Oncology Oral, Breast Cancer
Therapeutic Class Review (TCR)

October 1, 2016

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## FDA-APPROVED INDICATIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>FDA-Approved Indications</th>
</tr>
</thead>
</table>
| anastrozole (Arimidex®)¹ | AstraZeneca, generic | ▪ Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer  
▪ First-line treatment of postmenopausal women with hormone receptor 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 negative disease and patients who did not respond to previous tamoxifen therapy rarely respond to anastrozole (Arimidex) |
| capecitabine (Xeloda®)² | Genentech, generic | ▪ 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 | generic | ▪ Lymphomas: Hodgkin’s disease, lymphocytic lymphoma, mixed-cell type 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®)³ | Pfizer, generic | ▪ Adjuvant treatment of postmenopausal women with estrogen-receptor 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 |
| fulvestrant (Faslodex®)⁴ | AstraZeneca | ▪ Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following antiestrogen therapy  
▪ Treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy |
| lapatinib (Tykerb®)⁵ | Novartis | ▪ In combination with capecitabine (Xeloda), for the treatment of patients with advanced or metastatic breast cancer whose tumors over express human epidermal growth factor receptor 2 (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† |
### FDA-Approved Indications (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>FDA-Approved Indications</th>
</tr>
</thead>
</table>
| letrozole (Femara®)<sup>6</sup> | Novartis, generic | - Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer  
- Extended adjuvant treatment of early breast cancer in postmenopausal women, who have received 5 years of adjuvant tamoxifen therapy  
- First-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer; treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy |
| palbociclib (Ibrance®)<sup>7</sup> | Pfizer | - Treatment of estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:  
  - letrozole (Femara) as initial endocrine-based therapy for postmenopausal women<sup>8</sup> OR  
  - fulvestrant (Faslodex) in women with disease progression following endocrine therapy |
| tamoxifen citrate<sup>8</sup> | generic | - Adjuvant therapy for breast cancer in postmenopausal 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 |
| toremifene (Fareston®)<sup>9</sup> | ProStraken | - Treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors                                                                                                                                 |

* 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  
† 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 has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.  
§ The approval for palbociclib (Ibrance) was based on progression-free survival (PFS) data as part of an accelerated approval process. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
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.\textsuperscript{10} It is estimated that there will be 249,260 new cases of breast cancer diagnosed in the United States (U.S.) in 2016 and there will be an estimated 40,890 deaths.\textsuperscript{11} A woman in the U.S. has a 1 in 8 lifetime risk of developing breast cancer.\textsuperscript{12} Death rates from breast cancer have steadily decreased in women since 1989 due to improvements in both early detection and treatment.\textsuperscript{13} Localized disease is considered to be a curable disease while metastatic disease is almost never curable. The majority of patients who present with localized disease will experience long-term disease free survival; however, prognosis for patients presenting with metastatic disease is much poorer with a 5-year survival rate of only 24%.\textsuperscript{14} It is postulated that breast cancer in postmenopausal women is substantively different than breast cancer of premenopausal women. Breast cancer is predominantly a disease of the elderly. When it occurs in younger patients, the course of the disease is usually more aggressive.\textsuperscript{15}

All breast cancer tumors are analyzed for the tumor’s hormone receptor status as well as 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 and/or targeted therapy and also plays a role in determining prognosis.

About two thirds of patients with primary or metastatic breast cancer have hormone receptor-positive (HR+) tumors. Hormonal therapies to treat breast cancer can be beneficial in both the adjuvant as well as the metastatic setting of HR+ disease. In the treatment of cancer, adjuvant therapy is given after definitive surgery and/or radiation therapy for the purpose of lowering the risk of disease recurrence. Therapy for metastatic cancer is given either to palliate symptoms and/or prolong survival in the patient with incurable disease. The pharmacologic goals of endocrine therapy for breast cancer are either to decrease circulating levels of estrogen and/or prevent the effects of estrogen at the breast cancer cell. The menopausal status of the patient, as well as the hormone receptor status of the tumor, are important considerations in the therapeutic use of these agents. The prevalence and frequency of hormone receptor positive tumors are higher in postmenopausal patients as compared to premenopausal patients. Hormone receptor positivity is associated with a superior response to hormonal therapy. About 70% to 80% 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.

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 Invasive Breast Cancer outlines the treatment of breast cancer in the adjuvant setting as well as treatment for recurrent, potentially curable, disease and treatment in the setting of metastatic disease.\textsuperscript{16}

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.
For adjuvant therapy, an ASCO guideline published in 2016 provides guidance on assessing the need for systemic therapy in early-stage operable breast cancer based upon known patient and disease risk factors as there are some patients for whom chemotherapy may not be required. For patients who do require adjuvant therapy, there are ASCO clinical practice guidelines. These are regarding adjuvant treatment with endocrine therapy in hormone receptor (HR) positive disease, adjuvant chemotherapy for HER2-negative disease and adjuvant targeted therapy for HER2-positive disease, and a guideline addressing the use of biomarkers to guide decisions on adjuvant systemic therapy in patients with early-stage invasive breast cancer. In 2016, the guideline addressing adjuvant treatment with endocrine therapy in HR-positive disease was updated to address the role of ovarian suppression in premenopausal women.

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, the use of chemotherapy and targeted therapy for women with HER2-negative (or unknown) advanced breast cancer, systemic therapy for patients with advanced HER2-positive breast cancer, including those patients with brain metastases, and a guideline addressing the use of biomarkers to guide decisions on systemic therapy of metastatic breast cancer. There is also an ASCO practice guideline addressing the use of pharmacologic interventions for breast cancer risk reduction.

In the adjuvant setting, according to the NCCN guidelines, endocrine therapy should be considered for all patients with HR-positive disease regardless of menopausal status, age, or HER2 status of the tumor. The strength of the recommendation regarding adjuvant endocrine therapy varies based on the patient’s prognosis. For patients who have HR-positive, node-positive disease, adjuvant endocrine therapy is a category 1 recommendation while for patients with small tumors (< 0.5 cm) without other poor prognostic indicators; consideration of the use of adjuvant endocrine therapy is a category 2B recommendation. Premenopausal women with HR-positive disease should receive tamoxifen for 5 years with or without ovarian ablation (now category 1 instead of 2B). The use of an aromatase inhibitor for 5 years plus ovarian suppression may be considered as an alternative option in premenopausal women (category 1). The recent results of the Suppression of Ovarian Function Trial (SOFT) and the TEXT (Tamoxifen and Exemestane Trial) 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. 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. Women who subsequently became postmenopausal after the initial 5 years of adjuvant endocrine therapy may be treated with an aromatase inhibitor for an additional 5 years (category 1) or may continue tamoxifen for an additional 5 years to complete 10 years of adjuvant therapy. The American Society of Clinical Oncology (ASCO) also recently updated their guideline on the use of adjuvant endocrine therapy for women with HR-positive breast cancer to address data regarding ovarian suppression for premenopausal women. This update to the ASCO guideline is more specific than the NCCN guideline with regard to recommendations on which premenopausal patients with HR-positive breast cancer should receive ovarian suppression. Specifically, the ASCO guidelines state that women with stage 2 or 3 breast cancers who would ordinarily receive adjuvant chemotherapy should receive ovarian suppression with endocrine therapy while women with stage 1 breast cancers without a high risk of recurrence who do not warrant treatment with chemotherapy should not receive ovarian suppression, nor should women with node-
negative cancers of 1 cm or less. The ASCO guideline also states that ovarian suppression in premenopausal women is appropriate with either tamoxifen or an aromatase inhibitor (AI).

According to the NCCN guidelines, postmenopausal women should receive initial adjuvant therapy with either an AI for 5 years (category 1) or an AI for 2 to 3 years followed by tamoxifen to complete 5 years of endocrine therapy (category 1). Other options include tamoxifen for 2 to 3 years followed by up to 5 years of an AI (category 2B), tamoxifen for 4.5 to 6 years followed by an AI for 5 years (category 1), or continuation of tamoxifen for an additional 5 years to complete 10 years of therapy. The NCCN guidelines state that the 3 selective AIs (anastrozole, letrozole, exemestane) 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 aromatase inhibitors in adjuvant setting is uncertain. For patients who will receive adjuvant chemotherapy, endocrine therapy should be initiated after the completion of chemotherapy. Postmenopausal women intolerant of 1 AI may consider a different AI or tamoxifen. All of these regimens have been shown to increase overall survival and distant disease-free survival, reduce breast cancer-specific mortality, decrease the risk of recurrence, and decrease the risk of contralateral breast cancer. The ASCO guidelines for adjuvant treatment of postmenopausal women parallel the NCCN guidelines in this setting.

There is no established role for capecitabine (Xeloda) or lapatinib (Tykerb) in the adjuvant setting while 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 under “other regimens” in this setting rather than as a preferred regimen. Cyclophosphamide has a variety of other indications but this review will focus only on its role in the management of breast cancer.

Advanced breast cancer is defined as either locally advanced breast cancer that is unresectable or distant metastatic disease. According to NCCN guidelines, in the setting of HR-positive advanced breast cancer, regardless of HER2 status, menopausal status, or whether or not the patient has received prior endocrine therapy within 1 year, hormonal therapy is recommended as first-line. Hormone therapy is used sequentially until disease progression or unacceptable toxicity is reached with each hormonal regimen until a maximum of 3 sequential endocrine regimens have been utilized, at which time the patient should be considered for systemic chemotherapy. The exception to this would be patients with symptomatic visceral disease who should be considered for chemotherapy instead of endocrine therapy. Options for endocrine therapy-based regimens include monotherapy with tamoxifen, toremifene, fulvestrant, or an AI in addition to rarely utilized options such as progestin, estrogen, or androgen-based regimens, including megestrol or fluoxymesterone. There are now 3 options for combination endocrine-based regimens. These include the addition of everolimus (Afinitor) to exemestane or the addition of palbociclib to either letrozole or fulvestrant. Everolimus (Afinitor), a mammalian target of rapamycin (mTOR) inhibitor, may be useful in certain patients with hormone refractory disease, including those who have experienced progressive disease either while taking tamoxifen or an AI or who have had disease progression within 12 months of taking an aromatase inhibitor. Palbociclib (Ibrance) was first approved in 2015 for use in combination with letrozole for first-line treatment of advanced ER-positive, HER2-negative breast cancer. In 2016, the combination of palbociclib with fulvestrant was approved for postmenopausal women (or premenopausal women receiving ovarian suppression) with HR-positive and HER2-negative metastatic breast cancer that has progressed on prior endocrine therapy. This regimen of palbociclib plus fulvestrant has been given a category 1 NCCN recommendation for use in that setting.
The ASCO guideline regarding endocrine therapy for metastatic breast cancer states that first-line endocrine therapy should include an AI in postmenopausal women with HR-positive metastatic breast cancer. Combination therapy with a nonsteroidal AI plus fulvestrant may be offered to patients without prior exposure to adjuvant endocrine therapy in the first-line setting. The addition of HER2-targeted therapy to first-line AIs is indicated in patients who have HER2-positive breast cancer. In the second-line setting, sequential hormone therapy is indicated in patients with endocrine-responsive disease and no specific order of agents is recommended. With regard to the role of palbociclib, the ASCO guidelines state that a nonsteroidal AI plus palbociclib may be offered to patients in this setting who are treatment-naïve as this regimen has been shown to improve progression-free survival (PFS) but not overall survival (OS) compared to letrozole monotherapy. The combination of fulvestrant plus palbociclib is recommended in patients who experienced progression during prior treatment with AIs (with or without 1 prior line of chemotherapy) because PFS was improved compared to fulvestrant alone. Palbociclib should not be offered to patients with prior exposure to cyclin-dependent kinase 4/6 inhibitors.

Once a patient with advanced, hormone-receptor positive breast cancer has had no response or progressive disease with 3 sequential hormonal regimens, the NCCN guidelines recommend either systemic chemotherapy or palliative care depending on the sites of disease as well as the patient’s performance status. Capecitabine is considered 1 of many possible preferred single agents for the systemic treatment of recurrent or metastatic breast cancer. Capecitabine may also be used in combination with intravenous docetaxel (Taxotere) in this setting. Capecitabine plus trastuzumab (Herceptin) or lapatinib may also be used for trastuzumab-exposed HER2-positive recurrent or metastatic disease.

The 2014 ASCO clinical practice guideline for the systemic treatment of advanced HER2-positive breast cancer recommends the use of lapatinib in the third-line setting after failure of other HER2-targeted therapies including trastuzumab (Herceptin®), pertuzumab (Perjeta®), and ado-trastuzumab emtansine (Kadcyla®).

Oral cyclophosphamide may be utilized either as a single agent (not preferred) or as part of a regimen involving doxorubicin and fluorouracil (CAF) or methotrexate plus fluorouracil (CMF) for patients with recurrent or metastatic breast cancer.

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 2013 ASCO clinical practice guidelines on pharmacologic interventions for breast cancer risk reduction state that the use of tamoxifen (20 mg per day orally for 5 years) should be discussed as an option to reduce the risk of developing breast cancer, specifically ER+ breast cancer, in women ≥ 35 years of age who are at increased risk of developing breast cancer or with lobular carcinoma in situ (LCIS). The NCCN Breast Cancer Risk Reduction guidelines state that the risk/benefit ratio for tamoxifen use in premenopausal women at increased risk for breast cancer (≥ 1.7% 5-year risk for breast cancer as determined by the modified Gail model or who have had LCIS) is relatively favorable (category 1). 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. Neither
tamoxifen nor raloxifene should be used in women with history of deep vein thrombosis (DVT), pulmonary embolus (PE), or transient ischemic attack (TIA) or during prolonged immobilization. 44

Male breast carcinoma is a rare disease and represents only 0.6% of all breast carcinomas and less than 1% of all malignancies in men. Because of the rarity of breast carcinoma in men, limited information is available regarding this disease. No randomized trials have been performed to date and most published series have been retrospective chart reviews. Male breast cancer is associated with a higher percentage of ER positivity compared to female breast cancer. A population based study of 2,537 men with breast cancer found that greater than 90% of all male breast cancer tumors were ER positive. This finding is the basis for the use of tamoxifen as the standard adjuvant endocrine therapy in the treatment of male breast cancer. 45

FDA-approved breast cancer indications are the focus of this Therapeutic Class Review.

PHARMACOLOGY

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. 46 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. 47 There are 3 aromatase inhibitors (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. 48

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.
<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase Inhibitors</td>
<td>anastrozole (Arimidex) – nonsteroidal</td>
</tr>
<tr>
<td></td>
<td>letrozole (Femara) – nonsteroidal</td>
</tr>
<tr>
<td></td>
<td>exemestane (Aromasin) – steroidal</td>
</tr>
<tr>
<td>Selective Estrogen Receptor Down regulators (SERD)</td>
<td>fulvestrant (Faslodex)</td>
</tr>
<tr>
<td>Selective Estrogen Receptor Modulators (SERM)</td>
<td>tamoxifen</td>
</tr>
<tr>
<td></td>
<td>toremifene (Fareston)</td>
</tr>
</tbody>
</table>

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.49

Palbociclib (Ibrance) is a small molecule inhibitor of cyclin dependent kinases 4 and 6 (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.

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.
### PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life (hrs)</th>
<th>Protein Binding (percent)</th>
<th>Metabolism</th>
<th>Elimination (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>anastrozole (Arimidex)</td>
<td>50</td>
<td>40</td>
<td>Metabolism of anastrozole occurs by N-demethylation, hydroxylation and glucuronidation</td>
<td>Urine: 10</td>
</tr>
<tr>
<td>capecitabine (Xeloda)</td>
<td>0.75</td>
<td>&lt; 60</td>
<td>Enzymatically metabolized to 5-fluorouracil which is then hydrolyzed</td>
<td>Urine: 95.5 Feces: 2.6</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>3-12</td>
<td>20</td>
<td>CYP 2A6, 2B6, 3A4, 3A5, 2C9, 2C18, and 2C19</td>
<td>Urine: 10-20 (unchanged) Bile: 4</td>
</tr>
<tr>
<td>exemestane (Aromasin)</td>
<td>24</td>
<td>90</td>
<td>CYP3A4 to inactive metabolites</td>
<td>Urine: ≈ 50 Feces: ≈ 50</td>
</tr>
<tr>
<td>fulvestrant (Faslodex)</td>
<td>960</td>
<td>99</td>
<td>Extensive hepatic metabolism*</td>
<td>Feces: 90</td>
</tr>
<tr>
<td>lapatinib (Tykerb)</td>
<td>24</td>
<td>&gt; 99</td>
<td>CYP3A4, 3A5: major CYP2C19, 2C8: minor</td>
<td>Feces: 27 (parent compound) Urine: &lt; 2</td>
</tr>
<tr>
<td>letrozole (Femara)</td>
<td>48</td>
<td>Weakly</td>
<td>CYP3A4,CYP2A6 to inactive metabolites†</td>
<td>Urine: 90</td>
</tr>
<tr>
<td>palbociclib (Ibrance)</td>
<td>29</td>
<td>85</td>
<td>Hepatic metabolism involving primarily oxidation and sulfonation</td>
<td>Urine: 17.5 Feces: 74.1</td>
</tr>
<tr>
<td>tamoxifen</td>
<td>120-168</td>
<td>-</td>
<td>CYP3A4/5,CYP2C9,CYP2D6‡; endoxifen, catalyzed by CYP2D6 is an active metabolite with increased potency in suppressing estrogen dependent cell proliferation compared to tamoxifen§</td>
<td>Feces: primary route</td>
</tr>
<tr>
<td>toremifene (Fareston)</td>
<td>120</td>
<td>99.5</td>
<td>CYP3A4 to weakly active metabolite</td>
<td>Primary elimination route is feces</td>
</tr>
</tbody>
</table>

* 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.
‡ 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.60
CONTRAINDICATIONS/WARNINGS

Contraindications

All 3 aromatase inhibitors, anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara), are contraindicated in women who are or may become pregnant. They are also contraindicated in any patients who have shown a hypersensitivity reaction to the drug or any of its excipients.

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).

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.

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.

Boxed Warnings

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.

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 stroke 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.
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.

**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. Supplementation with vitamin D may be warranted in some patients. 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.

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 3.2% 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 increase 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.

Aromatase inhibitors are Pregnancy Category X; pregnancy is an absolute contraindication.

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.

Treatment with palbociclib (Ibrance) may result in neutropenia and complete blood counts should be obtained prior to starting palbociclib therapy and at the beginning of each cycle, as well as on day 14 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. Pulmonary embolism was reported in both studies involving the combination of letrozole plus palbociclib, as well as the combination of fulvestrant plus palbociclib. There were no cases of pulmonary embolism in patients treated with letrozole alone or fulvestrant plus placebo in those trials. 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.
Lapatinib 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 by 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. 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 beyond 24 hours, 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, or toxic epidermal necrolysis (TEN), are suspected, therapy with lapatinib should be discontinued.

Tamoxifen is classified as Pregnancy Category D. 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. 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.

Both toremifene 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. 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 Stevens-Johnson syndrome and TEN, can occur. Hand and foot syndrome (palmar-plantar erythrodysesthesia) may occur with capecitabine. Hyperbilirubinemia and hematologic toxicities may also occur.
Cyclophosphamide can cause myelosuppression, including 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 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. 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**

**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. Use of strong CYP2D6 inhibitors (e.g., bupropion, cinacalcet, fluoxetine, paroxetine, quinidine) should be avoided whenever possible.

**CYP3A4**

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 concentration of these agents. Co-administration of itraconazole with palbociclib increased the plasma exposure of palbociclib in healthy subjects by 87%. Concomitant use of toremifene 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 co-administration of palbociclib with a strong CYP3A inhibitor cannot be avoided, reduce the dose of palbociclib. Grapefruit juice may also increase plasma concentrations of toremifene and palbociclib and should therefore be avoided.
Exemestane (Aromasin) peak plasma concentrations, as well as overall area under the curve (AUC), were decreased by 41% and 54% respectively when administered with a CYP3A4 inducer. Dose modification to a larger dose is recommended for patients who are also receiving a potent CYP3A4 inducer (e.g., carbamazepine, dexamethasone, phenytoin, phenobarbital, rifampin).

Co-administration 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. Co-administration 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, pimozone, 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.

**CYP2C9**

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.

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

**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.

**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**

Co-administration of tamoxifen and anastrozole (Arimidex) has been shown to reduce anastrozole serum levels. The same is true of the co-administration 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.

Co-administration of capecitabine and leucovorin results in elevated levels of 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 less than 30 mL/minute.

Following co-administration of lapatinib and digoxin (P-glycoprotein substrate), systemic 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.

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

Co-administration 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.
## ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hot Flashes</th>
<th>Arthralgias</th>
<th>Fatigue</th>
<th>Vaginal Bleeding</th>
<th>Nausea or Vomiting</th>
<th>Bone Fractures</th>
<th>CV Disease</th>
<th>VTE</th>
<th>Stomatitis</th>
<th>Elevated Cholesterol</th>
<th>Depression</th>
<th>Diarrhea</th>
<th>Rash</th>
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</thead>
<tbody>
<tr>
<td>anastrozole (Arimidex)</td>
<td>36</td>
<td>15</td>
<td>19</td>
<td>5</td>
<td>11</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>nr</td>
<td>9</td>
<td>13</td>
<td>8</td>
<td>8</td>
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<tr>
<td>capecitabine (Xeloda) monotherapy in Stage IV breast cancer</td>
<td>0.1</td>
<td>9</td>
<td>41</td>
<td>nr</td>
<td>53</td>
<td>nr</td>
<td>nr</td>
<td>0.2</td>
<td>24</td>
<td>nr</td>
<td>0.1</td>
<td>57</td>
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<tr>
<td>exemestane (Aromasin)</td>
<td>33 (25)</td>
<td>29 (29)</td>
<td>11 (19)</td>
<td>nr</td>
<td>12 (16)</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>nr</td>
<td>nr</td>
<td>10 (7)</td>
<td>10 (1)</td>
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</tr>
<tr>
<td>fulvestrant (Faslodex)</td>
<td>7</td>
<td>8</td>
<td>7.5</td>
<td>&lt; 1</td>
<td>10</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
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<td>nr</td>
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<td>nr</td>
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<td>9 (8)</td>
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<td>15 (10)</td>
<td>3</td>
<td>nr</td>
<td>52</td>
<td>5</td>
<td>5</td>
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<tr>
<td>palbociclib (Ibrance) + fulvestrant (fulvestrant + placebo)</td>
<td>nr</td>
<td>nr</td>
<td>41 (29)</td>
<td>nr</td>
<td>34 (28)</td>
<td>nr</td>
<td>nr</td>
<td>1 (nr)</td>
<td>28 (13)</td>
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<tr>
<td>palbociclib (Ibrance) + letrozole (letrozole alone)</td>
<td>nr</td>
<td>nr</td>
<td>41 (23)</td>
<td>nr</td>
<td>25 (13)</td>
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<td>4 (nr)</td>
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<td>nr</td>
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</table>

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.
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.

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.

Cases of hepatitis, including cholestatic hepatitis, have been observed in clinical trials with exemestane and reported through post-marketing surveillance.

The most frequently reported adverse effect with fulvestrant (Faslodex) is injection site pain (12%).

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.

The most common adverse reactions of any grade reported in the palbociclib (Ibrance) plus letrozole study arm were neutropenia (75%), leukopenia (43%), fatigue (41%), anemia (35%), upper respiratory infection (31%), nausea (25%), stomatitis (25%), alopecia (22%), diarrhea (21%), thrombocytopenia (17%), decreased appetite (16%), vomiting (15%), asthenia (13%), peripheral neuropathy (13%), and epistaxis (11%). The most frequently reported adverse reactions that were graded as serious adverse reactions were pulmonary embolism (4%) and diarrhea (2%). An overall increase 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.

**SPECIAL POPULATIONS**

**Pregnancy**

The 3 aromatase inhibitors, anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara), are contraindicated in pregnancy and are classified as Pregnancy Category X.

Lapatinib (Tykerb), tamoxifen, toremifene (Fareston), fulvestrant (Faslodex), cyclophosphamide, and capecitabine (Xeloda) are classified as Pregnancy Category D. Females of reproductive potential should be advised to use effective contraception during treatment with fulvestrant and for 1 year after the last dose.

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 infertility may be compromised by treatment with palbociclib.
**Pediatrics**

There are no safety or efficacy data for exemestane, lapatinib, letrozole, palbociclib, 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 year long 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 less than 10 years old 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.

**Geriatrics**

Many of the endocrine breast cancer therapy trials enrolled a significant number of women over the age of 65 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.

No overall differences in safety or effectiveness were observed in patients over the age of 65 who received palbociclib in the clinical trials; however, greater sensitivity in some older patients cannot be ruled out.

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

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

Mild (CrCl, 60 to 90 mL/min) and moderate (CrCl, 30 to < 60 mL/min) renal impairment had no effect on the exposure of palbociclib. The pharmacokinetics of palbociclib in cases of severe renal impairment has not been studied.

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.

Hepatic Impairment

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 lapatinib dose from 1,250 mg PO daily to 750 mg PO daily (when given with capecitabine) and from 1,500 mg PO daily to 1,000 mg PO 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. Letrozole has not been studied in patients with severe hepatic impairment but, because letrozole is eliminated almost exclusively by hepatic metabolism, patients with severe hepatic impairment should be dosed with caution.

Mild hepatic impairment (total bilirubin ≤ ULN and AST < ULN or total bilirubin > 1 to 1.5 times the ULN and any AST) had no effect on exposure to palbociclib. The pharmacokinetics of palbociclib has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 times the ULN and any AST).
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.

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.
### DOSAGES

<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Adjuvant Therapy</strong></th>
<th><strong>Advanced or Metastatic Disease</strong></th>
<th><strong>DCIS</strong></th>
<th><strong>Prophylaxis</strong></th>
<th><strong>Duration</strong></th>
<th><strong>Other Indications</strong></th>
<th><strong>Administration</strong></th>
<th><strong>Dosage Forms</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>anastrozole (Arimidex)</td>
<td>1 mg once daily</td>
<td>1 mg once daily</td>
<td>-</td>
<td>-</td>
<td>For adjuvant therapy; optimal duration is unknown; no data to support more than 5 years of therapy For advanced disease, continue until tumor progression</td>
<td>-</td>
<td>Same time each day with or without food</td>
<td>1 mg tablet</td>
</tr>
<tr>
<td>capecitabine (Xeloda)</td>
<td>-</td>
<td>Monotherapy or in combination with docetaxel: 1,250 mg/m² twice daily for 2 weeks followed by a 1 week rest period for a 3 week cycle</td>
<td>-</td>
<td>-</td>
<td>Adjuvant for Dukes C CRC: 6 months (8 total 3 week cycles); for advanced breast cancer until disease progression or unacceptable toxicity Monotherapy for metastatic colorectal cancer (CRC) or adjuvant monotherapy for CRC: 1,250 mg/m² twice daily for 2 weeks followed by a 1 week rest period for a 3 week cycle</td>
<td>Monotherapy for metastatic colorectal cancer (CRC) or adjuvant monotherapy for CRC: 1,250 mg/m² twice daily for 2 weeks followed by a 1 week rest period for a 3 week cycle</td>
<td>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)</td>
<td>150, 500 mg tablets</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>100 mg/m² by mouth days 1 through 14 of a 28-day cycle when given as part of the CMF</td>
<td>100 mg/m² by mouth days 1 through 14 of a 28-day cycle when given as part of either the CMF or the CAF regimen; OR 50 mg orally daily on days 1 through 21 every 28 days as a single agent</td>
<td>-</td>
<td>-</td>
<td>For adjuvant therapy with CMF: given for 6 cycles For metastatic disease: given until disease progression or unacceptable toxicity</td>
<td>Nephrotic syndrome: 2 mg/kg daily for 8 to 12 weeks (maximum cumulative dose 168 mg/kg)</td>
<td>Capsules should not be opened, chewed or crushed</td>
<td>25, 50 mg capsules 25, 50 mg tablets</td>
</tr>
</tbody>
</table>
### Dosages (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adjuvant Therapy</th>
<th>Advanced or Metastatic Disease</th>
<th>DCIS</th>
<th>Prophylaxis</th>
<th>Duration</th>
<th>Administration</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>exemestane* (Aromasin)</td>
<td>25 mg once daily</td>
<td>25 mg once daily</td>
<td>-</td>
<td>-</td>
<td>Adjuvant therapy: 5 years OR Complete a total of 5 consecutive years after 2 to 3 years of tamoxifen Advanced disease: until disease progression or unacceptable toxicity</td>
<td>Take after a meal</td>
<td>25 mg tablets</td>
</tr>
<tr>
<td>fulvestrant (Faslodex)</td>
<td>-</td>
<td>Monotherapy: 500 mg IM days 1, 15, and 29 and monthly thereafter Combination therapy with palbociclib: 500 mg IM on days 1, 15, and 29 and once monthly thereafter</td>
<td>-</td>
<td>-</td>
<td>Until disease progression or unacceptable toxicity</td>
<td>Deep IM injection into buttock (gluteal area) slowly (1 to 2 minutes per injection) as two 5 mL injections, 1 into each buttock</td>
<td>2 x 5 mL (50 mg/mL) syringes</td>
</tr>
<tr>
<td>lapatinib† (Tykerb)</td>
<td>-</td>
<td>HER2+: 1,250 mg once daily for days 1 through 21 when given in conjunction with capecitabine (Xeloda) HER2+, HR+: 1,500 mg once daily when given in conjunction with letrozole (Femara)</td>
<td>-</td>
<td>-</td>
<td>Until disease progression or unacceptable toxicity</td>
<td>Take at least 1 hour before or 1 hour after food</td>
<td>250 mg tablets</td>
</tr>
</tbody>
</table>
### Dosages (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adjuvant Therapy</th>
<th>Advanced or Metastatic Disease</th>
<th>DCIS</th>
<th>Prophylaxis</th>
<th>Duration</th>
<th>Administration</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>letrozole (Femara)</td>
<td>2.5 mg once daily</td>
<td>2.5 mg once daily</td>
<td>-</td>
<td>-</td>
<td>Adjuvant: optimal duration of treatment is unknown; no data to support use beyond 5 years Advanced: until tumor progression is evident or unacceptable toxicity</td>
<td>Can be taken without regard to food</td>
<td>2.5 mg tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In combination with palbociclib: 2.5 mg taken once daily throughout the 28-day cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>palbociclib (Ibrance)</td>
<td>-</td>
<td>For combination therapy with either letrozole or fulvestrant: 125 mg once daily for 21 consecutive days followed by 7 days off, to complete a 28-day cycle</td>
<td>-</td>
<td>-</td>
<td>Until disease progression or unacceptable toxicity</td>
<td>Take with food; capsules should be swallowed whole without chewing, crushing or opening them prior to swallowing; take in combination with letrozole 2.5 mg once daily given continuously throughout the 28-day cycle</td>
<td>75, 100, 125 mg capsules</td>
</tr>
<tr>
<td>tamoxifen</td>
<td>20-40 mg daily</td>
<td>20-40 mg daily</td>
<td>20 mg daily</td>
<td>20 mg daily</td>
<td>Adjuvant: 5 to 10 years or 2 to 6 years followed by 2 to 3 years of an AI DCIS &amp; prophylaxis: 5 years</td>
<td>There is no evidence that doses &gt; 20 mg/day are more effective; 10 mg twice daily is the most common dose used in clinical practice, doses greater than 20 mg/day should be given in divided doses (morning and evening)</td>
<td>10, 20 mg tablets 10 mg/5 mL solution</td>
</tr>
<tr>
<td>toremifene (Fareston)</td>
<td>-</td>
<td>60 mg once daily</td>
<td>-</td>
<td>-</td>
<td>Until disease progression</td>
<td>Without regard to food</td>
<td>60 mg tablet</td>
</tr>
</tbody>
</table>

* If exemestane (Aromasin) is administered with a potent CYP3A4 inducer, increase dose of exemestane to 50 mg once daily.
† Modify lapatinib (Tykerb) dose for cardiac and other toxicities, severe hepatic impairment, diarrhea, and CYP3A4 drug interactions.

See package insert of various medications for recommended dosing modifications based on specific toxicities.
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).115 The International Breast Cancer Intervention Study (IBIS-1), currently with 16 years of published follow up, 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.116 The Royal Marsden Tamoxifen Prevention Trial demonstrated a HR of 0.61 (95% CI, 0.43 to 0.86) at 20 years of follow up data.117 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.118 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.119
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 ≥35 years who were at an increased risk of developing breast cancer. Women were randomized to 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. 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
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.

anastrozole (Arimidex) 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. 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 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).

letrozole (Femara) 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 disease-free survival. In 2005 at a planned interim analysis, a significant disease-free survival 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 disease free survival (HR, 0.86; 95% CI, 0.78 to 0.96) and overall survival (HR, 0.87; 95% CI, 0.77 to
enced therapy arms 0.99). There were no statistically significant differences for any of the sequenced therapy arms compared to letrozole monotherapy.  

**exemestane (Aromasin) versus tamoxifen**

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 disease-free survival, as compared with continued tamoxifen therapy.  

Patients were enrolled to either exemestane 25 mg daily (n=2362) or tamoxifen 20 mg daily (n=2380) to complete 5 years of adjuvant endocrine therapy. The primary endpoint was disease-free survival, 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, 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 hazard ratio 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 disease-free survival of 4.7% (95% CI, 2.6 to 6.8) at 3 years after randomization. Overall survival was not significantly different in the 2 groups, with 93 deaths occurring in the exemestane group and 106 in the tamoxifen group.

**exemestane (Aromasin) with ovarian suppression versus tamoxifen with ovarian suppression-premenopausal status**

TEXT/SOFT: In 2 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. Ovarian suppression was achieved through the use of a gonadotropin-releasing hormone, oophorectomy, or ovarian irradiation. After a median follow up of 68 months, disease-free survival 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).

**Breast Cancer – HR-Positive, Extended Adjuvant Therapy**

**tamoxifen – duration of therapy**

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).  

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 were 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).

**Letrozole (Femara) 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 disease-free survival. 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 disease-free survival analysis, 92 occurred in women in the letrozole arm of the trial and 155 occurred in women in the placebo arm. The 4-year disease-free survival 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 hazard ratio 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 hazard ratio for recurrence at a distant site was also statistically significant (HR, 0.6; 95% CI, 0.43 to 0.84; p=0.002). Overall survival 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, overall survival was statistically significantly improved with letrozole (HR, 0.61; 95% CI, 0.38 to 0.98; p=0.04).126

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

**Tamoxifen**

Historical trials have compared the response and adverse effects of tamoxifen versus diethylstilbestrol (DES), medroxyprogesterone, fluoxymesterone, and aminoglutethimide.127,128,129,130 While response rates were similar, tamoxifen had the lowest toxicity profile of any of these agents.

**Anastrozole (Arimidex) 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 overall survival. There was a significant difference between anastrozole and tamoxifen groups with regard to clinical benefit (defined as complete response + partial response + 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.131
**letrozole (Femara) 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.132 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 objective tumor response rate (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 overall survival. 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.

**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 overall survival 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.133
**palbociclib (Ibrance) plus letrozole (Femara) versus letrozole (Femara) alone**

PALOMA-1/TRIO-18 was a phase 2, multicenter, open-label, randomized trial involving 165 patients (n = 84 for palbociclib plus letrozole, n = 81 for letrozole alone).\(^{134}\) Patients were required to have ER-positive, HER2-negative disease, and to have either locally recurrent, unresectable disease, or metastatic disease, and to have received no previous treatment for their advanced disease. Slightly more than half of all enrolled patients had received chemotherapy and/or hormonal therapy in the neoadjuvant or adjuvant setting; however, patients were excluded if they received letrozole treatment within 12 months before study entry. Patients were stratified by disease site (visceral, bone, or both), as well as disease-free interval (greater than or less than 12 months). Study treatment was continued until disease progression, unacceptable toxic effects, study withdrawal, or death. The primary endpoint was PFS. At a median follow-up of 29.6 months for the palbociclib plus letrozole group, there were 19 of 84 patients still receiving treatment, compared to 8 of 81 patients in the letrozole alone group. There were 41 PFS events in the letrozole/palbociclib group compared to 59 in the letrozole alone group. Median PFS was 20.2 months (95% CI, 13.8 to 27.5) for palbociclib plus letrozole group and 10.2 months (95% CI, 5.7 to 12.6) for the letrozole alone group (HR, 0.488; 95% CI, 0.319 to 0.748; \(p=0.0004\)). All 83 patients who received palbociclib plus letrozole had at least 1 adverse effect, compared to 65 out of 77 (84%) patients who received letrozole alone. The most common adverse events in the palbociclib plus letrozole group were neutropenia, leukopenia, and 1 patient in the palbociclib plus letrozole group were pulmonary embolism (3 patients), back pain (2 patients), and diarrhea (2 patients). More patients in the palbociclib plus letrozole group had dose interruptions because of adverse events compared to the letrozole alone group (33% versus 4%, respectively). There were no significant differences in pain severity or the effect of pain on daily activities between the 2 treatment groups.

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

All 3 AIs (anastrazole, 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 other antiestrogen therapy or to have relapsed during or after receiving antiestrogen therapy. In general, these agents have demonstrated at least comparable efficacy to megestrol acetate in key outcomes, such as time to progression or overall response.\(^{135,136,137}\)

**fulvestrant (Faslodex) versus anastrozole (Arimidex)**

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.\(^{138}\) 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 (Aromasin)**

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 aromatase inhibitors (anastrozole or letrozole).\textsuperscript{139} 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 during treatment with a nonsteroidal aromatase inhibitor. Patients were categorized as AI sensitive if the investigator determined that the patient had a complete response (CR), partial response (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 hazard ratio 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.

**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 2 agents.\textsuperscript{140}

**exemestane (Aromasin) plus everolimus (Afinitor) versus exemestane (Aromasin) 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.\textsuperscript{141} Eligible patients had either experienced a recurrence or progression of disease while receiving therapy with a nonsteroidal aromatase inhibitor 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.142

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

PALOMA3 was a phase 3 trial involving 152 patients with advanced HR-positive, HER2-negative breast cancer that had relapsed or progressed during prior endocrine therapy.143 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, 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.

**Breast Cancer – Metastatic, Second-Line Therapy**

Capecitabine has demonstrated efficacy in combination with docetaxel in patients with metastatic breast cancer with anthracycline resistant disease as measured by TTP.144 It also has demonstrated efficacy as monotherapy in metastatic breast cancer patients who have anthracycline and taxane-pretreated disease.145

**Breast Cancer – HER2-Positive, Advanced**

**lapatinib (Tykerb) plus capecitabine (Xeloda) versus capecitabine (Xeloda) 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 IIIIB or IV breast cancer with HER2 over expression.146 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/m² every 12 hours on days 1 to 14) every 21 days or capecitabine alone (1,250 mg/m² every 12 hours on days 1 to 14) every 21 days. The primary endpoint was TTP 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 (Xeloda) 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. 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 hazard ratio 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 overall survival 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. Hazard ratio 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 overall survival with less toxicity than lapatinib plus capecitabine in patients with HER2-positive breast cancer previously treated with trastuzumab and a taxane.

lapatinib (Tykerb) plus letrozole (Femara) versus letrozole (Femara) 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.
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.\(^{149}\) 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 outcome.\(^{150}\) 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 (hazard ratio [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-ANALYSIS**

**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.\(^{151}\) 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 Therapy versus Placebo**

The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) was set up in 1984 to coordinate worldwide meta-analyses of the large volume of published trial data in the setting of early breast cancer. The EBCTCG publishes a meta-analysis update every 5 years reviewing the additional findings in the preceding 5 years, as well as updating the more mature data from older trials.\(^{152,153,154}\) The EBCTCG reviews involve central review of data on every individual patient in every trial. The Cochrane Collaborative Review has elected not to conduct their own review because it would be a duplication of the efforts of the EBCTCG. The Cochrane Collaborative Review has endorsed the EBCTCG systematic reviews, stating they represent the best available evidence on the effects of treatments on relapse, second cancer, and death. The EBCTCG reviews are of the highest quality, are updated every 5 years, and are published in prominent peer-reviewed journals.
In 2011, the EBCTCG published their most recent meta-analysis.\textsuperscript{155} This review analyzed data from 20 trials of about 5 years of tamoxifen versus no adjuvant tamoxifen. Information was available for 99\% of patients (21,457 patients out of 21,712 patients enrolled in the 20 trials). All women were randomly assigned evenly between tamoxifen and control. Six of the major trials described compliance with tamoxifen allocation, resulting in an overall mean of 80\% compliance. In ER positive disease, allocation to tamoxifen halved the recurrence rate during years 0 to 4 and reduced it by a third during years 5 through 9 with little further effect being seen after year 10. Over all the time periods analyzed the recurrence rate reduction (RR) averaged 39\% (RR, 0.61; p<0.00001) for any recurrence. In ER poor disease, however, there was no apparent effect on recurrence (RR, 0.97; 95\% CI, 0.88 to 1.07). The tumor ER status was the only risk factor that determined response to tamoxifen therapy, the risk reduction seen with tamoxifen was not affected by age, tumor size, or nodal status (node positive or node negative) of the patient. The EBCTCG analyses have also demonstrated that despite small absolute increases in thromboembolic disease and uterine cancer mortality (both only in women older than 55 years), overall non-breast cancer mortality was little affected such that all-cause mortality was substantially reduced with the use of 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.\textsuperscript{156} 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 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.

**Adjuvant Aromatase Inhibitors versus Tamoxifen**

The EBCTCG conducted a meta-analysis involving data from clinical trials that enrolled 31,920 postmenopausal women with estrogen receptor-positive early breast cancer who received adjuvant therapy with either an AI or tamoxifen.\textsuperscript{157} Duration of therapy with either an AI or tamoxifen was a total of 5 years regardless of which drug or combination of drugs they 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 about 15\% compared with tamoxifen.
SUMMARY

Chemotherapy and/or endocrine therapy are utilized in the management of breast cancer in both the adjuvant setting to decrease the risk of recurrence and for patients with advanced or metastatic breast cancer to palliate symptoms and/or prolong survival. Tamoxifen, a selective estrogen receptor modulator, was the first endocrine therapy to have proven benefit in both of these settings for patients with hormone receptor (HR)-positive breast cancer. However, aromatase inhibitors (AIs), including anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin), now play a large role in the management of HR-positive breast cancer.

Historically, AIs were only appropriate for postmenopausal women. However, recent information regarding the use of ovarian suppression in conjunction with AI therapy for premenopausal women has now changed that paradigm. The role of tamoxifen for adjuvant treatment of HR-positive breast cancer is less clear than in the past due to expanding data on the use of adjuvant AI therapy. Classically, tamoxifen has been 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, as well as overall survival. Recent guidelines now recommend women be offered extended adjuvant treatment with tamoxifen up to a total of 10 years of therapy. Other options for extended adjuvant therapy in postmenopausal women with HR-positive breast cancer include tamoxifen for 5 years then switching to an AI for up to 5 years for a total duration of 10 years of adjuvant endocrine therapy or tamoxifen for a duration of 2 to 3 years and switching to an AI for up to 5 years, for a total duration of up to 7 to 8 years of adjuvant endocrine therapy. A fourth option is taking an AI for 5 years.

In the setting of advanced HR-positive breast cancer, hormonal agents are often utilized as single agents given sequentially until the patient becomes hormone refractory. There is a role for both tamoxifen and the AIs for treatment of HR-positive advanced or metastatic disease. Fulvestrant (Faslodex) is only indicated in patients who have progressed on prior endocrine therapy. It is the only injectable (IM) product in this review. Toremifene (Fareston), with a similar mechanism of action to tamoxifen, is an alternative to tamoxifen in the setting of HR-positive advanced breast cancer but shows cross-resistance with tamoxifen and should not be used in patients who have experienced progressive disease while taking tamoxifen. Everolimus has been approved to be used in conjunction with exemestane in women who have experienced progressive disease either while taking tamoxifen or an AI or who have had disease progression within 12 months of taking an AI in an attempt to overcome acquired hormonal resistance. In 2015, the FDA approved palbociclib (Ibrance), a first in class oral selective inhibitor of cyclin-dependent kinases (CDKs) 4 and 6. Palbociclib, when given in combination with letrozole to postmenopausal patients with estrogen receptor (ER)-positive, HER2-negative advanced breast cancer, nearly doubled progression-free survival (PFS) compared to letrozole plus placebo (20.2 months versus 10.2 months). The combination of palbociclib plus letrozole is approved for use as initial endocrine-based therapy of ER-positive, HER2-negative advanced breast cancer. In 2016, the use of palbociclib was expanded by the FDA with approval of palbociclib for use in combination with fulvestrant for patients with HR-positive, HER2-negative, advanced breast cancer who have previously experienced disease progression with endocrine therapy. Initial study analysis demonstrated that PFS was 9.2 months (95% CI, 7.5 to not reached) with palbociclib/fulvestrant compared to 3.8 months (95% CI, 3.5 to 5.5) with placebo/fulvestrant. This therapy may be utilized in either postmenopausal women or may be given to premenopausal women in conjunction with ovarian suppression treatment.
Lapatinib (Tykerb) is an oral tyrosine kinase inhibitor that is active in women with breast cancers who over express Her2/neu, a tumor marker that is usually associated with a more aggressive form of the disease. It is approved in combination with capecitabine (Xeloda) for advanced or metastatic breast cancer as well as in combination with letrozole for the treatment of postmenopausal women with HR-positive metastatic breast cancer that over expresses HER2. Recent data indicate the combination of lapatinib and capecitabine is inferior to trastuzumab emtansine (Kadcyla) given intravenously and, therefore, lapatinib is currently considered a third line agent for the treatment of HER2-positive advanced breast cancer.

Pharmacotherapy aimed at actionable targets of many breast cancers, including the estrogen receptor, progesterone receptor, and HER2, 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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