre-and post-menopausal women ▪ Treatment of ductal carcinoma in situ (DCIS) following breast surgery and radiation therapy to reduce the risk of invasive breast cancer in pre-and post-menopausal women ▪ Breast cancer prophylaxis in women who are at high risk (5-year risk ≥ 1.67%) for developing the disease
tamoxifen citrate solution¶ (Soltamox®)[16]	Midatech	▪ For treatment of adult patients with estrogen receptor-positive metastatic breast cancer ▪ For adjuvant treatment of adult patients with early stage estrogen receptor-positive breast cancer ▪ To reduce risk of invasive breast cancer following breast surgery and radiation in adult women with ductal carcinoma in situ (DCIS) ▪ To reduce the incidence of breast cancer in adult women at high risk
toremifene (Fareston®)[17]	generic, Kyowa Kirin	▪ Treatment of metastatic breast cancer in postmenopausal women with ER-positive or unknown tumors

ER=estrogen receptor; HR=hormone receptor; HER2=human epidermal growth factor receptor 2

‖ Patients should be selected for therapy based on the presence of germline *BRCA* mutations detected by an FDA-approved companion diagnostic; details regarding this test are available at http://www.fda.gov/companiondiagnostics.

¶ Approved via the 505(b)(2) pathway that allows approval based on at least some data from other formulations of tamoxifen.

OVERVIEW

Breast cancer is the most common site of cancer in women and is second only to lung cancer as a cause of cancer death in American women.[18] It is estimated that there will be 276,480 new cases of breast cancer diagnosed in the United States (US) in 2020 and there will be an estimated 42,170 deaths.[19] Death rates from breast cancer have steadily decreased in women since 1989 due to improvements in both early detection and treatment.[20] The overall 5-year survival for women diagnosed with breast cancer is 89.9%. Patients who present with localized disease have a 98.8% 5-year survival rate; however, prognosis for patients presenting with distant metastatic disease is much poorer, with a 5-year survival rate of only 27.4%.[21] Several risk factors have been identified related to an increased risk of developing breast cancer. Aside from female gender, the variable most strongly associated with the occurrence of breast cancer is age. The incidence of breast cancer increases with advancing age.[22] Breast cancer is most frequently diagnosed in women between the ages of 55 to 64 with the median age at diagnosis being 62 years.[23] Other risk factors include various endocrine, genetic, environmental, and lifestyle factors. Some of these risk factors are modifiable, some are not, and the impact of these factors are variable.[24]

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All invasive breast cancer tumors are analyzed for the tumor's hormone receptor status and the presence or absence of the Her2/neu (HER2) receptor protein. Hormone receptor status is used clinically as an indicator of likely response to hormonal therapy. About two-thirds of patients with primary or metastatic breast cancer have hormone receptor (HR)-positive tumors.[25] Hormonal therapies to treat breast cancer can be beneficial in both the adjuvant and metastatic setting of HR-positive disease. The menopausal status of the patient and the hormone receptor status of the tumor are important considerations in the therapeutic use of these agents. The prevalence and frequency of HR-positive tumors are higher in postmenopausal patients as compared to premenopausal patients.[26] Hormone receptor positivity is associated with a superior response to hormonal therapy. About 60% to 70% of patients who are ER-positive (ER+) and PR-positive (PR+) will respond to hormonal-based therapy, while ER-negative patients rarely respond to hormonal therapy.[27]

Both the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) have published clinical practice guidelines regarding the treatment of breast cancer. The NCCN guideline on breast cancer outlines the treatment of breast cancer in the neoadjuvant, adjuvant, and metastatic disease settings.[28]

There are several ASCO clinical practice guidelines regarding the pharmacologic treatment of breast cancer, and these separately address treatment in either the adjuvant or advanced cancer settings. In addition, ASCO has published guidelines regarding the management of male breast cancer, the use of endocrine therapy for breast cancer risk reduction and details around biomarker testing (estrogen, progesterone, and HER2) in breast cancer.[29,30,31,32] For adjuvant therapy, there are 2 ASCO guidelines assessing the need for systemic adjuvant therapy in early-stage breast cancer, as there are some breast cancer patients for whom adjuvant systemic therapy may not be required. The first guideline is based upon known patient and disease risk factors, and the second guideline addresses the use of biomarkers to guide decisions regarding adjuvant therapy.[33,34] For patients who do require adjuvant therapy, there are several other ASCO clinical practice guidelines to inform clinical practice. These guidelines address adjuvant treatment with endocrine therapy in HR-positive disease and optimal adjuvant chemotherapy and targeted therapy for patients with early breast cancer.[35,36] For the treatment of patients with advanced or metastatic breast cancer, there are also several ASCO clinical practice guidelines. These guidelines separately address endocrine therapy for HR-positive metastatic breast cancer and systemic therapy for patients with advanced HER2-positive breast cancer, including those patients with brain metastases.[37,38,39] The ASCO guideline regarding the use of chemotherapy and targeted therapy for women with HER2-negative (or unknown) advanced breast cancer is currently being reviewed for updates.[40]

In the adjuvant setting, according to the NCCN V3.2020 guidelines, endocrine therapy should be considered for all patients with HR-positive disease, regardless of menopausal status, age, or HER2 status of the tumor.[41] For women who are postmenopausal at time of diagnosis, an aromatase inhibitor (AI) should be utilized as adjuvant endocrine therapy unless there is a contraindication, intolerance, or the patient declines AI therapy, in which case tamoxifen is recommended. Category 1 recommendations for initial adjuvant endocrine therapy in postmenopausal women include an AI for an initial 5 years followed by consideration of an additional 3 to 5 years of an AI or an AI for 2 to 3 years followed by tamoxifen to complete 5 years of endocrine therapy. Other options include tamoxifen for 2 to 3 years followed by an AI to complete 5 years of endocrine therapy (category 1), or tamoxifen for 4.5 to 6 years followed by an AI for 5 years (category 2B) or continuation of tamoxifen for an additional 5 years to complete 10 years of therapy (category 2A).[42] NCCN guidelines regarding

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premenopausal women with HR-positive disease recommend tamoxifen for 5 years, with or without ovarian suppression or ablation (category 1), or the use of an aromatase inhibitor (AI) for 5 years plus ovarian suppression or ablation (category 1) based on the results of the Suppression of Ovarian Function Trial (SOFT) and the TEXT (Tamoxifen and Exemestane Trial) trials. These trials indicated that premenopausal women at higher risk of recurrence (young age, high-grade tumor, lymph node involvement) may experience an improvement of 10% to 15% in 5-year breast cancer-free interval (BCFI) compared to those who received tamoxifen alone.[43,44,45] The NCCN guidelines further state that a balanced discussion of the risks and benefits associated with ovarian suppression is critical in the setting of women who are premenopausal at diagnosis.[46] After the initial 5 years of therapy, women who are still premenopausal may consider tamoxifen for an additional 5 years to complete 10 years or consider no further adjuvant endocrine therapy (both category 2A). Women who subsequently became postmenopausal after the initial 5 years of adjuvant endocrine therapy may be treated with an AI for an additional 5 years (category 1) or may continue tamoxifen for an additional 5 years to complete 10 years of adjuvant therapy (category 2A). The NCCN guidelines state that the 3 selective AIs, anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin), have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and neoadjuvant settings and that the optimal duration of treatment with AIs in adjuvant setting is uncertain.[47]

The most recent update of the ASCO guideline regarding the use of adjuvant endocrine therapy for women with HR- positive breast cancer addresses the emerging data about the optimal duration of AI treatment.[48] For women with node-positive breast cancer, the ASCO guideline recommends extended adjuvant endocrine therapy for up to a total of 10 years. Likewise, many women with node-negative breast cancer should consider extended adjuvant endocrine therapy based on individual risk recurrence established by prognostic factors. The ASCO guideline recommends shared decision making between clinicians and patients regarding extended adjuvant endocrine therapy. For patients who will receive adjuvant chemotherapy, endocrine therapy should be initiated after the completion of chemotherapy.

In 2018, ASCO published updated guidelines for the selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer.[49] Among other topics, this guideline addresses the role of adjuvant capecitabine for HER2-negative early stage breast cancer with residual invasive disease at time of surgery, following neoadjuvant chemotherapy. While there was previously no established role for adjuvant capecitabine, the ASCO guidelines state that patients with early stage, HER2-negative breast cancer who received standard preoperative anthracycline and taxane-based combination chemotherapy and were subsequently found to have invasive residual disease at surgery may be offered up to 6 to 8 cycles of adjuvant capecitabine. ASCO does qualify this statement by saying that it preferentially supports this use of adjuvant capecitabine in the subgroup of patients with both HR-negative and HER2-negative, or triple negative, disease. The NCCN V3.2020 guidelines specifically limit the role of adjuvant capecitabine to patients with triple negative breast cancer with residual invasive cancer following standard neoadjuvant chemotherapy (category 2A). These recommendations are based on the results of the CREATE-X (Capecitabine for Residual Cancer as Adjuvant Therapy) trial which showed statistically significant improvements in both disease-free survival (DFS) and overall survival (OS) for patients with HER2-negative residual invasive breast cancer after neoadjuvant chemotherapy (with an anthracycline, taxane or both). The rate of DFS and OS were even more significantly positive in the group of patients with triple negative disease.[50]

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The same ASCO guideline regarding optimal adjuvant chemotherapy and targeted therapy for early breast cancer also gives a moderate rating of approval for the use of extended adjuvant therapy with neratinib following trastuzumab in patients with early-stage HER2-positive breast cancer.[51] ASCO states they preferentially favor the use of neratinib in patients with HR-positive and node-positive disease. ASCO further states that neratinib causes substantial diarrhea and diarrheal prophylaxis must be used; patients who begin neratinib within 1 year of trastuzumab completion appear to derive the greatest benefit; and, at a median follow up of 5.2 years, no OS benefit has been observed for the use of extended adjuvant neratinib. Likewise, the NCCN guidelines state extended adjuvant neratinib may be considered following adjuvant trastuzumab-containing therapy in HR-positive, HER-2 positive, node positive patients with a perceived high risk of recurrence.[52]

Oral cyclophosphamide may be utilized as part of a regimen in combination with methotrexate and fluorouracil (CMF) in HER2-negative patients. The NCCN lists CMF with oral cyclophosphamide under "useful in certain circumstances" in this setting rather than as a preferred regimen (category 2A).[53] Cyclophosphamide has a variety of other indications, but this review will focus only on its role in the management of breast cancer.

A joint position statement issued by a number of organizations, including the International Osteoporosis Foundation, addresses the management of AI associated bone-loss in postmenopausal women with HR-positive breast cancer.[54] These guidelines state that real world studies have demonstrated a much higher fracture rate associated with AI therapy than was suggested by the randomized controlled trials. Specific recommendations include that all women initiating AI treatment should be assessed for fracture risk and given recommendations with regard to exercise and calcium/vitamin D supplementation. Bone-directed therapy should be given to all appropriate patients (T-score < -2, T-score < -1.5 SD with 1 additional risk factor, or ≥ 2 risk factors regardless of bone mineral density score) for the duration of AI treatment with compliance assessed regularly. These guidelines state that because of the decreased incidence of bone recurrence and breast cancer specific mortality, adjuvant bisphosphonates are recommended for all postmenopausal women at significant risk of breast cancer recurrence.

Advanced breast cancer is defined as either locally advanced breast cancer that is unresectable or distant metastatic disease. According to the NCCN V3.2020 guidelines, in the setting of HR-positive advanced breast cancer, hormonal therapy is recommended as first-line for nearly all patients except those patients with symptomatic visceral disease, who should be considered for initial chemotherapy treatment.[55] For HR-positive, HER2-negative patients the combination of a CDK4/6 inhibitor (abemaciclib [Verzenio], palbociclib [Ibrance], ribociclib [Kisqali]) with an AI is a category 1, preferred recommendation for first-line therapy in postmenopausal women or premenopausal women receiving ovarian ablation or suppression. Fulvestrant, with or without an AI, and fulvestrant plus a CDK4/6 inhibitor are also category 1 preferred options in this setting. Monotherapy with an AI (anastrozole, letrozole, or exemestane) or tamoxifen or toremifene are category 2A recommendations for first-line therapy of HR-positive, HER2-negative advanced breast cancer patients. Preferred endocrine regimens in the second or subsequent line of therapy for advanced breast cancer include fulvestrant plus a CDK4/6 inhibitor if a CDK4/6 inhibitor has not been previously used (category 1). Fulvestrant in combination with alpelisib (Piqray) for PIK3CA-mutated tumors is also a category 1, preferred option for these patients as second- or subsequent line of therapy. The use of everolimus plus either tamoxifen, fulvestrant, or exemestane is a category 2A recommendation. Other category 2A recommendations for second- or subsequent lines of therapy include monotherapy with an AI or

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fulvestrant or tamoxifen or toremifene. Single agent abemaciclib is listed as "useful in certain circumstances" for HR-positive, HER2-negative patients with advanced breast cancer who have experienced disease progression on both prior endocrine therapy and prior chemotherapy in the metastatic setting. The NCCN guidelines note that if the patient experienced disease progression on a CDK4/6 inhibitor-containing (e.g., palbociclib, ribociclib, abemaciclib) regimen in any line of endocrine-based therapy, there are no data to support a subsequent line of therapy with a CDK4/6 inhibitor. Likewise, if there is disease progression on an everolimus-containing regimen, there are no data to support additional lines of therapy with different everolimus-containing regimen.

A combination of a taxane plus pertuzumab (Perjeta) plus trastuzumab (Herceptin) is the preferred standard of care for advanced, HR-positive, HER2-positive advanced breast cancer. The NCCN-recommended endocrine therapy regimens in this population largely mirror those for women with HR-positive and HER2-negative disease, with the exclusion of CDK4/6 inhibitors in this population and consideration for addition of HER2-targeted therapy. These regimens include an AI with or without lapatinib and/or trastuzumab and fulvestrant or tamoxifen with or without trastuzumab (all category 2A). Neratinib plus capecitabine is now a category 2A recommendation (previously category 2B) for any patient with HER-2 positive advanced breast cancer.

The NCCN guidelines also list other relevant biomarkers with associated targeted therapies that may be utilized in the advanced/metastatic setting including olaparib (Lynparza) and talazoparib (Talzenna) as category 1, preferred options for BRCA1/BRCA2 mutation-positive patients. Patients with advanced breast cancer who have identified NTRK fusions or are found to have MSI-H/dMMR also have FDA-approved options for targeted therapies.

The ASCO guideline regarding endocrine therapy for HR-positive metastatic breast cancer, published in 2016, states that first-line endocrine therapy should include an AI with or without palbociclib in postmenopausal women.[56] Notably, at the time of the ASCO guideline publication, palbociclib was the only CDK4/6 inhibitor on the market. Combination therapy with a nonsteroidal AI plus fulvestrant may also be offered to patients without prior exposure to adjuvant endocrine therapy in the first-line setting. In the second-line setting, sequential hormone therapy is indicated in patients with endocrine-responsive disease and no specific order of agents is recommended. The combination of fulvestrant plus palbociclib may be offered to patients who experienced progression during prior treatment with AIs (with or without 1 prior line of chemotherapy) because progression-free survival (PFS) was improved compared to fulvestrant alone. The ASCO guidelines also note that palbociclib should not be offered to patients who have already received palbociclib or with prior exposure to other cyclin-dependent kinase 4/6 inhibitors. Premenopausal women should be offered ovarian suppression or ablation in addition to hormone therapy in the setting of HR-positive advanced breast cancer.

ASCO guidelines for the systemic treatment of HER2-positive advanced breast cancer were updated in 2018.[57] These guidelines recommend the inclusion of HER2-targeted therapy for first-line treatment except for patients with clinical congestive heart failure or significantly compromised left ventricular ejection fraction, who should be evaluated on a case-by-case basis. In particular, highly selected patients with HR-positive disease may be appropriate for endocrine therapy alone. The ASCO guidelines concur with the NCCN guidelines that first-line therapy for advanced HER2-positive breast cancer should be a combination of trastuzumab, pertuzumab, and a taxane, unless the patient has a contraindication to taxanes (strength of recommendation: strong). In the second-line setting, ASCO guidelines recommend trastuzumab emtansine (T-DM1) (strength of recommendation: strong). Once a patient has progressed through second-line therapy and has received pertuzumab and T-DM1, options

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include lapatinib plus capecitabine as well as other combinations of chemotherapy with trastuzumab or lapatinib. The ASCO guidelines differentiate between patients who finished adjuvant trastuzumab ≤ 12 months prior or > 12 months prior. If the patient develops advanced disease ≤ 12 months from adjuvant trastuzumab, therapy should begin with recommended second-line therapy, but if the patient is 12 months or more out from adjuvant trastuzumab then first-line therapy recommendations can be followed.

Tamoxifen, along with raloxifene (a similar drug indicated for treatment and prevention of osteoporosis), are the only FDA-approved agents for breast cancer prophylaxis. The NCCN guidelines regarding breast cancer risk reduction suggest women who have either a known genetic predisposition or a family history suggestive of a genetic predisposition and who also have a life expectancy of ≥ 10 years should receive risk-reduction counseling. Women with a lifetime risk of ≥ 20% based on established models largely dependent on family history and a life expectancy of ≥ 10 years should also receive risk-reduction counseling.[58] Based on this counseling, if the woman desires risk-reduction therapy and she is premenopausal, tamoxifen (category 1) or a clinical trial is recommended. Recommendations for postmenopausal woman meeting criteria and desiring risk-reduction therapy include a clinical trial, tamoxifen (category 1), raloxifene (category 1), or an AI (either exemestane or anastrozole; category 1). The NCCN guidelines note that despite exemestane and anastrozole not being FDA approved for breast cancer risk-reduction and no comparative data existing with these AIs and tamoxifen or raloxifene, in situations where tamoxifen or raloxifene use is contraindicated, AIs may be considered for breast cancer risk-reduction in postmenopausal women. In women ≥ 35 years of age and who have a life expectancy of ≥ 10 years who do not meet any of the familial risk criteria or who have tests indicating a genetic predisposition are negative, the modified Gail Model can be used to identify women with a 5-year breast cancer risk ≥ 1.7%. Those women should also receive risk-reduction counseling, and, if they desire risk-reduction therapy, the same recommendations would apply. In addition to the pharmacologic risk-reduction strategies, these guidelines include further screening recommendations, lifestyle modification interventions, and possible risk-reduction surgical interventions. The NCCN guidelines regarding raloxifene state that, while raloxifene in long-term follow-up appears to be less efficacious in risk reduction than tamoxifen, toxicity considerations may favor raloxifene in women with an intact uterus.

The American Society of Breast Surgeons published a consensus guideline on genetic testing for hereditary breast cancer in February 2019.[59] Genetic testing should be made available for all patients with newly diagnosed or a personal history of breast cancer, and updated testing may be beneficial in patients who had prior negative *BRCA1/2* testing and whose family has no pathogenic variants or if prior testing was before 2014. Genetic testing should be made available for patients who have no history of breast cancer but who meet NCCN guidelines (e.g., adoption or uncertain cancer type of affected family member). Referral to a certified genetic counselor or genetics professional when patient history and/or test results are complex may be helpful.

ASCO updated their guideline on pharmacologic interventions for breast cancer risk reduction in September 2019.[60] For postmenopausal women at increased risk, the guideline recommends either anastrozole, exemestane, raloxifene, or tamoxifen. The decision regarding choice of endocrine therapy should take into consideration patient age, baseline comorbidities, and the individual drug adverse event profiles. For premenopausal women who are ≥ 35 years old and have completed childbearing, only tamoxifen is considered an appropriate option.

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Male breast carcinoma is a rare disease and represents < 1% of all breast cancer diagnosis and < 0.1% of cancer-related deaths in men in the US.[61] Male breast cancer is associated with a higher percentage of estrogen receptor (ER) positivity compared to female breast cancer. A population based study of 2,537 men with breast cancer found that > 90% of all male breast cancer tumors were ER-positive.[62] In February 2020, ASCO published its first clinical practice guideline regarding the management of male breast cancer.[63] According to this guideline, many aspects of breast cancer management in males are similar to management of female breast cancer. These include surgery, adjuvant radiation therapy, gene expression profiling, and the use of chemotherapy and targeted therapies in both the adjuvant and the metastatic setting. Among the differences in pharmacologic management is the recommendation that tamoxifen alone should be used as adjuvant therapy for an initial duration of 5 years. In men with a contraindication to tamoxifen, therapy with a gonadotropin-releasing hormone agonist/antagonist plus an AI may be offered. In the metastatic setting, endocrine options include those utilized in the adjuvant setting (tamoxifen or GHRH agonist/antagonist plus an AI) or fulvestrant. CDK4/6 inhibitors can be used in men as they are used in women.

While select agents in this class review are approved for uses outside of breast cancer, this class review focuses on use for breast cancer.

PHARMACOLOGY[64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80]

The endocrine therapies utilized in the adjuvant treatment of breast cancer or in the management of metastatic breast cancer can be divided into 3 groups. These groups include selective estrogen receptor modulators (SERM), selective estrogen receptor down-regulators (SERD), or aromatase inhibitors (AI). Both tamoxifen, the prototype endocrine therapy for breast cancer, and toremifene (Fareston) are classified as SERMs. These agents have both antiestrogenic and estrogenic activity depending on the type of tissue and receptor involved. Tamoxifen blocks the effects of estrogen in breast tissue but displays agonist activity in bone, which leads to beneficial effects on bone mineral density in postmenopausal women.[81] Toremifene also has both estrogenic and antiestrogenic activity. Structurally, toremifene differs from tamoxifen only by the substitution of 1 chlorine atom. Toremifene appears to have efficacy in metastatic breast cancer based on its antiestrogenic activity in breast tissue. Toremifene binds to the estrogen receptor and, therefore, competes with estrogen for binding sites and blocking the growth-stimulating effects of estrogen in the tumor. The only pure estrogen receptor antagonist (SERD) on the market is fulvestrant (Faslodex). When fulvestrant binds to the estrogen receptor, there is a down-regulation of the receptor as opposed to a blocking of the receptor. This down-regulation results in multiple changes in ER function including impaired dimerization, increased turnover, and disrupted nuclear localization. Fulvestrant also triggers degradation of the ER, causing cellular levels of ER to be markedly reduced.[82] There are 3 AIs on the market: anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin). These AIs can be further divided into nonsteroidal (anastrozole, letrozole) and steroidal (exemestane). In postmenopausal or castrated women, the main source of estrogen is due to 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 tissue, including the breast itself, in postmenopausal women. Therefore, AIs effectively reduce the level of circulating estrogen, as well as estrogens in the target organ.[83]

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Anastrozole and letrozole exhibit reversible, competitive inhibition of aromatase and have no intrinsic hormonal activity. Exemestane binds irreversibly to aromatase, forming a covalent bond. Exemestane does exhibit some androgenic properties, but these are evident only at very high doses, generally much higher than what is used clinically in the treatment of breast cancer.

Endocrine Therapies Used for Adjuvant Treatment or Metastatic Breast Cancer	
Class	**Drug**
Aromatase Inhibitors (AI)	anastrozole (Arimidex) – nonsteroidal
	letrozole (Femara) – nonsteroidal
	exemestane (Aromasin) – steroidal
Selective Estrogen Receptor Down-Regulators (SERD)	fulvestrant (Faslodex)
Selective Estrogen Receptor Modulators (SERM)	tamoxifen
	toremifene (Fareston)

Capecitabine (Xeloda) is a fluoropyrimidine carbamate that is converted *in vivo* to 5-fluorouracil (5-FU) and causes cell injury by inhibiting DNA synthesis and interfering with RNA processing and protein synthesis.

Lapatinib (Tykerb) is a tyrosine kinase inhibitor that binds intracellularly to epidermal growth factor receptor (EGFR) and the human epidermal receptor type 2 (HER2). Tyrosine kinases are enzymes that use adenosine triphosphate (ATP) to add a phosphate group onto tyrosine residues of proteins. Autophosphorylation leads to cell proliferation pathway activation. Lapatinib binds to the intracellular domain of the EGFR and HER2 receptors and competes with ATP. Inhibition of ATP binding prevents phosphorylation of the receptors and, thus, prevents receptor activation of the cell proliferation pathway. Lapatinib has been shown both *in vitro* and in clinical studies to be non-cross resistant and possibly synergistic with trastuzumab (Herceptin). Although trastuzumab (Herceptin) and lapatinib both act by inhibiting HER2 signaling, they act at different sites, with trastuzumab (Herceptin) targeting the extracellular domain while lapatinib actions are mediated intracellularly. Therefore, tumors that are resistant to trastuzumab (Herceptin) may still have a response to lapatinib, and there is evidence that the combination of trastuzumab (Herceptin) and lapatinib may be superior to either single agent in select populations.[84]

Neratinib (Nerlynx) is a kinase inhibitor that irreversibly binds to and inhibits EGFR, HER2 and Human Epidermal Growth Factor Receptor 4 (HER4). Alpelisib (Piqray) is a kinase inhibitor that binds to and inhibits phosphatidylinositol-3-kinase (PI3K) with primary inhibitory activity against PI3Kα.

Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) are small molecule inhibitors of CDK4/6. Cyclin dependent kinases are enzymes involved in signaling pathways leading to cell proliferation. Downstream inhibition of CDK4/6 leads to cell cycle arrest by blocking transition from G1 to S phase in the cell cycle and is also believed to play a role in overcoming resistance to estrogen therapy.

Cyclophosphamide is an alkylating agent that inactivates DNA through interstrand DNA cross-links. It is a prodrug that requires hepatic activation in order to be cytotoxic and also has immunosuppressant effects.

Talazoparib (Talzenna) is a poly (ADP-ribose) polymerase (PARP) enzyme inhibitor, inhibiting PARP enzymes 1 and 2 (PARP1 and PARP2, respectively). PARP is involved in DNA repair, and talazoparib is

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thought to increase formation of PARP-DNA complexes, which in conjunction with PARP inhibition, leads to DNA damage, inhibition of cell proliferation, and cellular apoptosis.

PHARMACOKINETICS[85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100]

Drug	Half Life (hrs)	Protein Binding (%)	Metabolism	Elimination (%)
abemaciclib (Verzenio)	18.3	96	CYP3A4 (primary) to several metabolites	Urine: 3 Feces: 81
alpelisib (Piqray)	8-9	89	Hydrolysis to the metabolite BZG791 (primary), CYP3A4	Urine: 14 Feces: 81
anastrozole (Arimidex)	50	40	Metabolism of anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation	Urine: 10
capecitabine (Xeloda)	0.75	< 60	Enzymatically metabolized to 5-fluorouracil which is then hydrolyzed	Urine: 95.5 Feces: 2.6
cyclophosphamide	3-12	20	CYP 2A6, 2B6, 3A4, 3A5, 2C9, 2C18, and 2C19	Urine: 10-20 (unchanged) Bile: 4
exemestane (Aromasin)	24	90	CYP3A4 to inactive metabolites	Urine: 39-45 Feces: 36-48
fulvestrant (Faslodex)	960	99	Extensive hepatic metabolism*	Feces: 90
lapatinib (Tykerb)	24	> 99	CYP3A4, 3A5: major CYP2C19, 2C8: minor	Feces: 27 (parent) Urine: < 2
letrozole (Femara)	48	Weakly	CYP3A4 and 2A6 to inactive metabolites†	Urine: 90
neratinib (Nerlynx)	7-17	> 99%	CYP3A4	Feces: 97.1 Urine: 1.13
palbociclib (Ibrance)	24-34	85	Hepatic metabolism involving primarily oxidation and sulfonation	Urine: 17.5 Feces: 74.1
ribociclib (Kisqali)	30-55	70	CYP3A4	Feces: 69 Urine: 23
talazoparib (Talzenna)	90	74	Mono-oxidation, dehydrogenation, cysteine and glucuronide conjugation; minimal hepatic metabolism	Feces: 19.7 Urine: 68.7
tamoxifen (tablets, Soltamox‡)	120-168	99	CYP3A4/5, 2C9, 2D6§; endoxifen, catalyzed by CYP2D6 is an active metabolite with increased potency in suppressing estrogen dependent cell proliferation compared to tamoxifen‖	Feces: primary route
toremifene (Fareston)	120 (168 for females > 60 years)	99.5	CYP3A4 to weakly active metabolite	Primary elimination route is feces

* Patients with moderate hepatic impairment (Child-Pugh Class B) should receive a reduced dose of 250 mg of fulvestrant (Faslodex).

† Dose reduction of letrozole (Femara) is recommended in patients with cirrhosis and severe hepatic impairment.

‡ The rate and extent of absorption of tamoxifen solution was found to be bioequivalent to that of tamoxifen tablets under fasting conditions.

§ Patients with biliary stasis should receive a reduced dose of tamoxifen.

‖ Studies have shown poorer clinical outcomes in patients who have genetic polymorphisms that result in a decrease or loss of CYP2D6 function.[101]

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CONTRAINDICATIONS/WARNINGS[102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117]

Contraindications

Letrozole (Femara) is contraindicated in women who are or may become pregnant. All aromatase inhibitors (AIs) are contraindicated in any patients who have shown a hypersensitivity reaction to the drug or any of its excipients. Letrozole/ribociclib (Kisqali Femara Co-Pak) is also contraindicated in patients with known hypersensitivity to any of its components.

Capecitabine (Xeloda) is contraindicated in patients with known hypersensitivity to 5-fluorouracil, capecitabine or any of its components, and patients with severe renal impairment (Cockroft/Gault creatinine clearance [CrCl] < 30 mL/min).

Cyclophosphamide is contraindicated in patients with a history of severe hypersensitivity to the product and patients with urinary outflow obstruction.

Alpelisib (Piqray), fulvestrant (Faslodex), and lapatinib (Tykerb) are contraindicated in any patients who have shown a hypersensitivity reaction to the drug or any of its excipients.

Tamoxifen is contraindicated in women who require concomitant coumarin-type anticoagulant therapy and in women with a history of venous thromboembolic disease (VTE) or pulmonary embolism.

Toremifene (Fareston) is contraindicated in patients with known hypersensitivity to the drug. Toremifene should not be prescribed to patients with congenital/acquired QT prolongation (long QT syndrome) or uncorrected hypokalemia or hypomagnesemia.

Boxed Warnings

Capecitabine labeling has a boxed warning related to a severe interaction with oral coumarin-derivative anticoagulants. Concomitant use may significantly alter coagulation parameters and/or bleeding; deaths have been reported. The events can occur several days up to several months after initiation of capecitabine; 1 report occurred within 1 month of discontinuation of capecitabine therapy. Patients should have anticoagulant response [prothrombin time (PT) and/or international normalized ratio (INR)] monitored frequently in order to adjust anticoagulant doses appropriately. Age over 60 years and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

Lapatinib labeling has a boxed warning related to hepatotoxicity. Hepatotoxicity has been observed in clinical trials and post-marketing experience and may be severe and even fatal. Causality of the deaths is uncertain. Alanine transaminase (ALT) or aspartate aminotransferase (AST) greater than 3 times the upper limit of normal (ULN) and total bilirubin ≥ 2 times ULN have been observed in clinical trials (< 1% of patients) and post-marketing experience. Hepatotoxicity may occur days to several months after initiation of treatment. Liver function tests, including transaminases, bilirubin, and alkaline phosphatase, should be performed prior to initiation of therapy, every 4 to 6 weeks during treatment, and as clinically indicated. If lapatinib is to be administered to patients with severe pre-existing hepatic impairment, a dose reduction should be considered. For those patients who develop severe hepatotoxicity while on therapy, lapatinib should be discontinued, and patients should not be retreated with lapatinib.

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Tamoxifen carries a boxed warning to avoid use in patients with a history of thromboembolic disease. An increased risk of endometrial cancer, endometrial changes (including hyperplasia and polyps), and uterine sarcoma have been reported in association with tamoxifen treatment. Tamoxifen also carries a boxed warning regarding the increased risk of thromboembolic events (e.g., stroke, pulmonary embolism) in patients who are treated with tamoxifen. There is a mandatory medication guide dispensed with tamoxifen for women who are using tamoxifen for chemoprophylaxis or women with DCIS.

Toremifene labeling has a boxed warning regarding the risk of QT prolongation. Toremifene should not be administered to anyone with congenital or acquired QT prolongation, uncorrected hypokalemia, or uncorrected hypomagnesemia. The use of other medications that are known to prolong the QT interval or that strongly inhibit CYP3A4 should be avoided.

Selected Warnings and Recommended Monitoring

All 3 aromatase inhibitors (AIs) on the market (anastrozole, letrozole, and exemestane) have been shown to reduce bone mineral density over time. Declines in bone mineral density of both the hip and lumbar spine have been reported. Consideration should be given to obtaining baseline bone mineral density scores, as well as 25-hydroxy vitamin D levels prior to treatment initiation. Supplementation with vitamin D may be warranted in some patients.[118] During adjuvant treatment with exemestane, it is recommended that women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry at the commencement of treatment. Although not listed in the labeling as a contraindication like the other AIs, exemestane also can cause fetal harm and carries a warning for this risk; females of reproductive age should be advised of the potential risk to a fetus and to use effective contraception.

Both anastrozole and letrozole have been shown to increase serum cholesterol. In the Arimidex, Tamoxifen Alone, or in Combination (ATAC) trial, there was a higher reported incidence of elevated cholesterol in women receiving anastrozole compared to tamoxifen (9% versus 3.5%). In the adjuvant trial comparing letrozole to tamoxifen, there was an increase of greater than 1.5 times the ULN in total cholesterol in 8.2% of women receiving letrozole compared to 3.9% in the tamoxifen arm. Lipid-lowering medication was required in 25% of women receiving letrozole compared to only 16% receiving tamoxifen.

In women with pre-existing ischemic heart disease, an increased incidence of ischemic cardiovascular events was observed with anastrozole in the ATAC trial. Consider risk and benefits of anastrozole in patients with pre-existing ischemic heart disease.

Post-marketing reports of the use of letrozole in pregnancy indicate there have been cases of spontaneous abortions and congenital birth defects associated with letrozole exposure. All AIs have warnings specific to the potential for embryo-fetal toxicity.

Abemaciclib (Verzenio) carries warnings for diarrhea, neutropenia, hepatotoxicity, thromboembolism, and embryo-fetal toxicity. The incidence of diarrhea was high in clinical trials and greatest during the first month (median time to onset of grade 2 or 3 diarrhea, 6 to 8 days; median duration, 6 to 11 days), and episodes have been associated with dehydration and infection. If diarrhea occurs, patients should use antidiarrheal therapy and contact their healthcare provider. For severe diarrhea (grade 3 or 4 or requiring hospitalization), a dose interruption is recommended with a dose reduction upon restarting therapy. The incidence of neutropenia was 37% to 46% in key clinical trials (median time to onset, 29

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to 33 days; median duration, 11 to 15 days). Febrile neutropenia, including cases that have led to death, has also been reported. Patients should have complete blood counts (CBC) monitored prior to starting therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruptions and/or reductions are recommended for those who develop grade 3 or 4 neutropenia. In addition, liver function tests should be monitored on the same schedule to monitor for hepatotoxicity, which occurred in clinical trials as well. Venous thromboembolism was also reported in clinical trials; patients should be monitored for signs and symptoms of venous thromboembolism. Finally, abemaciclib can cause fetal harm when administered to a pregnant woman based on findings from animal studies and its mechanism of action.

Alpelisib (Piqray) carries warnings for severe hypersensitivity reactions, severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity. Stevens-Johnson syndrome (SJS) and erythema multiforme have occurred in a small proportion of patients taking alpelisib. Alpelisib may require permanent discontinuation or a dosage adjustment for any of those adverse. Prior to starting therapy, assess fasting plasma glucose (FPG), HbA1c, and maintain appropriate blood glucose levels. After starting therapy, assess blood glucose and/or FPG at least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically warranted. HbA1c should be evaluated every 3 months and as clinically warranted. Use of alpelisib in patients with Type 1 diabetes or uncontrolled Type 2 diabetes has not been determined.

Because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding disorders, thrombocytopenia, or receiving anticoagulant therapy. Injection site related events, including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy, have been reported with fulvestrant. Caution should be taken while administering fulvestrant at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve. Due to structural similarity, fulvestrant can interfere with estradiol measurement by immunoassay, resulting in falsely elevated estradiol levels. Fulvestrant also carries a warning of potential fetal harm; females of reproductive age should be advised of the potential risk to a fetus and to use effective contraception.

Treatment with palbociclib (Ibrance) may result in neutropenia and CBCs should be obtained prior to starting palbociclib therapy and at the beginning of each cycle, as well as on day 15 of the first 2 cycles and as clinically indicated. Monitor for signs and symptoms of infection when taking palbociclib, as infections have been reported at a higher rate than in patients receiving letrozole alone. Palbociclib can cause fetal harm and females of reproductive potential should use effective contraception during therapy and for at least 3 weeks after the last dose.

Ribociclib (Kisqali) increases the QT interval in a concentration-dependent manner. In the clinical trials, the electrocardiogram (ECG) changes occurred in the first 4 weeks of treatment and were reversible with dose interruption. There were no reported cases of torsades de pointes. Syncope occurred in 3% of patients receiving ribociclib plus letrozole compared to 1% of patients receiving letrozole plus placebo in the MONALEESA-2 trial. There was 1 sudden death in the clinical trial in a patient with grade 3 hypokalemia and grade 2 QT prolongation in the MONALEESA-2 trial, but no cases were reported in MONALEESA-7 or MONALEESA-3. Patients should have an ECG done prior to initiation of treatment. Treatment with ribociclib should only be initiated in patients with QTcF values < 450 msec. ECG should be repeated at Day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. In addition, serum electrolytes (including potassium, calcium, phosphorous, and magnesium) should be monitored prior to the initiation of treatment, at the beginning of the first 6 cycles and as clinically indicated. Any discovered electrolyte abnormalities should be corrected before starting ribociclib

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therapy. The use of ribociclib should be avoided in patients who have or are at significant risk of developing QTc prolongation. This includes patients with long QT syndrome, uncontrolled or significant cardiac disease, or electrolyte abnormalities. In a clinical trial of ribociclib plus either tamoxifen or a nonsteroidal AI, an increase of > 60 msec from baseline in the QTcF interval was observed at an increased incidence in the tamoxifen arm compared to the AI arm. Ribociclib is not indicated for concurrent use with tamoxifen.

Hepatobiliary toxicity may occur with ribociclib and liver function tests (LFTs) should be performed before initiating therapy and monitored every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles and as clinically indicated.

Neutropenia was the most commonly reported adverse event associated with ribociclib in clinical trials and grade 3 or 4 neutropenia was reported in 58% of patients receiving ribociclib plus letrozole or fulvestrant. Patients should have a CBC drawn before initiating therapy and serial CBCs every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

There are no available human data but based on animal studies and the mechanism of action, ribociclib can cause fetal harm when administered to pregnant women. Females of reproductive potential should be advised to use effective contraception during treatment with ribociclib and for at least 3 weeks after the last dose.

On September 13, 2019, the FDA issued a drug safety communication regarding the possibility of rare but severe lung inflammation associated with the CDK4/6 inhibitor class (including abemaciclib, palbociclib, and ribociclib).[119] The FDA states that the overall benefit of CDK4/6 inhibitors is still greater than the risks when used as prescribed. The FDA recommends that patients receiving CDK 4/6 inhibitors should be monitored regularly for pulmonary symptoms indicative of interstitial lung disease (ILD) and/or pneumonitis, including hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams in patients in whom infectious, neoplastic, and other causes have been excluded. Treatment with CDK 4/6 inhibitors should be interrupted in patients who have new or worsening respiratory symptoms, and should be restarted at a lower dose once the patient recovers. Treatment should be permanently discontinued in patients with severe ILD and/or pneumonitis. The package inserts have been updated accordingly in response to the drug safety communication.

Lapatinib (Tykerb) has been associated with hepatotoxicity, decreased left ventricular ejection fraction (LVEF), interstitial lung disease/pneumonitis, QT prolongation, severe cutaneous reactions, and diarrhea. Lapatinib should be discontinued in patients with a decreased LVEF that is grade 2 or greater based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3) and in patients with an LVEF that drops below the institution's lower limit of normal. Lapatinib in combination with capecitabine may be restarted at a reduced dose (1,000 mg/day) and in combination with letrozole may be restarted at 1,250 mg after a minimum of 2 weeks if the LVEF recovers to normal and the patient is asymptomatic. Recommended monitoring includes LVEF, liver function tests (LFTs) including transaminases, bilirubin, and alkaline phosphatase. Additional recommended monitoring includes pulmonary signs/symptoms, any change in bowel habits, and electrolytes including potassium and magnesium. Due to the potential for QT prolongation, hypokalemia and hypomagnesemia should be corrected before starting therapy; patients with or who may develop QTc prolongation (e.g., congenital long QT syndrome, cumulative high-dose anthracycline therapy) should be monitored during treatment. Diarrhea should be treated promptly with anti-diarrheal agents after the first unformed stool as diarrhea may be severe and deaths have been reported. If diarrhea is persistent

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beyond 24 hours or if there is fever or grade 3 or 4 neutropenia, interruption or discontinuation of lapatinib may be required. If life-threatening reactions, such as erythema multiforme, Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN) are suspected, therapy with lapatinib should be discontinued.

Neratinib (Nerlynx) may be associated with hepatotoxicity with increases in liver transaminases. Total bilirubin, AST, ALT, and alkaline phosphatase should be measured prior to starting treatment, monthly for the first 3 months of treatment, and then every 3 months while on treatment or as clinically indicated.

Severe diarrhea as well as subsequent dehydration, hypotension and renal failure have been reported during treatment with neratinib. Diarrhea was reported in 83% to 95% of neratinib-treated patients in key clinical trials. Diarrhea usually occurred within the first month and the median time to onset of ≥ grade 3 diarrhea was 8 to 11 days (range, 1 to 350 days). Antidiarrheal prophylaxis with loperamide should be initiated with the first dose of neratinib and continued during the first 2 cycles (56 days) of treatment. Loperamide should be administered at a dose of 4 mg three times daily for weeks 1 and 2, followed by 4 mg twice daily for weeks 3 through 8. Throughout the course of therapy, loperamide should be titrated to 1 to 2 bowel movements daily (maximum of 16 mg/day) and additional antidiarrheal agents may be required. This titration schedule may need to be repeated for dose interruptions or modifications to manage diarrhea.

Based on its mechanism of action and the findings of animal studies, neratinib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception during treatment and for ≥ 1 month after the last dose.

Talazoparib (Talzenna) carries warnings for myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), myelosuppression, and embryo-fetal toxicity. A total of 2 out of 584 (0.3%) of patients experienced MDS/AML; talazoparib therapy should not be initiated until hematological recovery from prior chemotherapy. Myelosuppression presenting as anemia, leukopenia/neutropenia, and/or thrombocytopenia can occur with talazoparib and may require discontinuation of therapy in a small percentage of patients. A CBC should be assessed at baseline and monthly; prolonged toxicity requires withholding talazoparib, more frequent CBC monitoring, and potentially a referral to a hematologist for assessment of MDS/AML. Myelosuppression may require dose interruption and/or dose reduction.

Tamoxifen is classified as Pregnancy Category D (tablet) or has descriptive labeling describing embryo-fetal toxicity (Soltamox). Sexually active premenopausal females should use barrier or non-hormonal contraceptive measures during treatment and for 2 months after discontinuing therapy. There are reports of teratogenesis, including abnormal reproductive anatomy, fetal death, spontaneous abortion, and vaginal bleeding in infants of those mothers exposed to tamoxifen during early pregnancy. Tamoxifen increases the risk of endometrial cancer, usually adenocarcinoma of the endometrium, but rare uterine sarcomas, including malignant mixed müllerian tumors (MMMT), have been reported, and some have been fatal. Uterine sarcoma has been reported to occur more frequently among those women who have received ≥ 2 years of tamoxifen compared to non-users. In general, women with pre-existing endometrial hyperplasia should not receive long-term tamoxifen therapy and should be counseled regarding the individualized risk versus benefit.

Tamoxifen has been associated with an increased risk of developing cataracts. Tamoxifen use was associated with cases of liver cancer in the Swedish Breast Cancer Cooperative Group trial (2 cases

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versus 1 case in observation group). In addition, it has also been associated with changes in liver enzymes and other severe liver abnormalities.

Endometrial cancer, hypertrophy, hyperplasia, and uterine polyps have been reported in some patients treated with toremifene. Long-term use of toremifene in patients with pre-existing endometrial hyperplasia has not been studied. All patients should have baseline and annual gynecological examinations, in particular patients at high risk of endometrial cancer.

Hepatotoxicity has been reported with toremifene in clinical trials and postmarketing cases. This toxicity may manifest as grade 3 and 4 transaminitis and hyperbilirubinemia and may include jaundice, hepatitis, and non-alcoholic fatty liver disease. Liver function tests should be performed periodically.

Both toremifene and tamoxifen have been associated with increased risk of hypercalcemia and tumor flare in patients with bone metastases during the first few weeks of treatment. Tumor flare is a syndrome of diffuse musculoskeletal pain and erythema with increased size of tumor lesions that later regress. It is often accompanied by hypercalcemia.

Capecitabine can induce diarrhea which is sometimes severe and patients should be monitored and given fluid and electrolyte replacement if they become dehydrated. Dehydration has been observed and may cause acute renal failure. Cardiac toxicity, including myocardial infarction, ischemia, angina, dysrhythmias, cardiac failure, and sudden death, may occur with capecitabine and is more common in patients with a prior history of coronary artery disease. Hyperbilirubinemia and hematologic toxicities may also occur. Patients with dihydropyrimidine dehydrogenase deficiency (DPD) are at increased risk for acute early-onset of toxicity and severe, life-threatening or fatal adverse reactions (e.g., mucositis, diarrhea, neutropenia, neurotoxicity) caused by capecitabine. No capecitabine dose has been proven safe for patients with complete absence of DPD activity, and there are insufficient data to recommend a specific dose of capecitabine in patients with partial DPD activity, as measured by any specific test.

Severe mucocutaneous reactions, such as SJS and TEN, can occur. Hand and foot syndrome (palmar-plantar erythrodysesthesia) may occur with capecitabine with a median time to onset of 79 days (range 11 to 360 days). Palmar-plantar erythrodysesthesia may range from a grade 1 toxicity which can involve painless swelling of the hands and/or feet up to grade 3 toxicity which involves severe pain in the hands and/or feet that causes the patient to be unable to work or perform activities of daily living. Persistent or severe hand and foot syndrome (≥ grade 2) can eventually lead to loss of fingerprints. A dose interruption should occur for grade 2 or 3 symptoms and a subsequent dose reduction for patient's experiencing grade 3 toxicity.

Based on its mechanism of action and findings from animal reproduction studies, capecitabine may cause fetal harm when given to a pregnant woman. Females of reproductive potential should be advised to use effective contraception during treatment and for 6 months following the last dose of capecitabine.

Cyclophosphamide can cause myelosuppression, including leukopenia, neutropenia, thrombocytopenia, and anemia, as well as bone marrow failure and severe immunosuppression, which may lead to serious and sometimes fatal infections. Latent infections can be reactivated. Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria may occur with cyclophosphamide treatment. Myocarditis, myopericarditis, pericardial effusion, and congestive heart failure have been reported with cyclophosphamide. Pneumonitis, pulmonary fibrosis, and other forms of pulmonary toxicity leading to respiratory failure have been reported with cyclophosphamide treatment. There is a risk of secondary

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malignancies associated with treatment with cyclophosphamide. Veno-occlusive liver disease has been reported both in the setting of bone marrow transplantation and long-term, low dose cyclophosphamide use. Cyclophosphamide may interfere with normal wound healing and hyponatremia may occur with a condition resembling syndrome of inappropriate antidiuretic hormone (SIADH). Cyclophosphamide can cause fetal harm when administered to a pregnant woman. Exposure during pregnancy may cause birth defects, miscarriage, and fetal growth retardation in the newborn. Female patients of reproductive potential should use highly effective contraception during treatment and up to 1 year after completion of therapy. Male and female reproductive function may be impaired in patients being treated with cyclophosphamide. Cyclophosphamide-induced sterility may be irreversible in some patients.

DRUG INTERACTIONS[120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136]

Cytochrome P450 Interactions

CYP2D6

Tamoxifen is converted to endoxifen, an active metabolite, by CYP2D6. Endoxifen has 100 times the affinity for the estrogen receptor compared to tamoxifen. Patients who received tamoxifen in combination with a CYP2D6 inhibitor had a significantly higher rate of breast cancer recurrence at 2 years (13.9% versus 7.5%, $p<0.001$). Paroxetine, in particular, has been associated with an increased risk of death from breast cancer in tamoxifen users.[137] Use of strong CYP2D6 inhibitors (e.g., bupropion, cinacalcet, fluoxetine, paroxetine, quinidine) should be avoided whenever possible.

CYP3A4

Exposure to abemaciclib (Verzenio) and its metabolites may be significantly increased in the presence of strong and moderate CYP3A4 inhibitors. Avoid use with ketoconazole and grapefruit products. When using with other strong inhibitors, a dose decrease is recommended. In patients with recommended starting doses of 150 mg to 200 mg twice daily, the abemaciclib dose should be reduced to 100 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, the abemaciclib dose should be further reduced to 50 mg twice daily. If the strong CYP3A inhibitor is subsequently discontinued, increase the abemaciclib dose back to the dose used prior to the inhibitor initiation. If used concurrently with a moderate CYP3A inhibitor, monitor for toxicity and consider dose reductions of abemaciclib in 50 mg increments, as needed. Likewise, coadministration of abemaciclib with rifampin, a strong CYP3A inducer, may decrease the plasma concentrations of abemaciclib and its active metabolites, leading to reduced efficacy; avoid concomitant use of strong or moderate CYP3A inducers.

Alpelisib (Piqray) is partially metabolized by CYP3A4, and strong CYP3A4 inducers may decrease alpelisib levels, resulting in decreased efficacy; avoid concurrent use of alpelisib with strong CYP3A4 inducers.

Tamoxifen and its metabolite, 4-hydroxytamoxifen, are metabolized by CYP3A4. Concurrent use with CYP3A4 inhibitors can inhibit the metabolism of tamoxifen. Concurrent administration with a CYP3A4 inducer may increase the metabolism of tamoxifen. However, the CYP3A4 interactions with tamoxifen are considered to be of less clinical importance than the CYP2D6 interactions.

The use of toremifene (Fareston) and palbociclib (Ibrance) with strong CYP3A4 inhibitors (e.g., protease inhibitors, clarithromycin, ketoconazole, itraconazole, voriconazole, cyclosporine) increases the serum

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concentration of these agents. Coadministration of itraconazole with palbociclib increased the plasma exposure of palbociclib in healthy subjects by 87%. Concomitant use of toremifene (Fareston) or palbociclib with a strong CYP3A4 inhibitor should be avoided. Should treatment with any of these agents be required, it is recommended that therapy with toremifene be interrupted. If interruption of treatment with toremifene is not possible, patients who require treatment with a drug that strongly inhibits CYP3A4 should be closely monitored for prolongation of the QT interval. If coadministration of palbociclib with a strong CYP3A inhibitor cannot be avoided, reduce the dose of palbociclib to 75 mg once daily. If the strong inhibitor is discontinued, the palbociclib dose should be increased (after 3 to 5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit juice may also increase plasma concentrations of toremifene and palbociclib and should therefore be avoided.

Concurrent use of exemestane (Aromasin) with strong CYP 3A4 inducers decreases exemestane exposure. Dose increase to 50 mg daily is recommended for patients who are also receiving a potent CYP3A4 inducer (e.g., carbamazepine, St. John's wort, phenytoin, phenobarbital, rifampin).

Coadministration of rifampin with palbociclib decreased the plasma exposure of palbociclib in healthy subjects by 85%. The use of concomitant strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine, St. John’s wort) should be avoided when using palbociclib. Coadministration of moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) may also decrease the plasma exposure of palbociclib and should be avoided.

Palbociclib is a time-dependent inhibitor of CYP3A and, therefore, the doses of sensitive CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) may need to be reduced when given concomitantly with palbociclib.

Lapatinib (Tykerb) is a substrate of CYP3A4 and concomitant administration of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, St. John’s wort) or inhibitors (e.g., ketoconazole, clarithromycin, nelfinavir) can alter lapatinib concentrations significantly. For example, administration with ketoconazole increased lapatinib levels by 3.6-fold and administration with carbamazepine decreased lapatinib serum levels by 72%. The use of lapatinib with concomitant strong CYP3A4 inducers or inhibitors should be avoided. If patients must be co-administered a strong CYP3A4 inhibitor, a dose reduction to 500 mg/day of lapatinib should be considered and, if a strong CYP3A4 inhibitor is discontinued, a washout period of approximately 1 week should be allowed before lapatinib dose is adjusted upward to the indicated dose. If patients must be administered a strong CYP3A4 inducer, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day in patients with HER2-positive metastatic breast cancer. In patients with HER2-positive, HR-positive breast cancer, the dose of lapatinib should be titrated gradually from 1,500 mg/day up to 5,500 mg/day based on tolerability. If the strong CYP3A4 inducer is discontinued, the lapatinib dose should be reduced to the indicated dose.

Lapatinib is a weak inhibitor of CYP3A4 *in vivo* and caution should be used when administering lapatinib with CYP3A4 substrates that have a narrow therapeutic index; monitoring is recommended.

An increase in the cytotoxic metabolites of cyclophosphamide may occur with concomitant administration of protease inhibitors and lead to increased toxicity from cyclophosphamide, including mucositis.

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Coadministration of ribociclib with strong CYP3A4 inhibitors (e.g., clarithromycin, conivaptan, ritonavir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, voriconazole) can increase ribociclib exposure 3.2-fold and, therefore, coadministration should be avoided; if coadministration cannot be avoided, the dose of ribociclib should be reduced to 400 mg once daily.

Coadministration of ribociclib with strong CYP3A4 inducers (e.g., phenytoin, rifampin, carbamazepine, St. John's wort) may decrease the plasma exposure of ribociclib by 89% and therefore coadministration should be avoided.

Coadministration of ribociclib with CYP3A substrates that have a narrow therapeutic index (e.g., midazolam, alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) may result in increased exposure of these medications and, therefore, a dose reduction may be needed.

The concomitant use of neratinib (Nerlynx) with strong or moderate CYP3A4 inhibitors (e.g., clarithromycin, conivaptan, ritonavir, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, voriconazole, ciprofloxacin, cyclosporine, fluconazole) or strong or moderate CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, St. John's wort, efavirenz, modafinil) should be avoided.

CYP2C9

Alpelisib may decrease plasma levels of CYP2C9 substrates such as warfarin, resulting in decreased efficacy of the CYP2C9 substrate; monitor patients carefully if concurrent use is required.

Toremifene is a weak inhibitor of CYP2C9. Concurrent use of toremifene with substrates of 2C9 that have a narrow therapeutic index, such as warfarin and phenytoin, should be used cautiously and require careful monitoring.

CYP2C8

Lapatinib is likely to increase exposure to concomitantly administered drugs that are CYP2C8 substrates (e.g., rosiglitazone).

P-glycoprotein

Lapatinib is a substrate of P-glycoprotein. If lapatinib is administered with an inhibitor of P-glycoprotein (e.g., ritonavir, verapamil, cyclosporine), increased concentrations of lapatinib are likely; caution should be exercised.

Concomitant use of neratinib and digoxin, a P-gp substrate, increased digoxin concentrations and neratinib may inhibit the transport of other P-gp substrates (e.g., dabigatran, fexofenadine).

Talazoparib concentrations can increase if used concurrently with the following P-gp inhibitors: amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil. Avoid concurrent use with these agents if possible. If use with talazoparib cannot be avoided, decrease the talazoparib dose to 0.75 mg once daily. Following discontinuation and 3 to 5 half-lives of the inhibitor, increase the talazoparib dose to the previous dose. If the P-gp inhibitor used concurrently is not one listed above, patients should be assessed for increased side effects.

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Warfarin

Patients receiving warfarin and tamoxifen should be monitored for potential increased INR, as well as signs and symptoms of bleeding.

Patients receiving warfarin and vemurafenib (Zelboraf) should have their INRs monitored closely.

Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine (Xeloda) concomitantly with coumarin-derivative anticoagulants such as warfarin. In a capecitabine drug interaction study with single-dose warfarin administration, there was a significant increase in the AUC of S-warfarin. The maximum observed INR value increased by 91%. The events can occur several days up to several months after initiation of capecitabine; 1 report occurred within 1 month of discontinuation of capecitabine therapy. Patients should have anticoagulant response (PT and/or INR) monitored frequently in order to adjust anticoagulant doses appropriately. Both increased and decreased anticoagulant effects have been reported in patients receiving concomitant cyclophosphamide.

Other Drug Interactions

Coadministration of tamoxifen and anastrozole (Arimidex) has been shown to reduce anastrozole serum levels. The same is true of the coadministration of tamoxifen and letrozole (Femara), where a 38% decrease in letrozole plasma levels has been demonstrated. Combinations of hormonal therapy agents have not demonstrated any efficacy benefits but have increased toxicity. Therefore, combinations of endocrine agents for breast cancer are not recommended.

The use of estrogens, including oral contraceptives, should generally be avoided in the setting of breast cancer.

Concurrent administration of alpelisib or talazoparib with a BCRP inhibitor may increase alpelisib or talazoparib levels, respectively, resulting in increased toxicity. Avoid concurrent use of these agents; if avoidance is not possible, monitor for increased side effects.

Coadministration of capecitabine and leucovorin results in elevated levels of 5-fluorouracil (5-FU) and toxicity.

Phenytoin levels should be monitored when capecitabine and phenytoin are co-administered as the level of phenytoin may increase and require a dose reduction of phenytoin.

Antacid administration with capecitabine resulted in a small increase in plasma concentrations of capecitabine and 1 metabolite; other metabolites were not affected.

Concurrent administration of tamoxifen and dabigatran should be avoided in patients with a creatinine clearance (CrCl) < 30 mL/minute.

Drugs that decrease renal calcium, such as thiazides, may increase the risk of hypercalcemia when used concomitantly with toremifene.

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Agents strongly associated with the risk of QT prolongation should be avoided when patients are receiving toremifene There is an established risk of QT prolongation with Class 1A antiarrhythmics (quinidine, procainamide, disopyramide), Class III antiarrhythmics (amiodarone, sotalol, ibutilide, dofetilide), certain antipsychotics (thioridazine, haloperidol), certain antidepressants (amitriptyline, venlafaxine), certain antiemetics (ondansetron, granisetron), and certain antibiotics (erythromycin, clarithromycin, levofloxacin, ofloxacin). If therapy with 1 of these agents associated with risk of QT prolongation is required, it is recommended that treatment with toremifene be interrupted. If interruption of therapy with toremifene is not possible, it is recommended that patients receive close monitoring for prolongation of QT interval. Avoid coadministration of ribociclib with drugs known to prolong the QT interval.

Following coadministration of lapatinib and digoxin (P-glycoprotein substrate), systemic area under the curve (AUC) of an oral digoxin dose increased approximately 2.8-fold. Serum digoxin concentrations should be monitored prior to initiation of lapatinib and throughout coadministration. If digoxin serum concentration is > 1.2 ng/mL, the digoxin dose should be reduced by half. Following coadministration of lapatinib and midazolam (CYP3A4 substrate), 24-hour systemic exposure (AUC) of orally administered midazolam increased 45%, while 24-hour AUC of intravenously administered midazolam increased 22%. In cancer patients receiving lapatinib and paclitaxel (CYP2C8 and P-gp substrate), 24-hour systemic exposure (AUC) of paclitaxel was increased 23%. This increase in paclitaxel exposure may have been underestimated from the in vivo evaluation due to study design limitations.

Fulvestrant (Faslodex) has no known drug-to-drug interactions.

Coadministration of cyclophosphamide with other drugs that have overlapping toxicities may potentiate the toxicity of cyclophosphamide. These toxicities include cardiotoxicity (e.g., anthracyclines, cytarabine, pentostatin, trastuzumab), pulmonary toxicity (e.g., amiodarone, colony stimulating factors), nephrotoxicity (e.g., amphotericin B, indomethacin), hepatotoxicity (e.g., azathioprine, busulfan), and hematologic toxicity (e.g., angiotensin converting enzyme [ACE] inhibitors, paclitaxel, thiazide diuretics, zidovudine).

The addition of etanercept to cyclophosphamide has been associated with a higher incidence of non-cutaneous malignant solid tumors.

Acute encephalopathy has been reported in patients receiving metronidazole and cyclophosphamide.

Concomitant use of tamoxifen and cyclophosphamide may increase the risk of thromboembolic complications.

Lower serum concentrations of cyclosporine have been reported in patients receiving concomitant cyclophosphamide.

Prolonged apnea may occur with concurrent depolarizing muscle relaxants (e.g., succinylcholine) if a patient has been treated with cyclophosphamide within 10 days of general anesthesia.

Concomitant use of neratinib with a proton pump inhibitor (PPI), H_2-receptor antagonist, or antacid may decrease neratinib plasma concentration. For example, lansoprazole resulted in a decrease of neratinib C_{max} by 71% and AUC by 65%. Concurrent use of neratinib and PPIs should be avoided. Neratinib should be taken ≥ 2 hours before or 10 hours after an H_2-receptor antagonist, and the neratinib dose should be separated by ≥ 3 hours following antacids.

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Concurrent use of capecitabine with allopurinol may lower exposure to capecitabine's active metabolites, resulting in decreased efficacy; avoid concurrent use of allopurinol during treatment.

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ADVERSE EFFECTS[138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153]

Drug	Hot Flashes	Arthralgias	Fatigue	Vaginal Bleeding	Nausea or Vomiting	Bone Fractures	CV Disease	VTE	Stomatitis	Elevated Cholesterol	Depression	Diarrhea	Rash
abemaciclib (Verzenio)	nr	15	40 - 65	nr	39 - 64	reported	nr	5	14 - 15	nr	nr	81 - 90	11 - 14
alpelisib (Piqray) in combination with fulvestrant	nr	nr	42	nr	45 (nausea) 27 (vomiting)	nr	nr	nr	30	nr	nr	58	52
anastrozole (Arimidex)	36	15	19	5	11	10	4	2	nr	9	13	8	8
capecitabine (Xeloda) monotherapy in Stage IV breast cancer	0.1	9	41	nr	53	nr	nr	0.2	24	nr	0.1	57	nr
exemestane (Aromasin)	33 (25)	29 (29)	11 (19)	nr	12 (16)	4	2	0.9	nr	nr	10 (7)	10 (1)	reported
fulvestrant (Faslodex)	6 - 11	8 - 17	6 - 32	< 1	9.7 - 34	nr	nr	reported	10 - 13	nr	6	6 - 25	4 - 7
lapatinib (Tykerb)	nr	nr	20	nr	44	nr	nr	nr	14	nr	nr	65	28
letrozole (Femara)	33	22 (18)	13 (8)	5	8 - 17	14	reported	3	reported	52	5	5 (6)	5
neratinib (Nerlynx)	nr	nr	27 (20)	nr	43 (22)	nr	nr	nr	14 (6)	nr	nr	95 (35)	18 (9)
palbociclib (Ibrance) + fulvestrant (fulvestrant + placebo)	nr	nr	41 (29)	nr	34 (28)	nr	nr	1 (nr)	28 (13)	nr	nr	24 (19)	17 (6)
palbociclib (Ibrance) + letrozole (letrozole alone)	nr	nr	37 (28)	nr	35 (26)	nr	nr	4 (nr)	30 (14)	nr	nr	26 (19)	18 (12)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses unless otherwise specified. nr = not reported.

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Adverse Effects (continued)

Drug	Hot Flashes	Arthralgias	Fatigue	Vaginal Bleeding	Nausea or Vomiting	Bone Fractures	CV Disease	VTE	Stomatitis	Elevated Cholesterol	Depression	Diarrhea	Rash
ribociclib (Kisqali) + aromatase inhibitor (aromatase inhibitor alone)	nr	33 (29)	37 (30)	nr	31 - 52 (20 - 29)	nr	nr	nr	10 - 12 (7 - 8)	nr	nr	35 (22)	17 (8)
ribociclib (Kisqali) + fulvestrant (fulvestrant alone)	nr	nr	nr	nr	45 (28)	nr	nr	nr	nr	nr	nr	29 (20)	nr
talazoparib (Talzenna)	nr	nr	62	nr	49 (nausea) 25 (vomiting)	nr	nr	nr	8	nr	nr	22	nr
tamoxifen	64 (48)	nr	nr	30 (15)	25 (19)	nr	nr	1.3 (0.4)	nr	nr	nr	7	13
toremifene (Fareston)	35	nr	nr	2	14	nr	1	2	nr	nr	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses unless otherwise specified. nr = not reported.

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Both tamoxifen (0.8%) and anastrozole (Arimidex) (0.2%) have been associated with the development of endometrial cancer.

For tamoxifen, increased bone and tumor pain, and also local disease flare, have occurred, which are sometimes associated with a good tumor response. Patients with soft tissue disease may have sudden increases in the size of pre-existing lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flares are seen shortly after starting tamoxifen and generally subside rapidly. Throat irritation has been reported with the oral solution formulation of tamoxifen.

Tamoxifen has been demonstrated to have beneficial effect on bone whereas anastrozole, exemestane (Aromasin), and letrozole (Femara) have a detrimental effect on bone.

Anastrozole, letrozole, tamoxifen, and toremifene (Fareston) have all been reported to increase the risk of developing cataracts.

The most common adverse reactions (incidence ≥ 20%) reported in clinical trials with abemaciclib as monotherapy or adjunct therapy not reported above were neutropenia, abdominal pain, infections, anemia, leukopenia, decreased appetite, headache, alopecia, and thrombocytopenia.

In patients receiving alpelisib, serious adverse reactions were reported in 35% of patients receiving therapy in combination with fulvestrant with the most common being hyperglycemia (10%), rash (3.5%), diarrhea (2.8%), acute kidney injury (2.5%), abdominal pain (2.1%), and anemia (2.1%). Osteonecrosis of the jaw (ONJ) occurred in 4.2% of patients receiving alpelisib in combination with fulvestrant compared to 1.4% of patients receiving placebo plus fulvestrant; all of these subjects had previously or were currently receiving bisphosphonates or RANK-ligand inhibitors.

Cases of hepatitis, including cholestatic hepatitis, as well as acute generalized exanthematous pustulosis, urticaria, pruritus, and paresthesia have all been observed in clinical trials with exemestane and reported through post-marketing surveillance. Other adverse effects associated with exemestane use include increased sweating, alopecia, hypertension, insomnia, and abdominal pain.

The most frequently reported adverse effect with fulvestrant (Faslodex) is injection site pain (12%). In addition, increased hepatic enzymes have been reported in > 15% of fulvestrant-treated patients, which was not dose dependent.

In the capecitabine (Xeloda) monotherapy trial for stage IV breast cancer, 57% of study participants developed hand and foot syndrome (palmar plantar erythrodysesthesia) with 11% of those cases being a grade 3 toxicity. Hematologic toxicity, including neutropenia, thrombocytopenia, and/or anemia, occurred in more than 25% of study participants.

Palmar-plantar erythrodysesthesia has occurred in 53% of study participants taking lapatinib in combination with capecitabine. Post marketing cases that have been reported with lapatinib use include nail disorders including paronychia, severe cutaneous adverse reactions including Stevens Johnson Syndrome (SJS) and toxic epidural necrolysis (TEN), and ventricular arrhythmias/Torsades de Pointes /electrocardiogram QT prolongation.

The most common adverse reactions of any grade reported in the palbociclib (Ibrance) plus letrozole study arm were neutropenia (80%), leukopenia (39%), fatigue (37%), anemia (24%), nausea (35%), stomatitis (30%), alopecia (33%), diarrhea (26%), thrombocytopenia (16%), decreased appetite (15%), vomiting (16%), asthenia (17%), peripheral neuropathy (13%), and epistaxis (9.2%). An overall increase

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in infections was observed in the palbociclib plus letrozole arm (55%) compared to the letrozole alone arm (34%).

The most common adverse events with cyclophosphamide include neutropenia, nausea and vomiting, anorexia, diarrhea, skin rash, and alopecia.

Additional common adverse events associated with neratinib (Nerlynx) occurring in > 5% of patients included abdominal pain, vomiting, decreased appetite, muscle spasms, dyspepsia, AST or ALT increase, nail disorder, dry skin, abdominal distention, weight decreased, and urinary tract infections.

Additional common adverse reactions associated with ribociclib (Kisqali) plus letrozole reported at a frequency ≥ 20% include neutropenia, leukopenia, alopecia, vomiting, constipation, headache, and back pain.

The most common adverse reactions (incidence ≥ 20%) reported with use of talazoparib (Talzenna) in clinical trials were anemia (53%), neutropenia (35%), thrombocytopenia (27%), decreased appetite (21%), headache (33%), nausea (49%), vomiting (25%), diarrhea (22%), alopecia (25%), and fatigue (62%). Other adverse reactions included abdominal pain (19%), dizziness (17%), leukopenia (17%), dysgeusia (10%), dyspepsia (10%), stomatitis (8%), and lymphopenia (7%).

SPECIAL POPULATIONS[154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170]

Pregnancy

Letrozole (Femara) is contraindicated in pregnancy. Anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin), which were previously assigned Pregnancy Category X, now have labeling consistent with the Pregnancy and Lactation Labeling Rule (PLLR). Anastrozole, exemestane, and letrozole labeling advise that females of reproductive potential should use effective contraception during therapy and for at least 3 weeks after the last dose (1 month for exemestane).

Based on its mechanism of action, abemaciclib (Verzenio) can cause fetal harm when administered to a pregnant woman; however, there are no available human data informing the drug-associated risk. Pregnancy testing is recommended prior to initiating treatment, and females of reproductive potential should use effective contraception during treatment and for at least 3 weeks after the last dose. In addition, abemaciclib may impair fertility in males of reproductive potential.

Alpelisib (Piqray) can cause fetal harm when given to a pregnant woman based on animal studies and its mechanism of action. A pregnancy test should be conducted before starting alpelisib. Females of reproductive potential should use effective contraception during therapy and for 1 week following the final dose. Male patients with female partners of reproductive potential should use condoms and effective contraception while receiving alpelisib and for 1 week following the final dose. Alpelisib may decrease fertility in patients of reproductive potential.

Tamoxifen tablets and toremifene (Fareston) are classified as Pregnancy Category D. Fulvestrant (Faslodex), cyclophosphamide, tamoxifen oral solution (Soltamox), and lapatinib (Tykerb), which were previously assigned Pregnancy Category D, now have labeling consistent with the Pregnancy and Lactation Labeling Rule (PLLR). Females of reproductive potential should be advised to use effective contraception during treatment with fulvestrant and for 1 year after the last dose. Exposure to cyclophosphamide during the first trimester has resulted in skeletal, palate, limb and eye malformations as well as miscarriage. Additionally, fetal growth retardation, leukopenia, anemia,

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pancytopenia, severe bone marrow hypoplasia, and gastroenteritis have been reported with exposure to cyclophosphamide. Females of reproductive potential should use highly effective contraception during treatment and for 1 year following the last dose of cyclophosphamide, and male patients with female partners should use effective contraception during treatment and for 4 months after the last dose. Females of reproductive potential should use effective non-hormonal contraception during therapy with tamoxifen and for 2 months after the final dose. Females of reproductive potential and male patients with female partners of reproductive potential should utilize effective contraception during lapatinib therapy and for 1 week following the final dose. Previously, capecitabine was assigned Pregnancy Category D, but its labeling was updated and replaced with a text description in compliance with the PLLR. Based on animal data and its mechanism, capecitabine can cause fetal harm when administered to a pregnant woman. Limited available human data are not sufficient to inform the drug-associated risk during pregnancy. Females of reproductive potential should use effective contraception during treatment and for 6 months following the last dose of capecitabine treatment. Males with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of capecitabine.

Palbociclib (Ibrance) can cause fetal harm when administered to pregnant women based on findings in animals and the mechanism of action. There are no available human data informing the drug-associated risk. Females of reproductive potential should use effective contraception during treatment and for at least 3 weeks after the last dose of palbociclib. Male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months after the last dose. Male fertility may be compromised by treatment with palbociclib.

There are no available human data, but based on animal studies and the mechanism of action, ribociclib (Kisqali) can cause fetal harm when administered to pregnant women. Females of reproductive potential should be advised to use effective contraception during treatment with ribociclib and for at least 3 weeks after the last dose. Based on animal studies, ribociclib may impair fertility in males of reproductive potential.

There are no available human data, but based on animal studies and the mechanism of action, neratinib (Nerlynx) can cause fetal harm when administered to pregnant women. Females of reproductive potential should have a pregnancy test prior to starting neratinib and should use effective contraception during treatment with neratinib and for at least 1 month after the last dose. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for 3 months after the last dose of neratinib.

Based on animal studies and the mechanism of action, talazoparib (Talzenna) can cause fetal harm when administered to pregnant women. Pregnant women and females of reproductive potential should be made aware of the risk to a fetus, and a pregnancy test should be conducted in females of reproductive potential before starting talazoparib. Females of reproductive potential should use effective contraception during treatment and for at least 7 months after the final dose; male patients with female partners of reproductive potential as well as pregnant partners should use effective contraception during treatment and for a minimum of 4 months after the final dose. Talazoparib may decrease fertility in males of reproductive potential.

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Pediatrics

There are no safety or efficacy data for abemaciclib, alpelisib, exemestane, lapatinib, letrozole, neratinib, palbociclib, ribociclib, talazoparib, or toremifene in pediatric patients.

Tamoxifen, fulvestrant, and anastrozole have been utilized in small numbers of pediatric patients either for the treatment of girls with McCune-Albright Syndrome (MAS) or for the treatment of pubertal boys with gynecomastia. Tamoxifen was utilized in 27 girls (ages 2 to 10 years) with MAS and progressive precocious puberty. Results of the 1-year trial were generally positive; there was a 50% decrease in the incidence of vaginal bleeding from baseline and a decrease in the mean rate of increasing bone age. However, the mean uterine volume doubled at the end of the yearlong study, and this raises concerns for the possible increased risk of endometrial cancer. The safety and efficacy of tamoxifen for girls aged 2 to 10 years with McCune-Albright syndrome and precocious puberty have not been studied beyond 1 year of treatment. The long-term effects of tamoxifen therapy in girls have not been established.

Anastrozole was studied in 28 girls aged 2 to < 10 years with MAS and progressive precocious puberty. In this study, there were no statistically significant benefits shown for the use of anastrozole. Anastrozole was utilized in 80 boys (ages 11 to 18 years) with gynecomastia. No statistical improvement was noted with anastrozole therapy and the most common side effects in the boys were acne and headache.

Thirty girls with MAS associated with progressive precocious puberty (ages 1 to 8 years old) were treated with fulvestrant in a 12-month trial. Complete cessation of vaginal bleeding was seen in 35% of the girls at the end of the 12 months. There was also a reduction in the rate of bone age advancement during the 12-month study period compared to baseline, as well as a reduction in mean growth velocity z-score compared to baseline.

Capecitabine has been studied in 2 pediatric single-arm trials in children with brainstem and high-grade gliomas. No clinical benefit was demonstrated in these trials. The adverse reaction profile was consistent with the known adverse reaction profile in adults with the exception of laboratory abnormalities which occurred more commonly in pediatric patients, including increased ALT, lymphocytopenia, leukopenia, hypokalemia, thrombocytopenia, hypoalbuminemia, neutropenia, low hematocrit, hypocalcemia, hypophosphatemia, and hyponatremia.

Cyclophosphamide has been used in pre-pubescent girls who normally develop secondary sexual characteristics and have regular menses. Prolonged late pre-pubescent exposure to cyclophosphamide has resulted in ovarian fibrosis with complete loss of germ cells. If ovarian functions remains intact following cyclophosphamide treatment, females are at risk for premature menopause. Pre-pubescent males exposed to cyclophosphamide develop secondary sexual characteristics normally but may have oligospermia or azoospermia and increased gonadotropin secretion along with testicular atrophy. Azoospermia may be reversible, in some cases, several years after cessation of cyclophosphamide.

Geriatrics

Many of the endocrine breast cancer therapy trials enrolled a significant number of women > 65 years of age and many trials included women in their seventies and even eighties. No clinically relevant differences in pharmacokinetics have been demonstrated and no overall differences with regard to safety and efficacy have been noted between elderly and younger patients.

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No overall differences in safety or effectiveness were observed in patients > 65 years of age who received abemaciclib, palbociclib, or talazoparib, in the clinical trials; however, greater sensitivity in some older patients cannot be ruled out. There were no overall differences in safety or effectiveness of ribociclib observed in clinical studies between younger patients and those ≥ 75 years of age.

No differences in the efficacy of alpelisib were seen in patients ≥ 65 years compared to younger patients; however, 44% of elderly patients experienced grade 3 or 4 hyperglycemia with alpelisib plus fulvestrant compared to 32% of younger patients.

In clinical trials with neratinib, there was a higher frequency of treatment discontinuations due to adverse reactions in patients ≥ 65 years of age compared to those who were < 65 years of age. The serious adverse reactions most frequently reported in the ≥ 65 years group were vomiting (2.3%), diarrhea (1.7% to 16%), renal failure or acute kidney injury (1.7% to 8%), and dehydration (1.2% to 7%).

Elderly patients receiving capecitabine should be carefully monitored for adverse effects.

There is insufficient data to define safety or efficacy differences with cyclophosphamide for patients ≥ 65 years of age. Conservative dosing is recommended with consideration for hepatic, renal, and cardiac functioning in addition to drug interactions.

Renal Impairment

No dosage adjustment of abemaciclib or alpelisib is required for patients with mild or moderate renal impairment (CrCl ≥ 30 to 89 mL/min); however, the pharmacokinetics of abemaciclib or alpelisib in patients with severe renal impairment, end stage renal disease, or those on dialysis is unknown.

No specific guidelines are established for the dosing of any of the endocrine therapies or lapatinib for patients with renal impairment.

No dose adjustment is required in patients taking palbociclib with mild, moderate, or severe renal impairment; however, the pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

No adjustment to the starting dose of capecitabine is recommended in patients with mild renal impairment (CrCl, 51 to 80 mL/min). Doses of capecitabine when used as monotherapy or in combination with docetaxel should be reduced by 25% in patients with moderate renal impairment (CrCl, 30 to 50 mL/min); capecitabine is contraindicated in severe renal impairment (CrCl < 30 mL/min).

Monitor patients with severe renal impairment (CrCl, 10 to 24 mL/min) for signs and symptoms of increased toxicity with cyclophosphamide.

Ribociclib (Kisqali) dose adjustment is not necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR], 30 to <90 mL/minute/1.73 m^2). Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment (eGFR, 15 to < 30 mL/min/1.73 m^2), a starting dose of 200 mg once daily is recommended. Ribociclib has not been studied in breast cancer patients with severe renal impairment. Letrozole (Femara) does not require a dose adjustment in patients with a CrCl ≥ 10 mL/min.

Talazoparib (Talzenna) does not require a dose adjustment in mild renal impairment (CrCl, 60 to 89 mL/min), but the dose should be decreased to 0.75 mg once daily for patients with moderate renal impairment (CrCl, 30 to 59 mL/min). In patients with severe renal impairment (CrCl, 15 to 29 mL/min) the recommended dose is 0.5 mg once daily. It has not been studied in patients requiring hemodialysis.

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Hepatic Impairment

No dosage adjustments or abemaciclib are required in patients with mild or moderate hepatic impairment (Child-Pugh A or B), but the dosing frequency should be adjusted to once daily in patients with severe hepatic impairment (Child-Pugh C).

No differences in the pharmacokinetics of alpelisib are expected in patients with mild to severe hepatic impairment (Child-Pugh A, B, or C); no dosage adjustments for patients with hepatic impairment are recommended.

No guidelines are available for dosing patients on toremifene, anastrozole, or tamoxifen with hepatic impairment.

Fulvestrant dose should be decreased to 250 mg in patients with moderate hepatic impairment (Child-Pugh Class B). Fulvestrant has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

The pharmacokinetics of lapatinib were examined in subjects with pre-existing moderate (n=8) or severe (n=4) hepatic impairment (Child-Pugh class B/C, respectively) and in 8 healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100-mg dose increased approximately 14% and 63% in subjects with moderate and severe pre-existing hepatic impairment, respectively. Administration of lapatinib in patients with severe hepatic impairment should be undertaken with caution due to increased exposure to the drug. A dose reduction should be considered for patients with severe pre-existing hepatic impairment. Consider a reduction of the oral lapatinib dose from 1,250 mg daily to 750 mg daily (when given with capecitabine) and from 1,500 mg daily to 1,000 mg daily (when given with letrozole) for patients with severe hepatic impairment (Child-Pugh Class C); the lower lapatinib dose is predicted to adjust the AUC to the range seen in patients without hepatic impairment, but there are no clinical data to support this dose adjustment. Discontinue lapatinib in patients who develop severe hepatic impairment during treatment; do not restart lapatinib in these patients. In patients who develop severe hepatotoxicity while on therapy, lapatinib should be discontinued and patients should not be retreated with lapatinib.

It appears there is no adjustment necessary for letrozole in patients with mild to moderate hepatic impairment. The letrozole dose in patients with cirrhosis and severe hepatic dysfunction is 2.5 mg every other day. The effect of hepatic impairment on letrozole exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined.

In patients with severe hepatic impairment (Child-Pugh C), the starting dose of neratinib should be reduced to 80 mg. There are no dose modifications recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B).

Palbociclib dose adjustment is not required in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended palbociclib dose is 75 mg once daily for 21 consecutive days followed by 7 days off treatment, repeated every 28 days.

Caution should be exercised when using capecitabine in patients with mild to moderate hepatic dysfunction due to liver metastases. The effect of severe hepatic dysfunction on capecitabine is not known.

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The AUC of exemestane was increased in subjects with moderate or severe hepatic impairment (Child-Pugh B or C). However, based on experience with exemestane at repeated doses up to 200 mg daily that demonstrated a moderate increase in non-life-threatening adverse events, dosage adjustment does not appear to be necessary.

Patients with severe hepatic impairment may have reduced efficacy associated with cyclophosphamide.

Ribociclib (Kisqali) dose adjustment is not necessary in patients with mild hepatic impairment (Child-Pugh A). A reduced starting dose of 400 mg is recommended in patients with moderate and severe hepatic impairment (Child-Pugh B and C).

A dose adjustment of talazoparib (Talzenna) is not required in patients with mild hepatic impairment; it has not been evaluated in patients with moderate or severe hepatic impairment.

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DOSAGES[171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189]

Drug	Adjuvant Therapy	Advanced or Metastatic Disease	DCIS	Prophylaxis	Duration	Other Indications	Administration	Dosage Forms
abemaciclib (Verzenio)	-	Monotherapy: 200 mg twice daily Combination therapy with AI or fulvestrant: 150 mg twice daily Pre/perimenopausal women should also receive a GnRH agonist if receiving abemaciclib with fulvestrant	-	-	Continue until disease progression or unacceptable toxicity	-	Take orally at the same time each day with or without food; swallow whole; do not crush or cut tablets	Tablet: 50 mg, 100 mg, 150 mg, 200 mg
alpelisib (Piqray)	-	Combination therapy with fulvestrant: 300 mg once daily	-	-	Continue until disease progression or unacceptable toxicity	-	Take orally at the same time each day with food; swallow whole; do not chew, crush, or split	Tablet: 50 mg, 150 mg, 200 mg supplied in daily dose blister packs of 200 mg, 250 mg, 300 mg
anastrozole (Arimidex)	1 mg once daily	1 mg once daily	-	-	For adjuvant therapy: optimal duration is unknown; no data to support more than 5 years of therapy For advanced disease: continue until tumor progression	-	Same time each day with or without food	Tablet: 1 mg

GnRH = gonadotropin-releasing hormone

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Dosages (continued)

Drug	Adjuvant Therapy	Advanced or Metastatic Disease	DCIS	Prophylaxis	Duration	Other Indications	Administration	Dosage Forms
capecitabine (Xeloda)	-	Monotherapy or in combination with docetaxel: 1,250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period for a 3-week cycle	-	-	Advanced breast cancer: Continue until disease progression or unacceptable toxicity Dukes C colon cancer: 6 months (8 total 3 week cycles)	Monotherapy for metastatic colorectal cancer (CRC) or adjuvant monotherapy for CRC: 1,250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period for a 3-week cycle	Swallow whole with water within 30 minutes after a meal; do not crush or cut tablets; dose is calculated according to body surface area (BSA)	Tablet: 150 mg, 500 mg
cyclophosphamide	100 mg/m^2 by mouth days 1 through 14 of a 28-day cycle when given as part of the CMF	100 mg/m^2 by mouth days 1 through 14 of a 28-day cycle when given as part of CMF	-	-	For adjuvant therapy with CMF: given for 6 cycles For metastatic disease: given until disease progression or unacceptable toxicity	Nephrotic syndrome: 2 mg/kg daily for 8 to 12 weeks (maximum cumulative dose 168 mg/kg)	Swallow whole with adequate fluid to force diuresis; do not open, chew or crush	Capsule: 25 mg, 50 mg
exemestane* (Aromasin)	25 mg once daily	25 mg once daily	-	-	Adjuvant therapy: 5 years OR Complete a total of 5 consecutive years after 2 to 3 years of tamoxifen Advanced disease: continue until disease progression or unacceptable toxicity	-	Take after a meal	Tablet: 25 mg

* If exemestane (Aromasin) is administered with a potent CYP3A4 inducer, increase dose of exemestane to 50 mg once daily.

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Dosages (continued)

Drug	Adjuvant Therapy	Advanced or Metastatic Disease	DCIS	Prophylaxis	Duration	Other Indications	Administration	Dosage Forms
fulvestrant (Faslodex)	-	Monotherapy or combination therapy with abemaciclib, palbociclib, or ribociclib: 500 mg intramuscularly (IM) on days 1, 15, and 29 and monthly thereafter	-	-	Continue until disease progression or unacceptable toxicity	-	Deep IM injection into buttock (gluteal area) slowly (1 to 2 minutes per injection) as two 5 mL injections, 1 into each buttock	Single-dose prefilled syringe: 250 mg/ 5 mL
lapatinib† (Tykerb)	-	HER2+: 1,250 mg once daily for days 1 through 21 when given in conjunction with capecitabine 2,000 mg/m^2 on days 1 to 14 for a 21-day cycle HER2+, HR+: 1,500 mg once daily when given in conjunction with letrozole	-	-	Continue until disease progression or unacceptable toxicity	-	Take at least 1 hour before or 1 hour after food	Tablet: 250 mg
letrozole (Femara)	2.5 mg once daily	2. 5 mg once daily	-	-	Adjuvant: optimal duration of treatment is unknown; treatment should be discontinued at relapse Advanced: continue until disease progression or unacceptable toxicity	-	Can be taken without regard to food	Tablet: 2.5 mg

† Modify lapatinib (Tykerb) dose for cardiac and other toxicities, severe hepatic impairment, diarrhea, and CYP3A4 drug interactions.

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Dosages (continued)

Drug	Adjuvant Therapy	Advanced or Metastatic Disease	DCIS	Prophylaxis	Duration	Other Indications	Administration	Dosage Forms
neratinib (Nerlynx)	240 mg once daily (up to 1 year)	240 mg once daily on days 1 through 21 of a 21-day cycle, in combination with oral capecitabine (750 mg/m^2 twice daily) on days 1 through 14 of a 21-day cycle	-	-	Adjuvant: 1 year Advanced or metastatic disease: continue until disease progression or unacceptable toxicity	-	Take with food; swallow tablets whole; do not chew, crush or split prior to swallowing Loperamide should be initiated with the first dose of neratinib and continued as described above (. Weeks 1-2: 4 mg three times daily Weeks 3-8: 4 mg twice daily Weeks 9-52: as needed, max 16 mg daily, titrated to 1-2 bowel movements daily)	Tablet: 40 mg
palbociclib (Ibrance)	-	For combination therapy with either an AI or fulvestrant: 125 mg once daily for 21 consecutive days followed by 7 days off, to complete a 28-day cycle	-	-	Continue until disease progression or unacceptable toxicity	-	Take with food (capsules) or with or without food (tablets); swallow whole; do not chew, crush, or open (capsules) prior to swallowing	Capsule: 75 mg, 100 mg, 125 mg Tablet: 75 mg, 100 mg, 125 mg
ribociclib (Kisqali)	-	600 mg once daily for 21 consecutive days followed by 7 days off treatment to complete a 28-day cycle Pre-/perimenopausal women should also receive a LHRH agonist if receiving ribociclib with an AI or fulvestrant	-	-	Continue until disease progression or unacceptable toxicity	-	Take with or without food at the same time each day, preferably in the morning; swallow whole; do not chew, crush, or split prior to swallowing	Tablet: 200 mg supplied in daily dose blister packs of 200 mg, 400 mg, and 600 mg

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Dosages (continued)

Drug	Adjuvant Therapy	Advanced or Metastatic Disease	DCIS	Prophylaxis	Duration	Other Indications	Administration	Dosage Forms
ribociclib/ letrozole (Kisqali Femara Co-Pack)	-	ribociclib: 600 mg once daily for 21 consecutive days followed by 7 days off to complete a 28-day cycle letrozole: 2.5 mg once daily continuously for a 28-day cycle Pre-/perimenopausal women should also receive a LHRH agonist according to current clinical practice standards	-	-	Continue until disease progression or unacceptable toxicity	-	Take with or without food at the same time each day, preferably in the morning; swallow whole; do not chew, crush, or split prior to swallowing	Co-packaged cartons of 28-day cycle: 200 mg-2.5 mg co-pack tablets, 400 mg-2.5 mg co-pack tablets, 600 mg-2.5 mg co-pack tablets (ribociclib uses 200 mg tablets to achieve daily dose for packs)
talazoparib (Talzenna)	-	1 mg once daily	-	-	Continue until disease progression or unacceptable toxicity	-	Swallow capsules whole with or without food; do not open or dissolve capsules	Capsule: 0.25 mg, 1 mg
tamoxifen (generic, Soltamox)	20 mg daily	20 mg to 40 mg daily	20 mg daily	20 mg daily	Adjuvant: 5 to 10 years DCIS and prophylaxis: 5 years	-	With or without food There is no evidence that doses > 20 mg/day are more effective; 10 mg twice daily is the most common dose used in clinical practice, doses > 20 mg/day should be given in divided doses (morning and evening)	Tablet: 10 mg, 20 mg (generic only) Solution: 10 mg/5 mL (Soltamox)
toremifene (Fareston)	-	60 mg once daily	-	-	Continue until disease progression	-	With or without food	Tablet: 60 mg

See individual product labeling for recommended dosing modifications based on specific toxicities.

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CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and the FDA-approved indications. Comparative clinical trials have been performed with some of the agents in this class. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Breast Cancer – Prevention

tamoxifen versus placebo

Four phase 3 randomized, placebo-controlled trials have prospectively evaluated tamoxifen for breast cancer risk reduction in premenopausal and postmenopausal women ranging in age from 30 to 70 years. The NSABP-P1 trial included 13,388 women with a 5-year predicted risk of breast cancer of greater than 1.67% who were at least 35 years of age. These women were randomized to receive either tamoxifen or placebo for 5 years. At 7 years of follow up, the overall risk reduction for women receiving tamoxifen was 0.57 (95% confidence interval [CI], 0.46 to 0.7) and the risk reduction for the development of ER positive breast cancer was 0.38 (95% CI, 0.28 to 0.5).[190] The International Breast Cancer Intervention Study (IBIS-1), showed an overall risk reduction of 0.71 (95% CI, 0.6 to 0.83; $p<0.001$). The risk reduction seen in the tamoxifen group was of similar magnitude in years 0 to 10 and after 10 years. The greatest risk reduction was seen in invasive ER-positive breast cancer and DCIS; there was no effect noted for invasive ER-negative breast cancer.[191] The Royal Marsden Tamoxifen Prevention Trial demonstrated a hazard ratio (HR) of 0.61 (95% CI, 0.43 to 0.86) at 20 years of follow up data.[192] The Italian Randomized Tamoxifen Prevent Trial enrolled 5,408 otherwise healthy women who had undergone hysterectomy and randomly assigned them in a double-blind manner to either tamoxifen (20 mg daily) or placebo for 5 years. This trial originally found no reduction in the risk of breast cancer with tamoxifen use.[193] However, subsequent analysis of the data with 11 years of follow up determined that, although the rates of breast cancer were similar in both groups (tamoxifen or placebo) among women at low risk, there was a significant risk reduction in the women at high risk. In this study, high-risk women with at least 1 intact ovary randomized to tamoxifen had a risk reduction of 0.24 (95% CI, 0.1 to 0.59) compared to the placebo group.[194]

tamoxifen versus raloxifene

The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial was a prospective, double-blind, randomized trial that examined the incidence of invasive breast cancer in postmenopausal women $\geq$ 35 years who were at an increased risk of developing breast cancer.[195] Women were randomized to

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tamoxifen (20 mg daily) or raloxifene (60 mg daily) for 5 years. At 81 months median follow up, the risk reduction (raloxifene: tamoxifen) was 1.24 (95% CI, 1.05 to 1.47) for the development of invasive breast cancer indicating that raloxifene was about 24% less effective than tamoxifen in reducing the risk of invasive breast cancer. There were no significant mortality differences between the 2 arms. Raloxifene was associated with a more favorable adverse effect profile compared to tamoxifen. Women receiving raloxifene had a lower risk of thromboembolic disease, uterine cancer, hot flashes, and vaginal bleeding compared to tamoxifen.

Breast Cancer – HR-Positive, Adjuvant Therapy

anastrozole versus tamoxifen

The ATAC (Anastrozole alone or in combination with tamoxifen versus tamoxifen alone) trial was conducted in 9,366 postmenopausal women in the adjuvant treatment of early breast cancer.[196] The trial randomized patients in a 1:1:1 ratio to receive active anastrozole plus tamoxifen placebo, active tamoxifen plus anastrozole placebo, or active anastrozole plus active tamoxifen. Disease-free survival (DFS) at 3 years was 89.4% on anastrozole and 87.4% on tamoxifen (HR, 0.83; 95% CI, 0.71 to 0.96; p=0.013). Results with the combination were not significantly different from those with tamoxifen alone (87.2%; HR, 1.02 [95% CI, 0.89 to 1.18]; p=0.8). Anastrozole was significantly better tolerated than tamoxifen with respect to endometrial cancer (p=0.02), vaginal bleeding and discharge (p<0.0001 for both), cerebrovascular events (p=0.0006), venous thromboembolic events (p=0.0006), and hot flashes (p<0.0001). Tamoxifen was significantly better tolerated than anastrozole with respect to musculoskeletal disorders and fractures (p<0.0001 for both).

cyclophosphamide (oral) methotrexate and fluorouracil

The combination of cyclophosphamide given orally in combination with intravenous methotrexate and fluorouracil was evaluated as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. After 27 months, treatment failure occurred in 24% of the 179 control patients and in 5.3 % of the combination chemotherapy patients.[197]

exemestane after 2 to 3 years of tamoxifen versus tamoxifen alone for 5 years

The Intergroup Exemestane Study (IES) was a phase 3 double-blind, randomized trial designed to investigate whether exemestane, when given to postmenopausal women who remained free of recurrence after receiving adjuvant tamoxifen therapy for 2 to 3 years for primary breast cancer, could prolong DFS, as compared with continued tamoxifen therapy.[198] Patients were enrolled to either exemestane 25 mg daily (n=2,362) or tamoxifen 20 mg daily (n=2,380) to complete 5 years of adjuvant endocrine therapy. The primary endpoint was DFS, defined by the time from randomization to recurrence of breast cancer at any site, diagnosis of a second primary breast cancer, or death from any cause. Secondary endpoints included overall survival (OS), the incidence of contralateral breast cancer, and long-term tolerability. After a median follow-up of 30.6 months, 449 first events (local or metastatic recurrence, contralateral breast cancer, or death) were reported — 183 in the exemestane group and 266 in the tamoxifen group. The unadjusted HR in the exemestane group as compared with the tamoxifen group was 0.68 (95% CI, 0.56 to 0.82; p<0.001 by the log-rank test), representing a 32% reduction in risk and corresponding to an absolute benefit in terms of DFS of 4.7% (95% CI, 2.6 to 6.8) at 3 years after randomization. OS was not significantly different in the 2 groups, with 93 deaths occurring in the exemestane group and 106 in the tamoxifen group. At a median follow up of 120

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months, there were continued sustained benefits with the exemestane group in terms of reduction of disease recurrence and breast cancer mortality. A modest improvement in OS was seen with exemestane at 120 months.[199]

exemestane with ovarian suppression versus tamoxifen with ovarian suppression-premenopausal status

TEXT/SOFT: In two phase 3 trials, 4,690 premenopausal women with early stage HR-positive breast cancer were randomly assigned to exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 years.[200] Ovarian suppression was achieved through the use of a gonadotropin-releasing hormone, oophorectomy, or ovarian irradiation. After a median follow up of 68 months, DFS was 91.1% in the exemestane group and 87.3% in the tamoxifen group (HR for disease recurrence, second invasive cancer, or death = 0.72; 95% CI, 0.6 to 0.85; p<0.001). Overall, survival did not differ significantly between the 2 groups (HR for death in the exemestane group, 1.14; 95% CI, 0.86 to 1.51; p=0.37). Grade 3 or 4 adverse events were reported in similar frequency (30.6% of exemestane-treated patients and 29.4% of tamoxifen-treated patients). At 8 years, in SOFT the DFS rate was 78.9% with tamoxifen alone, 83.2% with tamoxifen plus ovarian suppression, and 85.9% with exemestane plus ovarian suppression (p=0.009 for difference in tamoxifen groups).[201] OS was 91.5% with tamoxifen alone, 93.3% with tamoxifen plus ovarian suppression, and 92.1% with exemestane plus ovarian suppression (p=0.01 for difference in tamoxifen groups). Among those with HER2-negative cancer who received chemotherapy, the rate of distant recurrence with exemestane plus ovarian suppression was lower than the rate with tamoxifen plus ovarian suppression (difference of 7% in SOFT and 5% in TEXT). Grade 3 or higher adverse events were still reported in similar frequency (31% of exemestane-treated patients and 32.3% of tamoxifen-treated patients).

letrozole versus tamoxifen

The Breast International Group (BIG) 1-98 study was a multicenter, randomized, double-blind phase 3 trial involving 8,010 postmenopausal women. The study was conducted in the adjuvant setting and was designed to answer 2 primary questions: whether letrozole 2.5 mg daily for 5 years was superior to tamoxifen 20 mg daily for 5 years (Primary Core Analysis) and whether switching endocrine treatments at 2 years was superior to continuing the same agent for a total of 5 years (Sequential Treatments Analysis). Specifically, BIG 1-98 compared 5 years of tamoxifen or letrozole monotherapy, or sequential treatment with 2 years of 1 of these drugs followed by 3 years of the other. The primary endpoint was DFS. In 2005 at a planned interim analysis, a significant DFS benefit was seen for patients receiving letrozole compared with patients receiving tamoxifen. Therefore, patients assigned to tamoxifen monotherapy were notified and permitted to crossover to letrozole. At a median follow up of 8.7 years from randomization, intention to treat analysis showed superior results for letrozole monotherapy as compared to tamoxifen monotherapy. Letrozole resulted in improved DFS (HR, 0.86; 95% CI, 0.78 to 0.96) and OS (HR, 0.87; 95% CI, 0.77 to 0.99). There were no statistically significant differences for any of the sequenced therapy arms compared to letrozole monotherapy.[202]

letrozole versus anastrozole

FACE: A total of 4,136 postmenopausal women with node-positive early stage breast cancer were randomized to either letrozole or anastrozole to be taken daily for 5 years or until disease recurrence.[203] Patients were stratified based on number of positive lymph nodes and tumor HER2 status. The primary endpoint was 5-year DFS and secondary endpoints were OS and safety. The 5-year

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estimated DFS rate and OS rates were 84.9% and 89.9% versus 82.9% and 89.2% for letrozole and anastrozole, respectively. Grade 3 to 4 adverse events were similar between the 2 groups. The authors concluded that letrozole did not demonstrate significantly superior efficacy or safety compared with anastrozole in postmenopausal women with node-positive early breast cancer.

Breast Cancer – HR-Positive, Extended Adjuvant Therapy

letrozole versus placebo

The National Cancer Institute of Canada Clinical Trials Group Study MA 17 was a phase 3, double-blind trial that randomized 5,187 patients to either letrozole 2.5 mg daily or placebo after completion of 5 years of adjuvant tamoxifen therapy. Primary endpoint was DFS. Patients were eligible for the study if they were postmenopausal and had ER positive disease. Letrozole or placebo was initiated within 3 months after the end of tamoxifen therapy (4.5 to 6 years of tamoxifen were required for study entry). At the time of unblinding, 247 breast cancer events had occurred. Among the 247 events observed for the DFS analysis, 92 occurred in women in the letrozole arm of the trial and 155 occurred in women in the placebo arm. The 4-year DFS for patients receiving letrozole was 94.4 and for patients receiving placebo was 89.8%, representing an absolute reduction in recurrence of 4.6% for patients receiving letrozole. The HR for recurrence or contralateral breast cancer in those receiving letrozole relative to those receiving placebo was 0.58 (95% CI, 0.45 to 0.76), a relative reduction in risk of disease recurrence of 42% for women receiving letrozole. The HR for recurrence at a distant site was also statistically significant (HR, 0.6; 95% CI, 0.43 to 0.84; p=0.002). OS was the same in both arms (HR for death from any cause, 0.82; 95% CI, 0.57 to 1.19; p=0.3). However, among lymph node-positive patients, OS was statistically significantly improved with letrozole (HR, 0.61; 95% CI, 0.38 to 0.98; p=0.04).[204]

exemestane alone or following tamoxifen for a total of 5 years

The TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial was a phase 3, open label, randomized trial involving 9,776 postmenopausal women with HR-positive breast cancer.[205] Patients were randomized to exemestane 25 mg orally once daily for 5 years or tamoxifen 20 mg once daily for 2.5 to 3 years followed by exemestane for a total of 5 years of therapy (sequential therapy). At 5 years, DFS was 85% in the sequential group and 86% in the exemestane alone group (HR, 0.97; 95% CI, 0.88 to 1.08; p=0.6). Patients in the sequential treatment arm had a higher incidence of gynecologic symptoms while musculoskeletal effects, hypertension, and hyperlipidemia were seen more frequently in the exemestane alone arm. A 10-year follow up of the TEAM trial reviewed 6,120 of the original 9,776 patients and found that DFS was 67% (95% CI, 65 to 69) for the exemestane alone arm and 67% (95% CI, 65 to 69) for the sequential therapy arm (HR, 0.96; 95% CI, 0.88 to 1.05; p=0.39).[206] The authors concluded that adjuvant endocrine therapy options may be individualized based on patient preferences, comorbidities, and tolerability.

letrozole – extended adjuvant therapy to 10 years versus 5 years of adjuvant therapy + placebo

MA.17R was a phase 3, randomized (1:1), double-blind, placebo-controlled trial that enrolled 1,918 postmenopausal women to assess the effects of extending letrozole adjuvant therapy to 10 years compared to 5 years of adjuvant therapy.[207] Patients were stratified by nodal status, prior adjuvant chemotherapy, the interval from the last dose of aromatase inhibitor (AI) therapy, and the duration of treatment with tamoxifen. Eligible patients were HR-positive and were disease-free after completing 4.5 to 6 years of therapy with any AI. Most patients had also had tamoxifen treatment prior to the AI

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therapy. After a median follow up of 6.3 years, there were 67 and 98 events involving disease recurrence or the occurrence of contralateral breast cancer in the letrozole and placebo groups, respectively (HR, 0.66; p=0.01). The rate of 5-year OS was not different between the 2 groups, 93% (95% CI, 92 to 95) in the letrozole group and 94% (95% CI, 92 to 95) in the placebo group (HR, 0.97; p=0.83). Bone-related toxic effects, including bone pain, bone fractures, and new-onset osteoporosis, occurred more frequently among the letrozole-treated patients compared to placebo-treated patients.

IDEAL was a phase 3, randomized trial involving 1,824 postmenopausal patients with HR-breast cancer.[208] Patients were randomized to receive either an additional 2.5 years or an additional 5 years of letrozole after the initial 5 years of endocrine therapy (patients were stratified by prior endocrine therapy with either 5 years of tamoxifen or 5 years of an AI or 2 to 3 years of tamoxifen followed by an AI). Other stratifications included nodal status, the use adjuvant chemotherapy, and time after completion of treatment (from 0 to 24 months). The primary endpoint was DFS. Secondary endpoints included OS, distant metastasis-free interval (DMFi), new primary breast malignancies, and safety. With a median follow up of 6.6 years, a DFS event occurred in 152 patients in the 5-year group compared with 163 patients in the 2.5-year group (HR, 0.92; 95% CI, 0.74 to 1.16). Likewise, OS and DMFi were not significantly different between the 2 groups. None of the subgroups were identified as having benefitted from the 5-year extension compared to the 2.5-year extension of adjuvant letrozole.

tamoxifen – 5 years versus 10 years

The worldwide Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial randomly assigned 12,894 women to continue open-label tamoxifen in the adjuvant setting to 10 years or to discontinue tamoxifen after 5 years (open control group).[209] Continuing tamoxifen reduced the risk of breast cancer recurrence (617 versus 711, p=0.002), reduced breast cancer mortality (331 deaths versus 397 deaths, p=0.01), and reduced overall mortality (639 deaths versus 722 deaths, p=0.01). The cumulative risk of recurrence during years 5 to 14 was 21.4% for women receiving tamoxifen versus 25.1% for controls (absolute recurrence reduction 3.7%). The risk reductions were greater during years 5 to 9 than after year 9. Breast cancer mortality during years 5 to 14 was 12.2% for prolonged tamoxifen versus 15% for the control group (absolute mortality reduction 2.8%). There was a higher incidence of PE, stroke, ischemic heart disease, and endometrial cancer in the 10-year tamoxifen group. However, mortality without recurrence from causes other than breast cancer was similar (691 deaths without recurrence in 6,454 women allocated to continue versus 679 deaths in 6,440 controls; recurrence rate ratio, 0.99 [95% CI, 0.89 to 1.1]; p=0.84).

Breast Cancer – HER2-positive, extended adjuvant therapy

neratinib (Nerlynx) after trastuzumab-based adjuvant therapy

ExteNET: A multicenter, double-blind, placebo-controlled, phase 3 trial randomized 2,840 women with stage 1-3 HER2-positive breast cancer who had completed adjuvant trastuzumab within the previous 2 years to either neratinib or placebo.[210] The majority of the patients (81%) were enrolled within 1 year of completion of trastuzumab. The median time from last adjuvant trastuzumab treatment to randomization on the neratinib arm was 4.4 months compared to 4.6 months in the placebo arm. The major efficacy outcome endpoint was invasive disease-free survival (iDFS). At a 2 year follow up, 70 iDFS events had occurred in the neratinib group compared to 109 events in the placebo group (HR, 0.67; 95% CI, 0.5 to 0.91; p=0.0091). The 2 year iDFS rate was 93.9% in the neratinib group and 91.6% in the placebo group. Diarrhea, nausea, and vomiting occurred more frequently in the neratinib-

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treated patients with 40% of neratinib-treated patients experiencing ≥ grade 3 diarrhea. QT prolongation occurred in 3% of neratinib patients and 7% of placebo patients. At the time of the analysis, OS data were not yet mature. At a median follow-up of 5.2 years, the neratinib-treated patients had significantly fewer iDFS events compared to those in the placebo group (116 versus 163 events, respectively; stratified HR, 0.73 [95% CI, 0.57 to 0.92; p=0.0083]).[211] Five-year iDFS were 90.2% (95% CI, 88.3 to 91.8) and 87.7% (95% CI, 85.7 to 89.4) in the neratinib group and placebo groups, respectively.

Breast Cancer – Advanced HR-Positive, First-Line Therapy

abemaciclib (Verzenio) plus an aromatase inhibitor versus an aromatase inhibitor plus placebo

MONARCH 3, a multicenter, randomized, double-blind, placebo-controlled study, assessed the efficacy of abemaciclib in combination with an AI in 493 postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer as initial endocrine-based therapy.[212,213] Patients were randomized 2:1 to either abemaciclib plus an AI (anastrozole or letrozole) or placebo plus an AI (anastrozole or letrozole), and randomization was stratified by disease site and prior (neo)adjuvant endocrine therapy (AI versus other versus no prior endocrine therapy). The primary endpoint was PFS evaluated according to RECIST version 1.1, confirmed by an independent review committee. The patient median age was 63 years (range, 32 to 88 years), the majority were Caucasian (58%) or Asian (30%), and 51% had received prior systemic therapy (39% chemotherapy). The median PFS was 28.2 months (95% CI, 23.5 to not reached) in the abemaciclib/AI group compared to 14.8 months (95% CI, 11.2 to 19.2) in the placebo/AI group (HR, 0.54; 95% CI, 0.418 to 0.698; p<0.0001). The ORR (complete response [CR] plus partial response [PR]) was 55.4% (95% CI, 49.5 to 61.4) in the group treated with abemaciclib/AI compared to 40.2% (95% CI, 31.8 to 48.5) in those treated with placebo/AI.

anastrozole versus tamoxifen

Anastrozole 1 mg daily was compared to tamoxifen 40 mg daily in 238 postmenopausal women with ER positive advanced breast cancer in a prospective, randomized phase 3 trial. The patients had received no prior therapy for advanced breast cancer and had not received hormonal adjuvant therapy. The primary endpoints were response rates (overall response [OR] and clinical benefit), time to progression (TTP), and OS. There was a significant difference between anastrozole and tamoxifen groups with regard to clinical benefit (defined as CR + PR + stable disease ≥ 24 weeks). Clinical benefit with anastrozole was 83% compared to 56% with tamoxifen (p<0.001). The median TTP in patients achieving clinical benefit was significantly longer in the anastrozole arm (18 months) compared with the tamoxifen arm (7 months) (HR, 0.13; 95% CI, 0.08 to 0.2; p<0.01). Median time to death was significantly improved in the anastrozole arm (17.4 months) compared with the tamoxifen arm (16 months) (HR, 0.64; 95% CI, 0.47 to 0.86; p<0.003). All deaths were due to disease progression and anastrozole was associated with less toxicity than tamoxifen.[214]

fulvestrant (Faslodex) versus anastrozole

FALCON: A phase 3, randomized, double-blind trial enrolled 524 patients with HR-positive locally advanced or metastatic breast cancer who were endocrine therapy-naive.[215] Patients were randomized to fulvestrant 500 mg IM on days 0, 14, 28, and every 28 days thereafter or anastrozole 1 mg orally once daily. The primary endpoint of PFS was significantly longer in the fulvestrant group (16.6 months) than in the anastrozole group (13.8 months) (HR, 0.797; 95% CI, 0.637 to 0.999; p=0.0486). There was a

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higher incidence of arthralgias and hot flushes in the fulvestrant group compared to the anastrozole group but only 7% of patients in the fulvestrant group and 5% of patients in the anastrozole group discontinued therapy because of adverse events.

letrozole versus tamoxifen

The Letrozole International Breast Cancer Group conducted a phase 3, randomized, double-blind, multicenter trial comparing letrozole 2.5 mg daily and tamoxifen 20 mg daily as first-line endocrine therapy in 939 postmenopausal women with HR-positive advanced breast cancer.[216] Patients could not have received prior endocrine therapy for the treatment of advanced disease and must have had disease progression no sooner than 12 months after receiving tamoxifen in the adjuvant setting. The trial was originally designed as a 3-armed trial with 2 monotherapy arms and a combination arm. However, pharmacokinetic studies determined that adding tamoxifen to letrozole decreased letrozole serum levels by 38% on average. Therefore, the combination arm was dropped from the study and continued with just the 2 monotherapy arms. Therefore, 23 patients who were originally enrolled in the combination arm were excluded from the intent to treat analysis. TTP was the primary endpoint and secondary endpoints included overall tumor ORR, duration of overall response, rate of clinical benefit, duration of clinical benefit, time to treatment failure (TTF), time to response (TTR), number of deaths, and OS. Letrozole was superior to tamoxifen in TTP, reducing the risk of progression by 30% (HR, 0.7; 95% CI, 0.6 to 0.82; p<0.0001) compared with tamoxifen. Median TTP was prolonged by 57%, 41 weeks for letrozole and 26 weeks for tamoxifen. Letrozole was superior to tamoxifen in TTF (p=0.0001), with a median of 40 weeks for letrozole and 25 weeks for tamoxifen. Treatment failure occurred in 75% of letrozole-treated patients, compared with 85% of patients treated with tamoxifen. ORR was significantly higher for letrozole patients at 30%, (p=0.0006), as was clinical benefit at 49% for letrozole compared with 38% for tamoxifen (p=0.001). There was, however, no significant difference between letrozole and tamoxifen in the duration of overall response or in duration of overall clinical benefit. TTR did not differ significantly in the 2 arms. Median TTR was 14 weeks for both treatments.

palbociclib (Ibrance) plus letrozole versus letrozole alone

PALOMA-2 was a phase 3, double-blind study involving 666 postmenopausal women with ER-positive, HER2-negative breast cancer who had received no previous therapy for advanced disease.[217] Patients were randomized 2:1 to either receive palbociclib plus letrozole or placebo plus letrozole. The primary endpoint was PFS and secondary endpoints included OS and safety. The median PFS favored the palbociclib plus letrozole arm (24.8 months) compared to the placebo plus letrozole group (14.5 months) (HR, 0.58; 95% CI, 0.46 to 0.72; p<0.001). Grade 3 to 4 neutropenia and febrile neutropenia occurred in 66.4% and 1.8%, respectively, of the palbociclib/letrozole-treated patients compared to 1.4% and 0% of the placebo/letrozole-treated patients, respectively. Permanent discontinuation of the medications due to adverse events occurred in 9.7% of palbociclib/letrozole-treated patients and 5.9% of the placebo/letrozole-treated patients. Further follow up at approximately 38 months continued to show improved median PFS for palbociclib/letrozole (27.6 months) versus placebo/letrozole (14.5 months). There were no new safety issues identified with longer follow up.[218]

ribociclib (Kisqali) plus letrozole versus letrozole plus placebo

MONALEESA-2 was a randomized, multicenter, double-blind, placebo-controlled, phase 3 trial involving 668 postmenopausal women with HR-positive, HER2-negative recurrent or metastatic breast cancer who had not received previous therapy for advanced disease.[219] Patients were randomized to either

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ribociclib 600 mg/day for 21 days, then 7 days off plus letrozole 2.5 mg daily or placebo plus the same dose of letrozole. The primary endpoint was investigator-assessed PFS. Secondary endpoints included OS, ORR, and safety. Patients continued treatment until disease progression, unacceptable toxicity, death, or drug discontinuation. Patients who discontinued ribociclib or placebo were allowed to continue taking letrozole; however, no treatment crossover was allowed. A planned interim analysis occurred after 243 patients had disease progression or had died. At the time of planned interim analysis, the median duration of follow-up was 15.3 months. The median duration of PFS was not reached in the ribociclib group versus 14.7 months in the placebo group (HR, 0.56; 95% CI, 0.43 to 0.72). At 18 months, the PFS rate was 63% in the ribociclib group compared to 42.2% in the placebo group. The ORR in the intention-to-treat population was 40.7% for the ribociclib arm compared to 27.5% in the placebo arm (p<0.001). OS data were not mature at the time of the interim analysis. Neutropenia occurred in 59.3% of patients in the ribociclib group compared to 0.9% of patients in the placebo group. Febrile neutropenia occurred in 1.5% of ribociclib-treated patients compared to no patients in the placebo group. In the ribociclib group, 11 patients (3.3%) experienced ≥ 1 average QTcF interval of > 480 msec above baseline while 1 patient (0.3%) in the placebo group experienced this complication. Dose reductions related to adverse events occurred in 53.9% of the ribociclib-treated patients and 7% of patients treated with placebo. The most frequent adverse event leading to dose reduction was neutropenia in the ribociclib arm.

ribociclib (Kisqali) plus fulvestrant (Faslodex) versus fulvestrant (Faslodex)

MONALEESA-3 was a multinational, phase 3, randomized, double-blind, placebo-controlled study that compared ribociclib plus fulvestrant in HR-positive, HER2-negative patients with advanced breast cancer who were treatment-naïve or had received ≤ 1 line of prior endocrine therapy in the advanced setting (n=726).[220] Patients were randomized 2:1 to ribociclib plus fulvestrant or placebo plus fulvestrant, and the primary endpoint was the locally assessed PFS. Other key endpoints included OS, ORR, and adverse events. The median PFS was higher in the combination treatment group compared to fulvestrant alone (20.5 months [95% CI, 18.5 to 23.5 months] versus 12.8 months [95% CI, 10.9 to 16.3 months], respectively; HR, 0.593 [95% CI, 0.48 to 0.732; p<0.001]). Effects were similar in patients who were treatment-naïve and those who had received ≤ 1 prior endocrine therapy (HR, 0.577 [95% CI, 0.415 to 0.802] versus HR, 0.565 [95% CI, 0.428 to 0.744], respectively). In those with measurable disease, ORR was 40.9% in the combination treatment group compared to 28.7% in the fulvestrant only group. Grade 3 neutropenia and leukopenia occurred in 46.6% and 13.5% of patients, respectively, in the combination group but no cases were reported in those treated with fulvestrant only. Grade 4 neutropenia occurred in 6.8% of patients with combination therapy; again, no cases were reported in the fulvestrant and placebo group. The second interim analysis of OS occurred after 275 deaths.[221] The estimated OS at 42 months was 57.8 % (95% CI, 52 to 63.2) for the ribociclib group compared to 45.9% (95% CI, 36.9 to 54.4) in the placebo group (HR, 0.72; 95% CI, 0.57 to 0.92; p=0.00455). The updated PFS for patients receiving first-line therapy was 33.6 months (95% CI, 27.1 to 41.3) in the ribociclib arm and 19.2 months (95% CI, 14.9 to 23.6) in the placebo group. There were no new safety signals.

ribociclib (Kisqali) plus tamoxifen or nonsteroidal aromatase inhibitor versus tamoxifen or nonsteroidal aromatase inhibitor given with goserelin in premenopausal patients

MONALEESA-7, a multinational, phase 3, randomized, double-blind, placebo-controlled trial, compared the efficacy of ribociclib plus endocrine therapy in premenopausal women with advanced, HR-positive breast cancer (n=672).[222] Premenopausal/perimenopausal women ages 18 to 59 years old with HR-

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positive, HER2-negative, advanced breast cancer were randomized 1:1 to oral ribociclib 600 mg/day for the first 21 days of a 28-day cycle or matching placebo with either oral tamoxifen 20 mg daily or a non-steroidal AI (letrozole 2.5 mg or anastrozole 1 mg) orally daily. Both regimens were also given with subcutaneous goserelin 3.6 mg on the first day of every 28-day cycle. Eligible patients were allowed to have had endocrine therapy and chemotherapy in the adjuvant or neoadjuvant setting and ≤ 1 line of chemotherapy for advanced disease. The primary endpoint was investigator-assessed PFS. The median PFS was 23.8 months (95% CI, 19.2 to not reached) in the ribociclib group compared with 13 months (95% CI, 11 to 16.4) in the placebo group (HR, 0.55; 95% CI, 0.44 to 0.69; p<0.0001). Serious adverse events were reported in 18% of ribociclib-treated patients compared to 12% of the placebo-assigned groups. No treatment-related deaths were reported, although 5 deaths occurred in the ribociclib group and 6 deaths occurred in the placebo group during or within 30 days following treatment, the majority of which were related to disease progression. A secondary endpoint of OS was reported at the time of a protocol-specified interim analysis.[223] The estimated OS at 42 months was 70.2% (95% CI, 63.5 to 76) in the ribociclib group and 46% (95% CI, 32 to 58.9) in the placebo group (HR, 0.71; 95% CI, 0.54 to 0.95; p=0.00973). The percentage of patients who received subsequent antineoplastic therapy was 68.9% in the ribociclib group and 73.2% in the placebo group and the time from randomization to disease progression or death was longer in the ribociclib group compared to the placebo group (HR, 0.69; 95% CI, 0.55 to 0.87).

tamoxifen

Historical trials have compared the response and adverse effects of tamoxifen versus diethylstilbestrol (DES), medroxyprogesterone, fluoxymesterone, and aminoglutethimide.[224,225,226,227] While response rates were similar, tamoxifen had the lowest toxicity profile of any of these agents.

toremifene (Fareston) versus tamoxifen

A randomized, open-label phase 3 trial with 643 patients compared 3 arms: tamoxifen 20 mg daily and 2 separate doses of toremifene 60 mg daily and toremifene 200 mg daily in postmenopausal patients with HR-positive or receptor status unknown metastatic breast cancer. The combined response rates (by intent to treat) were tamoxifen: 44%; toremifene 60 mg daily: 50%; and toremifene 200 mg daily: 48%. Complete and partial response rates were 19%, 21%, and 23% respectively for tamoxifen, toremifene 60 mg daily, and toremifene 200 mg day. None of these numbers were statistically different. Median times to progression and OS were not significantly different either. Adverse events were similar in all 3 arms, except that patients in the toremifene 200 mg daily arm had a statistically significantly increased rate of nausea. Quality-of-life assessments were not different among the 3 arms. The authors concluded that the activity, toxicity, and side effects of toremifene in postmenopausal women with HR-positive or receptor status unknown metastatic breast cancer are similar, if not equivalent, to those of tamoxifen. Also, no clear evidence of a dose-response effect for toremifene was demonstrated.[228]

Breast Cancer – Advanced HR-positive, Second-Line Therapy

All 3 AIs (anastrozole, letrozole, exemestane) have been compared to megestrol acetate in patients with advanced HR+ breast cancer in the second-line setting. At the time of these studies, megestrol acetate was an established second-line agent for the treatment of advanced breast cancer. In these trials, patients were required to have evidence of disease progression while receiving tamoxifen or another antiestrogen therapy or to have relapsed during or after receiving antiestrogen therapy. In

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general, these agents have demonstrated at least comparable efficacy to megestrol acetate in key outcomes, such as time to progression or overall response.[229,230,231]

abemaciclib (Verzenio)

MONARCH 1 was a phase 2, single-arm, open-label, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer disease in patients whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting (n=132).[232,233] Patients received 200 mg abemaciclib orally twice daily on a continuous schedule until development of progressive disease or unmanageable toxicity. At baseline, the median age was 58 years (range, 36 to 89 years), 85% were Caucasian, the median duration of metastatic disease was 27.6 months, and 51% of patients had 1 prior line of chemotherapy in the metastatic setting. The primary outcome, ORR, was 19.7% (95% CI, 13.3 to 27.5) and the median duration of response was 8.6 months (95% CI, 5.8 to 10.2).

abemaciclib (Verzenio) plus fulvestrant (Faslodex) versus fulvestrant (Faslodex) plus placebo

MONARCH 2 was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting (n=669).[234,235] Patients were randomized 2:1 to either abemaciclib 150 mg or placebo twice daily until development of progressive disease or unmanageable toxicity, both with an intramuscular (IM) injection of 500 mg fulvestrant on days 1 and 15 of cycle 1 and then day 1 of cycle 2 and beyond (28-day cycles). Pre/perimenopausal women (17%) also received goserelin for ≥ 4 weeks prior to and for the duration of the trial. The primary endpoint was PFS. At baseline, the median age was 60 years (range, 32 to 91 years), 37% were ≥ 65 years, and 56% were Caucasian. Abemaciclib significantly extended PFS versus fulvestrant alone (median, 16.4 versus 9.3 months, respectively; HR, 0.55 [95% CI, 0.45 to 0.68]; p=0.001). The objective response rate (ORR) was 48.1% of those treated with abemaciclib compared to 21.3% in the placebo arm.

alpelisib (Piqray) plus fulvestrant versus fulvestrant plus placebo

SOLAR-1 was a multicenter, randomized, phase 3, placebo-controlled trial comparing alpelisib 300 mg daily plus fulvestrant 500 mg IM monthly (after initial loading dose on days 1, 15, and 29) with placebo plus fulvestrant at the same dose in 572 patients with HR-positive, HER2-negative advanced breast cancer who had previously received endocrine therapy in either the neoadjuvant, adjuvant, or metastatic disease setting.[236] Patients who had previously received chemotherapy for metastatic disease or fulvestrant and patients with type 1 or uncontrolled type 2 diabetes (FPG > 140 mg/dL or glycosylated hemoglobin level of > 6.4%) were excluded. Patients were enrolled in 2 cohorts on the basis of phosphatidylinositol-3-kinase α-subunit (PIK3CA) mutation status in the tumor tissue. Of the 572 overall patients, 341 of those were identified as having PIK3CA-mutated disease. The primary endpoint was PFS while secondary endpoints included overall response and safety. An additional secondary endpoint was OS in the cohort with PIK3CA-mutated cancer. At a median follow up of 20 months (range, 10.7 to 33.3 months) in the PIK3CA-mutated cohort, the median PFS was 11 months (95% CI, 7.5 to 14.5) in the alpelisib-fulvestrant group and 5.7 months (95% CI, 3.7 to 7.4) in the placebo-fulvestrant group (HR, 0.65; 95% CI, 0.5 to 0.85; p<0.001). By contrast, in the cohort without the PIK3CA-mutation, the median PFS was 7.4 months (95% CI, 5.4 to 9.3) in the alpelisib-fulvestrant arm and 5.6 months (95% CI, 3.9 to 9.1) in the placebo-fulvestrant arm (HR, 0.85; 95% CI, 0.58 to 1.25) and the proof of concept was not met for this cohort. The entire 572-patient study population was

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utilized for assessing safety. The most common adverse events of grade 3 or 4 occurring in ≥ 5% of patients were hyperglycemia (36.6% of patients who received alpelisib-fulvestrant and 0.7% of patients who received placebo-fulvestrant), rash (in 9.9% and 0.3%, respectively), and diarrhea (in 6.7% and 0.3%, respectively). Permanent discontinuation due to adverse events occurred in 25% of patients receiving alpelisib-fulvestrant and 4.2% of patients receiving placebo-fulvestrant.

exemestane plus everolimus (Afinitor) versus exemestane plus placebo

BOLERO-2 was a phase 3, double blind trial in which 724 patients with HR-positive, HER-2-negative advanced breast cancer were randomized to everolimus plus exemestane or exemestane plus placebo.[237] Eligible patients had either experienced a recurrence or progression of disease while receiving therapy with a nonsteroidal AI either in the adjuvant setting or to treat advanced disease (or both). The primary endpoint of PFS was 6.9 months for everolimus plus exemestane versus 2.8 months for placebo plus exemestane according to local investigators (HR, 0.43; 95% CI 0.35 to 0.54; p<0.001) and 10.6 months versus 4.1 months, respectively, as assessed by a central review (HR, 0.36; 95% CI 0.27 to 0.47; p<0.001). The most common grade 3 or 4 adverse events were stomatitis (8% versus 1%), anemia (6% versus less than 1%), dyspnea (4% versus 1%), hyperglycemia (4% versus less than 1%), fatigue (4% versus 1%), and pneumonitis (3% versus 0%) in the exemestane-everolimus group compared to the exemestane-placebo group, respectively. OS was a secondary endpoint. At time of data cutoff, 410 deaths had occurred and 13 patients remained on treatment. Median OS in patients receiving exemestane plus everolimus was 31 months (95% CI, 28 to 34.6 months) compared with 26.6 months (95% CI, 22.6 to 33.1 months) in patients receiving exemestane plus placebo (HR, 0.89; 95% CI, 0.73 to 1.1; p=0.14). The authors concluded that the combination of exemestane plus everolimus did not result in a statistically significant improvement in the secondary endpoint of OS, despite producing statistically significant improvement in the primary endpoint of PFS.[238]

fulvestrant (Faslodex) versus anastrozole

In a North American randomized, double-blind trial, fulvestrant 250 mg IM monthly was compared to anastrozole 1 mg orally daily in 400 postmenopausal women with advanced breast cancer whose disease had progressed on prior endocrine therapy.[239] More than 95% of patients on both arms of the trial had received prior tamoxifen. The patients were followed for a median of 16.8 months. Primary outcome was defined as TTP of disease. At the time of analysis, 83.5% of the fulvestrant group and 86.1% of the anastrozole group had experienced disease progression. There was no significant difference for TTP between the 2 treatment groups (HR, 0.92; 95% CI, 0.74 to 1.14; p=0.43). Median TTP was 5.4 months for fulvestrant and 3.4 months for anastrozole. These data indicated non-inferiority of fulvestrant compared to anastrozole in this patient population. Both fulvestrant and anastrozole were well tolerated with 5 patients on each arm withdrawing due to adverse effects.

fulvestrant (Faslodex) versus exemestane

The EFECT (Evaluation of Faslodex versus Exemestane Clinical Trial) study was a phase 3, randomized, placebo-controlled multicenter trial in 693 postmenopausal women with HR-positive advanced breast cancer who had progressive or recurrent disease after receiving nonsteroidal AIs (anastrozole or letrozole).[240] A loading dose of fulvestrant was used in this trial with fulvestrant 500 mg IM given on day 1 followed by 250 mg IM given on days 14 and 28 and monthly thereafter. Anastrozole was dosed at 1 mg daily. The study enrolled patients whose disease had relapsed during treatment with (or within 6 months of discontinuation of) an adjuvant nonsteroidal AI, or whose advanced disease progressed

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during treatment with a nonsteroidal an AI. Patients were categorized as AI sensitive if the investigator determined that the patient had a CR, PR, or stable disease (SD) for at least 6 months during treatment with the AI for advanced breast cancer. All other patients, including all those who received the AI as adjuvant therapy, were defined as AI resistant. Approximately 60% of women randomized to each group had AI sensitive disease and only 10 of those women had received their AI as adjuvant therapy. The primary endpoint of this study was TTP. Clinical benefit rate (CBR) was a secondary outcome and was defined as a patient having a best overall response of a CR, PR, or SD for at least 24 weeks. At a median follow up of 13 months, 82.1% of the fulvestrant group and 87.4% of the exemestane group had experienced a defined progression event. The median time to progression in both groups was 3.7 months (p=0.65) with a HR of 0.93 (95% CI, 0.819 to 1.133). There were no statistically significant differences in any of the predetermined covariates, including women with AI sensitive or AI resistant disease. The CBR was 32.2% and 31.5% in the fulvestrant and exemestane arms, respectively (odds ratio, 1.03; 95% CI, 0.72 to 1.487; p =0 .853). Both fulvestrant and exemestane were well tolerated in this study, with only 2% of fulvestrant-treated patients and 2.6% of exemestane-treated patients withdrawing because of an adverse event.

palbociclib (Ibrance) plus fulvestrant (Faslodex) versus fulvestrant (Faslodex) plus placebo

PALOMA-3 was a phase 3 trial involving 521 patients with advanced HR-positive, HER2-negative breast cancer that had relapsed or progressed during prior endocrine therapy.[241] Patients were randomized 2:1 to receive palbociclib plus fulvestrant or placebo plus fulvestrant. Women who were premenopausal or perimenopausal received ovarian suppression therapy. The primary endpoint was PFS. Secondary endpoints included OS, ORR, rate of clinical benefit, patient reported outcomes (PROs), and safety. At the preplanned interim analysis after 195 events of disease progression or death had occurred, the median PFS was 9.2 months (95% CI, 7.5 to not reached) with palbociclib/fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo/fulvestrant. The HR for disease progression or death was 0.42 (95% CI, 0.31 to 0.56; p<0.001). The most common grade 3 or 4 adverse events in the palbociclib-containing arm were neutropenia, leucopenia, anemia, thrombocytopenia, and fatigue. The rate of discontinuation due to adverse events was 2.6% with palbociclib and 1.7% with placebo. With a median follow up of approximately 45 months and 60% data maturity (310 deaths of 521 patients), the median OS was 34.9 months (95% CI, 28.8 to 40) in the palbociclib-fulvestrant group and 28 months (95% CI, 23.6 to 34.6) in the placebo-fulvestrant group (HR, 0.81; 95% CI, 0.64 to 1.03; p=0.09).[242] The estimated rate of OS at 3 years in the Kaplan-Meier analysis was 50% (95%, CI 44 to 55) in the palbociclib-fulvestrant group and 41% (95% CI, 33 to 48) in the placebo-fulvestrant group. The median time to receipt of chemotherapy was 17.6 months compared to 8.8 months for the palbociclib-fulvestrant group versus the placebo-fulvestrant group, respectively. No new safety signals were identified with longer term follow up.

talazoparib (Talzenna) versus physician choice chemotherapy for gBRCAm, HER2-negative advanced breast cancer

EMBRACA was a randomized, phase 3, open-label trial of 431 patients with advanced breast cancer and a germline *BRCA1/2* mutation who had received no more than 3 previous cytotoxic regimens for advanced/metastatic breast cancer.[243] There was no limit on the number of previous hormone therapies patients may have received. Patients were required to have a history of treatment with a taxane, an anthracycline, or both in the neoadjuvant, adjuvant, and/or metastatic setting unless there was a contraindication to those therapies. Patients were excluded if they experienced disease

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progression while receiving a platinum-based chemotherapy or if they relapsed within 6 months while receiving neoadjuvant or adjuvant platinum therapy. Patients were randomized 2:1 to talazoparib 1 mg orally daily or single-agent chemotherapy of the physician choice (capecitabine, eribulin, gemcitabine, or vinorelbine) given in continuous 21-day cycles. Patients were stratified by the number of previous cytotoxic chemotherapy regimens they had received for metastatic disease (0 or 1 to 3), as well as by HR status and history of central nervous system (CNS) metastasis. The primary endpoint, PFS as measured by a blinded independent committee review (BICR), was significantly longer in the talazoparib group (8.6 months) than in the standard therapy group (5.6 months) after a median follow up of 11.2 months (HR, 0.54; 95% CI, 0.41 to 0.71; p<0.0001). At the time of the primary analysis, the median OS was 22.3 months for the talazoparib group and 19.5 months in the standard treatment group, which was not statistically significantly different (HR, 0.76; 95% CI 0.55 to 1.06; p=0.11); however, these data are not yet mature. Grade 3 or higher hematologic toxicity occurred in 55% of the talazoparib group compared to 38% of the standard therapy group. Patients in the standard therapy group had a higher incidence of nonhematologic toxicities (38% versus 32%). Adverse events resulted in drug discontinuation in 5.9% of talazoparib patients and 8.7% of patients who received standard therapy. PROs were also collected during the trial and were measured with the use of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire (QLQ-30) and the breast cancer-specific QLQ-BR23. Measurements were conducted at baseline and throughout the treatment as pre-specified exploratory endpoints to examine the change from baseline in the global health status quality of life scale and the time to clinically meaningful deterioration in quality of life. For the talazoparib group there was a significant improvement in global health status-quality of life from baseline compared to the standard therapy group who demonstrated a significant deterioration for that measure. Likewise, as compared to standard therapy, the talazoparib-treated patients had a significant delay in the time to onset of clinically meaningful deterioration in quality of life (24.3 months versus 6.3 months, respectively; HR, 0.38 [95% CI, 0.26 to 0.55]).

toremifene (Fareston) versus tamoxifen crossover

Toremifene is considered to display cross resistance with tamoxifen such that women who have experienced progressive disease on tamoxifen generally have very low to no response to toremifene. An open-label, crossover trial was conducted of toremifene (240 mg per day) and tamoxifen (40 mg per day) in 66 postmenopausal women with advanced breast cancer (ER positive or receptor status unknown) after disease progression on either toremifene or tamoxifen, patients were crossed over to the opposite treatment. Objective response rates for first-line therapy were 29% with toremifene and 42% with tamoxifen (p value not significant between treatments). Forty-four patients who progressed on first-line toremifene or tamoxifen were assessable for second-line response. No objective responses were observed, which the authors stated is indicative of the cross resistance of the two agents.[244]

Breast Cancer – Advanced, Second-Line Therapy (regardless of HR status)

Capecitabine has demonstrated efficacy in combination with docetaxel in patients with metastatic breast cancer with anthracycline resistant disease as measured by TTP.[245] It also has demonstrated efficacy as monotherapy in metastatic breast cancer patients who have anthracycline and taxane-pretreated disease.[246]

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Breast Cancer – HER2-Positive, Advanced

lapatinib (Tykerb) plus capecitabine versus capecitabine alone

A multicenter, open-label randomized trial was conducted to assess the relative efficacy and tolerability of lapatinib plus capecitabine versus capecitabine alone in patients with stage IIIB or IV breast cancer with HER2 over expression.[247] A total of 399 patients were enrolled and randomized to either lapatinib (1,250 mg once daily on days 1 to 21) plus capecitabine (1,000 mg/m^2 every 12 hours on days 1 to 14) every 21 days or capecitabine alone (1,250 mg/m^2 every 12 hours on days 1 to 14) every 21 days. The primary endpoint was TPP defined as time from randomization to tumor progression or death from breast cancer. Median TTP was 27.1 versus 18.6 weeks (HR, 0.57; p=0.00013) favoring the lapatinib plus capecitabine arm. Response rates were 23.7% (lapatinib plus capecitabine) versus 13.9% (capecitabine alone). Adverse effects observed in the lapatinib and capecitabine combination arm were generally similar to those in the capecitabine alone arm; higher incidences of diarrhea and rash were noted with the combination. Grade 3 or 4 adverse reactions occurring in greater than 5% of patients on the combination arm were diarrhea (13%) and palmar-plantar erythrodysesthesia (12%). There was a 2% incidence of reversible decreased left ventricular function in the combination arm.

lapatinib (Tykerb) plus capecitabine versus trastuzumab emtansine (Kadcyla)

The EMILIA trial was a phase 3 randomized, open-label trial in 991 patients with HER-2 positive advanced breast cancer who had previously been treated with trastuzumab and a taxane.[248] Patients were randomly assigned to trastuzumab emtansine (T-DM1) or lapatinib plus capecitabine. The primary endpoints were PFS as assessed by an independent review, OS, and safety. Secondary endpoints included ORR and time to symptom progression. At the first interim analysis with a median duration of follow-up of approximately 13 months, median survival was 9.6 months for the T-DM1 arm and 6.4 months for the lapatinib plus capecitabine arm; stratified HR for progression or death from any cause, 0.65 (95% CI, 0.55 to 0.77; p<0.001). At the second interim analysis, with a median duration of follow up of 19 months, the difference in OS was significantly increased in the T-DM1 group (30.9 months) compared to the lapatinib plus capecitabine group (25.1 months) and crossed the stopping boundary for efficacy. HR for death from any cause was 0.68 (95% CI, 0.55 to 0.85; p<0.001). Results for all secondary endpoints favored T-DM1. The ORR was 43.6% for T-DM1 (95% CI, 38.6 to 48.6) and 30.8% for lapatinib-capecitabine (95% CI, 26.3 to 35.7; p<0.001) and the median duration of response was longer with T-DM1 (12.6 months) compared to 6.5 months for the lapatinib-capecitabine arm. The incidence of grade 3 or 4 adverse events was 57% in the lapatinib-capecitabine group compared to 40.8% in the T-DM1 group. Diarrhea and palmar-plantar erythrodysesthesia were the most commonly reported grade 3 or 4 events in the lapatinib-capecitabine group whereas thrombocytopenia and elevated serum concentrations of AST and ALT were the most common grade 3 or 4 adverse events in the T-DM1 arm. The authors concluded that T-DM1 significantly prolonged progression-free and OS with less toxicity than lapatinib plus capecitabine in patients with HER2-positive breast cancer previously treated with trastuzumab and a taxane. In the final published analysis, despite the crossover from control to trastuzumab emtansine that was permitted after the second interim analysis, median OS still favored trastuzumab emtansine (29.9 months [95% CI, 26.3 to 34.1]) compared to capecitabine plus lapatinib (25.9 months [95% CI, 22.7 to 28.3]; HR=0.75).[249]

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lapatinib (Tykerb) plus letrozole versus letrozole and placebo

A randomized, double-blind, multicenter phase 3 trial was conducted to examine the effect of adding lapatinib to letrozole as first-line therapy in 1,286 postmenopausal women with HR-positive metastatic breast cancer. No prior therapy for advanced or metastatic disease was allowed. Prior neoadjuvant/adjuvant antiestrogen therapy was allowed, as was adjuvant AI and/or trastuzumab, provided it was completed more than 1 year before study entry. The combination regimen consisted of lapatinib 1,500 mg orally and letrozole 2.5 mg orally daily. The control arm consisted of letrozole 2.5 mg daily with matching lapatinib placebo pill. The primary endpoint was PFS. Seventeen percent of women in each arm of the trial were confirmed to have HER2 positive disease. After a median follow-up time of 1.8 years, median PFS for patients in the HER2-positive population increased from 3 months for letrozole-placebo to 8.2 months for letrozole lapatinib, demonstrating a significant reduction in the risk of progression for the combination (HR, 0.71; 95% CI, 0.53 to 0.96; p=0.019). In the 952 patients with centrally confirmed HER2-negative tumors, there was no improvement in PFS (HR, 0.9; 95% CI, 0.77 to 1.05; p=0.188). The most common adverse events were diarrhea, rash, nausea, arthralgia, and fatigue (majority were grade 1 or 2), with a higher incidence in the combination arm for diarrhea and rash. Any serious adverse event related to study drug occurred in 8% of patients receiving the combination compared with 4% of patients receiving letrozole/placebo.[250]

neratinib (Nerlynx) versus lapatinib (Tykerb), both in combination with capecitabine

The NALA trial, an open-label, multicenter, randomized trial, compared the efficacy for neratinib to lapatinib for the treatment of metastatic HER2 positive breast cancer in 621 patients who had previously received ≥ 2 anti-HER2 based regimens in the metastatic setting.[251] Included patients were randomized 1:1 to neratinib 240 mg orally once daily on days 1 through 21 and oral capecitabine 750 mg/m^2 twice daily on days 1 through 14 of a 21-day cycle or lapatinib 1,250 mg orally once daily on days 1 through 21 and oral capecitabine 1,000 mg/m^2 twice daily on days 1 through 14 of a 21-day cycle until disease progression or unacceptable toxicity. At baseline, 59% were HR-positive and 81% had visceral disease. Notably, patients with asymptomatic or stable brain metastases were included. ORR and median duration of response, respectively, occurred in 32.8% (95% CI, 27.1 to 38.9) and at 8.5 months (95% CI, 5.6 to 11.2) in those assigned to neratinib compared to 26.7% (95% CI, 21.5 to 32.4) and 5.6 months (95% CI, 4.2 to 6.4) in those assigned lapatinib. The median duration of PFS was 5.6 months (95% CI, 4.9 to 6.9) in those assigned to neratinib compared to 5.5 months (95% CI, 4.3 to 5.6) in those assigned to lapatinib (HR, 0.76; 95% CI, 0.63 to 0.93; p=0.0059). Median OS was 21 months (95% CI, 17.7 to 23.8) in those assigned to neratinib compared to 18.7 months (95% CI, 15.5 to 21.2) in those assigned lapatinib (HR, 0.88; 95% CI, 0.72 to 1.07; p=not significant [NS]).

Ductal Carcinoma in Situ (DCIS)

tamoxifen versus placebo

The National Surgical Bowel and Breast Project (NSABP) B-24 trial was a double-blind, controlled trial that randomized women diagnosed with DCIS to tamoxifen or placebo after standard therapy of lumpectomy and local radiation. The tamoxifen arm demonstrated a 37% reduction in relative risk of local recurrence and a decrease in contralateral breast cancer of comparable magnitude.[252] This trial was undertaken at a time before the relationship between ER positive tumors and tamoxifen was fully understood and before it was considered standard of care to establish the hormone receptor status of DCIS. A recent retrospective review examined the relationship of the ER hormone status and patient

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outcome.[253] Information on ER/PR status was available for 732 women enrolled in the NSABP B-24 trial, representing 41% of the original study population. In the patients with available data, ER was positive in 76% of patients. Patients with ER-positive DCIS treated with tamoxifen (versus placebo) showed significant decreases in subsequent breast cancer at 10 years (HR, 0.49; p<0.001) and overall follow-up (HR, 0.6; p=0.003), which remained significant in multivariable analysis (overall HR, 0.64; p=0.003). No significant benefit was seen in ER-negative DCIS patients.

META-ANALYSES

Postoperative Tamoxifen for Ductal Carcinoma In Situ (DCIS)

Two randomized controlled trials including 3,375 women were analyzed as a Cochrane systemic review and meta-analysis examining the benefit of postoperative tamoxifen for DCIS.[254] Tamoxifen was given after surgery for DCIS to women regardless of ER status with or without adjuvant radiotherapy. Tamoxifen reduced the recurrence of ipsilateral DCIS (HR, 0.75; 95% CI, 0.61 to 0.92) and contralateral DCIS (RR, 0.5; 95% CI, 0.28 to 0.87). Contralateral invasive cancer was reduced (RR, 0.57; 95% CI, 0.39 to 0.83) and there was a trend towards decreased ipsilateral invasive cancer (HR, 0.79; 95% CI, 0.62 to 1.01). The number needed to treat (NNT) in order for tamoxifen to have a protective effect against all breast events was 15; however, there was no evidence of a difference in all-cause mortality (RR, 1.11; 95% CI, 0.89 to 1.39). There was a non-significant trend towards more endometrial cancer in the tamoxifen-treated patients. The review concluded that while tamoxifen after local excision for DCIS reduced the risk of recurrent DCIS, it did not reduce the risk of all-cause mortality.

Adjuvant Aromatase Inhibitors versus Tamoxifen

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis involving data from clinical trials that enrolled 31,920 postmenopausal women with ER-positive early breast cancer who received adjuvant therapy with either an AI or tamoxifen.[255] Duration of therapy with either an AI or tamoxifen was a total of 5 years regardless of which drug or combination of drugs the patient received during the 5 years. Primary outcomes examined were recurrence of breast cancer, breast cancer mortality, death without recurrence, and all-cause mortality. The authors concluded that AI reduces 10-year breast cancer mortality rates by approximately 15% compared with tamoxifen.

Adjuvant Therapy versus Extended Adjuvant Therapy

A meta-analysis comparing the efficacy of 5 years of adjuvant hormonal therapy (standard) with that of additional years of adjuvant hormonal therapy (extended) was conducted.[256] The aim of the meta-analysis was to determine whether a longer period of adjuvant hormonal therapy (with either tamoxifen or an AI) after at least 5 years of an initial course of endocrine treatment, was associated with a reduced risk of death and relapse. All randomized trials that compared a fixed duration (5 years) with an extended course of endocrine therapy (more than 5 years) in patients with early-stage breast cancer were reviewed. Primary outcome measures were OS, breast-cancer specific survival (BCSS), and relapse-free survival (RFS). Eight studies reporting on 29,138 patients were included in the meta-analysis. Of the 29,138 patients, 14,540 received tamoxifen for 5 years and 14,598 received extended endocrine therapy with either tamoxifen (n=21,554) or an AI (n=7,584). In the 6 trials where ER status was reported, OS was significantly longer for ER+ patients in the extended arm (OR, 0.89; 95% CI, 0.8 to 0.99; p=0.03). Data according to nodal status and menopausal status were not significantly different in the experimental and control arms. Data were similar according to type of agent. In ER-positive

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populations, BCSS was significantly better with extended hormonal therapy compared to 5 years of tamoxifen (OR, 0.78; 95% CI, 0.69 to 0.9; p=0.0003). The result for BCSS was significant for tamoxifen but not for AI studies. RFS was increased with extended hormonal therapy (OR, 0.79; 95% CI, 0.68 to 0.92; p=0.002). Results of RFS were similar for tamoxifen or an AI.

Another meta-analysis examining the benefits of extended adjuvant therapy involved 11 randomized, controlled trials involving 29,000 patients.[257] The findings of this meta-analysis showed no OS advantage from all-cause mortality. However, the extended adjuvant therapy was associated with improvement in breast cancer-specific survival, disease free survival, disease recurrence and contralateral breast recurrence. The improvements in DFS or disease recurrence were not shown in studies that compared 5 years of tamoxifen with extended tamoxifen therapy. Subgroup analysis suggested that extended treatment conferred more benefit for patients with positive lymph nodes.

SUMMARY

All invasive breast cancer tumors are analyzed to determine the hormone receptor (HR) status and the human epidermal growth factor receptor 2 (HER2) status to drive appropriate pharmacologic interventions. All patients with HR-positive breast cancer who require adjuvant therapy should be offered endocrine therapy regardless of age, menopausal status, or HER2 status. Tamoxifen was the first endocrine therapy to have proven benefit and was originally given for a duration of 5 years to decrease the risk of recurrence, decrease the risk of contralateral breast cancer, decrease the risk of breast-cancer specific mortality, and improve distant disease-free survival and overall survival. Aromatase inhibitors (AIs), including anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin), now play an important role in the management of HR-positive breast cancer as well. AIs were originally only utilized in postmenopausal women; however, more recent information regarding the use of AI therapy in conjunction with ovarian suppression for premenopausal women has changed that paradigm. Guidelines indicate there are no substantial differences between the 3 AIs in terms of efficacy outcomes. The National Comprehensive Cancer Network (NCCN) guidelines state the optimal duration of adjuvant AI therapy is uncertain and provide multiple options for either an AI alone as adjuvant therapy or a combination of an AI plus tamoxifen for lengths of time varying from 5 to 10 years of total therapy. The American Society of Clinical Oncology (ASCO) guidelines regarding adjuvant endocrine therapy for HR-positive breast cancer recommend women with node-positive disease receive extended adjuvant therapy, including an AI for up to a total of 10 years. For patients with HER2-positive early breast cancer, guidelines now recommend consideration of the use of extended adjuvant therapy with neratinib (Nerlynx) following trastuzumab (Herceptin) in patients with early stage HER2-positive breast cancer, particularly in those patients with a perceived high risk of recurrence. The guidelines also now outline a role for adjuvant capecitabine in patients with HER2-negative disease who are found to have invasive residual disease at the time of surgery following preoperative anthracycline/taxane-based chemotherapy. The ASCO guidelines recommend this be offered preferentially to the subgroup of patients with both HR-negative and HER2-negative, or triple negative, disease while the NCCN guidelines limit the role of adjuvant capecitabine to patients with triple negative breast cancer with residual invasive cancer following standard neoadjuvant chemotherapy. For the treatment of HR-positive, HER2-negative advanced breast cancer, the combination of a cyclin-dependent kinase (CDK) 4/6 inhibitor (abemaciclib [Verzenio], palbociclib [Ibrance], ribociclib [Kisqali]) with an AI is recommended for first-line therapy in postmenopausal

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women or men or premenopausal women receiving ovarian ablation or suppression. Fulvestrant, with or without an AI, and fulvestrant plus a CDK4/6 inhibitor are also options in this setting.

The addition of the CDK4/6 inhibitors has significantly changed the management of HR-positive, HER2-negative advanced or metastatic breast cancer, and these drugs are now considered to be part of the standard of care for the majority of patients.

For advanced breast cancer that is HER2-positive, lapatinib (Tykerb) is approved in combination with capecitabine or in combination with letrozole.

Recently, additional targeted therapies beyond endocrine-directed and HER2-directed have been FDA approved for use in advanced breast cancer. In 2018, the FDA approved talazoparib (Talzenna) for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (*BRCA*)-mutated (*gBRCAm*) HER2-negative locally advanced or metastatic breast cancer. Talazoparib is a poly ADP-ribose polymerase (PARP) inhibitor and has been incorporated into the NCCN breast cancer guidelines as a preferred chemotherapy regimen for patients with *gBRCAm*, HER2-negative, recurrent or metastatic disease as a category 1 recommendation. In 2019, the FDA approved alpelisib (Piqray) in combination with fulvestrant for the treatment of men and postmenopausal women with HR-positive, HER2-negative, *PIK3CA*-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen, and it has been included in the NCCN breast cancer guidelines in combination with fulvestrant as a preferred regimen for patients with *PIK3CA*-mutated tumors with a category 1 recommendation.

Pharmacotherapy aimed at actionable targets of many breast cancers, including the estrogen receptor, progesterone receptor, HER2, and most recently BRCA and PIK3CA, have improved treatment responses and long-term outcomes for many women diagnosed with breast cancer. Continued research is needed to clarify the optimal choice or sequence of agents, as well as the optimal duration of therapy with these agents in the adjuvant setting.

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