Delaying Chemotherapy in the Treatment of Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer

Adam M. Brufsky

Professor of Medicine, Associate Division Chief of Hematology/Oncology, Medical Director of Women's Cancer Center at Magee-Womens Hospital, Codirector of Comprehensive Breast Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

ABSTRACT: Global guidelines for the management of locally advanced or metastatic hormone receptor–positive (HR-positive), human epidermal growth factor 2–negative (HER2-negative) breast cancer recommend endocrine therapy as first-line treatment for all patients, regardless of age or postmenopausal status. However, current practice patterns in the United States and Europe suggest that these modes of therapy are not being used as recommended, and many patients with advanced HR-positive, HER2-negative disease are being treated first-line with chemotherapy or switched to chemotherapy after a single endocrine therapy. Given that chemotherapy is associated with increased toxicity and reduced quality of life (QOL) compared with endocrine therapy, prolonging the duration of response obtained with endocrine therapy may help delay chemotherapy and its attendant toxicities. Several strategies to delay or overcome endocrine resistance and thereby postpone chemotherapy have been explored, including the use of second-line endocrine agents with different mechanisms of action, adding targeted agents that inhibit specific resistance pathways, and adding agents that act in complementary or synergistic ways to inhibit tumor cell proliferation. This review analyzes the different therapy options available to HR-positive, HER2-negative patients with advanced breast cancer that can be used to delay chemotherapy and enhance QOL.

KEYWORDS: delaying chemotherapy, HR-positive, breast cancer, targeted therapy

CITATION: Brufsky. Delaying Chemotherapy in the Treatment of Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer. *Clinical Medicine Insights: Oncology* 2015:9 137–147 doi: 10.4137/CMO.S31586.

TYPE: Review

RECEIVED: July 10, 2015. **RESUBMITTED:** October 27, 2015. **ACCEPTED FOR PUBLICATION:** November 02, 2015.

ACADEMIC EDITOR: William C. S. Cho, Editor in Chief

PEER REVIEW: Five peer reviewers contributed to the peer review report. Reviewers' reports totaled 1087 words, excluding any confidential comments to the academic editor.

FUNDING: Editorial support was provided by Novartis Pharmaceuticals Corporation. The author confirms that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: A. M. Brufsky is a paid consultant for Novartis.

CORRESPONDENCE: brufskyam@upmc.edu

Introduction

Breast cancer is the most common cancer in women globally, with an estimated 1.67 million newly diagnosed cases and 522,000 related deaths in 2012 alone.[1] It is the leading cause of cancer death among women in less developed countries and the second highest cause of cancer-related deaths (after lung cancer) among women in more developed countries.[1] In the United States, an estimated 231,840 new cases of breast cancer will be diagnosed in 2015 and an estimated 40,290 women will die from their disease.[2]

At diagnosis, most cases of breast cancer are invasive and have spread beyond the ductal or glandular walls into the surrounding breast tissue.[3] Although the majority of breast cancers are diagnosed at early stages, ~5%–10% of women have metastatic disease at the time of diagnosis.[4] Five-year survival rates depend on disease stage at diagnosis; the 5-year survival rate for patients with localized disease is ~100%, but it is only ~25% for those with distant (metastatic) disease.[3,5] In addition, ~30% of women diagnosed with early stage breast cancer will go on to develop advanced or metastatic disease despite treatment.[6]

Treatment options for breast cancer have expanded considerably in the past decade due to a greater understanding of the molecular mechanisms underlying specific subtypes of breast tumors and the development of targeted agents for those specific subtypes.[7,8] Treatment options include endocrine therapies, different types of chemotherapy, and radiation therapy. Although radiation therapy is sometimes used to treat the symptoms of advanced breast cancer,[3] the use of endocrine therapies and chemotherapy is more common. The choice of treatment for breast cancer depends on several patient-related factors (eg, age and menopausal status) and cancer-specific factors, such as tumor size, lymph node involvement, and molecular subtype (eg, estrogen receptor [ER] positive or negative and human epidermal growth factor receptor 2 [HER2] positive or negative).[9]

All primary invasive breast cancers should be analyzed for hormone receptor (HR) status.[9] ER-positive breast cancer, the most common subtype, accounts for ~65% of cases among premenopausal women and ~80% of cases among postmenopausal women.[10] The expression of HER2 should also be analyzed in breast cancer patients, with overexpression

occurring in ~15%–23% of patients.[11] The vast majority of breast cancer patients are HR-positive, HER2-negative. A study of 1134 breast cancer patients confirmed that HR-positive, HER2-negative was the most common type of breast cancer, with 68.9% of patients forming this subgroup.[12] For patients with HR-positive disease, the National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant endocrine therapy, regardless of patient age, lymph node status, menopausal status, HER2 status, or whether adjuvant chemotherapy is to be administered.[9] For patients with early breast cancer who are postmenopausal at diagnosis, the NCCN guidelines recommend the use of aromatase inhibitors (AIs) as initial adjuvant therapy for 5 years or tamoxifen for several years followed by AI therapy.[9] The use of tamoxifen alone is reserved for those patients who decline or have contraindications to AI treatment.[9]

For patients with HR-positive advanced (metastatic) breast cancer, endocrine therapy is the recommended first-line treatment.[9] Endocrine therapy options for postmenopausal patients include third-generation AIs (ie, anastrozole, letrozole, and exemestane), selective ER modulators (ie, tamoxifen and toremifene), ER downregulators (fulvestrant), or hormonal therapy (ie, androgens, high-dose estrogen, or progestin).[9] In premenopausal patients, endocrine therapy options include selective ER modulators, luteinizing hormone-releasing hormone agonists, or hormonal therapy.[9] The combination of endocrine therapy plus ovarian ablation or suppression is appropriate in premenopausal patients as well.[9]

AI therapy has been shown to provide a survival benefit versus tamoxifen in patients with advanced breast cancer. In a meta-analysis of randomized trials, patients with advanced breast cancer receiving a third-generation AI in the first-, second-, or subsequent-line setting had a statistically significant survival benefit versus those who received therapy with tamoxifen or a progestational agent (hazard ratio for death, 0.87; 95% confidence interval [CI], 0.82–0.93).[13] Despite a number of head-to-head studies, there is little evidence to support the use of one third-generation AI over another for the first-line treatment of advanced or metastatic breast cancer.[14,15]

A phase 2 trial of 205 patients with treatment-naive, HR-positive advanced breast cancer compared fulvestrant 500 mg to anastrozole 1 mg as first-line endocrine therapy.[16] Although the two regimens were found to be equivalent with regard to clinical benefit rate (CBR), fulvestrant therapy provided a significant time to progression (TTP) and overall survival (OS) benefit. Patients randomly assigned to receive fulvestrant had a 34% reduction in the hazard of progression versus those who received anastrozole (hazard ratio, 0.66; 95% CI, 0.47–0.92).[16] The median TTP was 23.4 months for fulvestrant versus 13.1 months for anastrozole.[16] In addition, patients treated with fulvestrant survived a median of 54.1 months compared with 48.4 months for those treated with anastrozole.[16] Fulvestrant was also associated with a 30% reduction in death (hazard ratio, 0.70; 95% CI, 0.50–0.98).[16] At the time of the analysis, 22.5% of patients in the fulvestrant arm were alive versus 9.7% in the anastrozole arm.[16] Results from a phase 3 trial comparing these two regimens will help determine whether fulvestrant will become a first-line treatment for HR-positive advanced or metastatic breast cancer (NCT01602380). However, women with HR-positive breast cancers who respond to a first-line endocrine therapy and subsequently experience disease progression may benefit from additional lines of endocrine therapy.[9,17]

Guidelines and Current Practice Patterns for Chemotherapy Use in HR-Positive Advanced Breast Cancer

According to the guidelines from the NCCN, the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), and Canadian institutions, cytotoxic chemotherapy should be considered as first-line treatment only for a small subset of patients with HR-positive advanced breast cancer, primarily those in symptomatic visceral crisis or those who have clear evidence of endocrine resistance.[4,9,18,19] Approximately 20%–25% of HR-positive breast cancer patients receive upfront chemotherapy.[20]

The NCCN guidelines recommend chemotherapy as an option for patients with HR-positive tumors who are refractory to endocrine therapy (ie, patients who do not respond to three sequential endocrine therapies) or as first-line consideration for patients with symptomatic visceral disease.[9] Similarly, the ASCO guidelines recommend that endocrine therapy, rather than chemotherapy, be used as standard first-line treatment for all patients with HR-positive advanced breast cancer and that chemotherapy be reserved for patients who have immediate life-threatening complications (eg, visceral crisis) or physicians' concerns about endocrine resistance.[18] The ASCO guidelines cite the superior toxicity profile and quality-of-life (QOL) benefits of endocrine therapy versus chemotherapy in their rationale for the recommendation.[18] Although metastatic breast cancer might progress rapidly and prove fatal if the disease is not responsive to endocrine therapy, the risk of this clinical scenario is thought to be low.[18]

The ESMO guidelines are consistent with the NCCN and ASCO guidelines and recommend endocrine therapy as a first-choice treatment for HR-positive, HER2-negative disease, regardless of metastatic site, unless a rapid response is required or when there is clear evidence of endocrine resistance.[4] According to the ESMO guidelines, endocrine therapy, with its low attendant toxicity, can be given even in the case of limited visceral metastases or as maintenance therapy.[4] The ESMO guidelines state, however, that endocrine therapy and chemotherapy should not be given concomitantly.[4]

Canadian guidelines recommend that the patient's age, functional status, and comorbidities be considered in the selection of an endocrine therapy.[19] In cases of disease

progression on a nonsteroidal AI (NSAI) or endocrine resistance, alternative endocrine options are recommended, including a trial of exemestane plus everolimus or exemestane or fulvestrant alone, if the exemestane/everolimus combination is not tolerated.[19] Exemestane plus everolimus is also recommended for many endocrine-resistant patients.[19] Because of the increased risk of serious adverse events (AEs) with everolimus plus exemestane, the use of a proactive toxicity management strategy is recommended to maximize clinical benefit.[19] The use of chemotherapy is limited to endocrine-resistant patients with symptomatic visceral disease.[19]

Despite clear guidelines from institutions worldwide on the preferential use of multiple lines of endocrine therapy versus chemotherapy in patients with HR-positive advanced breast cancer, current practice patterns in the United States and Europe suggest that these modes of therapy are not being used as recommended.[21,22] Reviews of practice patterns show that chemotherapy is still used as first-line treatment in a substantial portion of patients with HR-positive metastatic breast cancer. In Europe, a retrospective chart review of 355 postmenopausal women with HR-positive, HER2-negative advanced breast cancer found that 31% had received first-line chemotherapy, while 61% and 7% switched from hormone therapy to chemotherapy in the second and third lines, respectively.[23]

A US retrospective chart review of 144 patients with HR-positive, HER2-negative advanced breast cancer found that 24% received first-line chemotherapy and 40% received only one line of endocrine therapy before receiving chemotherapy, despite guidelines that recommend endocrine therapy as second-line and subsequent therapy.[21] In this cohort, <10% of the patients had three or more lines of endocrine therapy before receiving chemotherapy.[21] Treatment duration was longer for endocrine therapy than for chemotherapy in the first-line setting and decreased for both in the second-line setting.[21] Although the number of patients involved in the European and US retrospective chart reviews was small, the results indicate that the number of patients receiving first-line chemotherapy is unusually high.

Benefits of Delaying Chemotherapy in HR-Positive, HER2-Negative Advanced Breast Cancer

The guidelines recommending that endocrine therapy, and not chemotherapy, be used as first-line treatment for HR-positive advanced breast cancer are supported by both clinical evidence and patient-reported outcomes. A survey of 200 patients from the United States and 160 from the European Union who used either endocrine therapy or chemotherapy in the first-line setting for metastatic breast cancer found that those receiving endocrine therapy versus chemotherapy reported greater health-related QOL (HRQOL; $P < 0.05$), greater satisfaction with treatment, and better feelings about AEs ($P < 0.001$).[22] Those receiving endocrine therapy also reported fewer problems with treatment side effects (0–5 scale; $P < 0.001$) and less activity impairment than those receiving chemotherapy ($P < 0.001$).[22]

Delaying chemotherapy in patients with HR-positive, HER2-negative advanced breast cancer may provide unquantifiable benefits for physicians and patients because it can help mitigate concerns about chemotherapy-related AEs, their management, and their impact on the patient. Using chemotherapy only after the failure of multiple lines of endocrine therapy is also consistent with global guidelines, which recommend using therapies with the optimal benefit-to-risk ratio.[4,9,18,19] Following appropriate prescribing guidelines (eg, timing, sequence, and indicated population) for endocrine therapy and chemotherapy may also help facilitate reimbursement from third-party payers. With the increased emphasis on considering patient-reported outcomes in the selection of treatment, physicians can be more confident that delaying chemotherapy is in line with patient preferences for a less toxic therapy that has a less negative impact on daily activities and QOL. A survey of 1342 women with metastatic breast cancer from 13 countries reported that the majority of patients had serious concerns related to their disease, including the fear of dying, possible treatment-related AEs, and deterioration in their QOL.[24] The importance of maintaining HRQOL cannot be overemphasized. Indeed, HRQOL is an important prognostic factor, with several HRQOL components, including role functioning, social functioning, fatigue, and appetite loss, having a significant association with treatment response.[22]

Treatment Options for Delaying Chemotherapy

Strategies to delay chemotherapy. Several strategies to extend the benefits of endocrine therapy and to help delay chemotherapy and its associated toxicities have been proposed (Table 1). The sequential use of endocrine therapies with different modes of action may help prolong the duration of response, reduce the risk of resistance, and delay the need for chemotherapy.[25] The available endocrine therapies all slow the growth and proliferation of tumor cells by interfering with estrogen-ER signaling, but they do so through different modes of action.[25] The NSAIs anastrozole and letrozole reversibly inhibit the enzyme aromatase, which catalyzes the synthesis of estrogen from adrenal androgens, the main source of estrogen in postmenopausal women.[25] The steroidal AI exemestane binds irreversibly to and inactivates aromatase.[25] There is evidence that NSAI-resistant tumors may not be entirely cross-resistant to exemestane.[26] The selective ER modulators such as tamoxifen and toremifene work by binding to the ER and blocking its interaction with estrogen and then blocking the proliferative action of estrogen on breast tissue.[25] Although selective ER modulators are antiestrogenic in breast tissue, they have estrogen agonist properties in endometrial tissue and bone.[25] Fulvestrant, an ER downregulator, binds to the ER and inhibits its dimerization, thereby preventing the ER from becoming transcriptionally

active.[25] Fulvestrant also induces the rapid turnover and degradation of the ER.[25] Unlike tamoxifen or toremifene, fulvestrant is a pure estrogen antagonist.[25]

Patients may not respond to first-line or subsequent endocrine therapy due to intrinsic or acquired resistance.[25] The tumor may develop resistance to a specific endocrine therapy but still remain ER and estrogen dependent; in this case, a switch to an endocrine agent with a different mode of action may restore tumor sensitivity.[25] In other cases, the ER may be activated independent of estrogen binding; agents such as AIs, which reduce estrogen levels, would not be expected to be effective, but other agents directed at the ER, such as fulvestrant, might have activity.[25] Some tumors may develop resistance by activating growth factor receptor (GFR) pathways, leading to the expression of ER target genes independent of estrogen or the ER.[25] For these estrogen-independent, ER-independent tumors, estrogen- and ER-directed therapies are not likely to be effective. In these cases, combining endocrine therapy with agents that target specific GFR pathway components may help overcome resistance.[25,27] Patients who have progressive disease after treatment with multiple endocrine therapies are likely to need chemotherapy to control disease progression.[28] Chemotherapy should also be chosen over endocrine therapy if the disease is clinically aggressive and a quicker response to control progression is required.[28] Although chemotherapy is an effective choice of treatment, the side effects and associated toxicities have been shown to potentially reduce QOL.

Types of Therapy

Endocrine therapies. Endocrine therapies are established treatments used for patients with advanced or metastatic breast cancer, although endocrine resistance can be a problem. One way to overcome resistance to AI therapy is to switch to an endocrine agent or agents with a different mechanism of action. In a double-blind, randomized, placebo-controlled trial of fulvestrant versus exemestane in postmenopausal women with HR-positive advanced or metastatic breast cancer who had progressed on AI therapy, the two agents were not significantly different with respect to median TTP or CBR.[26] Median TTP was 3.7 months in both groups (hazard ratio, 0.963; 95% CI, 0.819–1.133; $P = 0.6531$), and the CBR was 32.2% and 31.5% ($P = 0.853$) in the fulvestrant and exemestane groups, respectively.[26] Both agents were well tolerated, and the most common treatment-related AEs with both agents were hot flashes, injection site pain, nausea, and fatigue.[26]

In addition, a phase 3 study of fulvestrant 500 mg versus 250 mg in patients who experienced progression after prior endocrine therapy found a significant increase in progression-free survival (PFS; 6.5 months vs 5.5 months; hazard ratio, 0.80; 95% CI, 0.68–0.94; $P = 0.006$) and OS (26.4 months vs 22.3 months; hazard ratio, 0.81; 95% CI, 0.69–0.96; $P = 0.02$) with the 500 mg versus 250 mg dose, respectively.[29,30] AEs were similar between the two dose groups.[29,30]

In the SoFEA randomized, multicenter, phase 3 study, fulvestrant plus anastrozole, fulvestrant plus placebo, and exemestane alone were compared in 723 postmenopausal patients with locally advanced or metastatic HR-positive breast cancer who had progressed or relapsed on NSAI therapy.[31] The study found no differences between fulvestrant 250 mg plus anastrozole, fulvestrant plus placebo, or exemestane alone. Median PFS was 4.4 months (95% CI, 3.4–5.4) in the fulvestrant plus anastrozole group, 4.8 months (95% CI, 3.6–5.5) for fulvestrant plus placebo, and 3.4 months (95% CI, 3.0–4.6) for exemestane alone.[31] The most common AEs were lethargy, arthralgia, and nausea and vomiting; grade 3/4 AEs were rare.[31] The frequency of dyspnea and pain were higher in the fulvestrant arm than in the fulvestrant–anastrozole arm, but no other differences in AE rates were observed.[31]

In a phase 2 trial in postmenopausal patients with HR-positive advanced or metastatic breast cancer, the combination of fulvestrant plus exemestane did not improve overall clinical benefit compared with that seen with single-agent fulvestrant or exemestane in the first- or second-line setting.[32] However, pharmacokinetic data indicated that this was not due to altered drug exposure.[32] The most common AEs in the fulvestrant–exemestane group were grade 2 fatigue, bone pain, and arthralgia.[32]

In a randomized, controlled trial in 91 postmenopausal women with HR-positive breast cancer who progressed during or after NSAI therapy, toremifene 120 mg was compared to exemestane 25 mg and found to have a similar CBR (41.3% vs 26.7%; $P = 0.14$), objective response rate (ORR; 10.8% vs 2.2%; $P = 0.083$), and OS (32.3 months vs 21.9 months; hazard ratio, 0.60; 95% CI, 0.26–1.39; $P = 0.22$). However, the PFS with toremifene was longer than with exemestane (7.3 months vs 3.7 months; hazard ratio, 0.61; $P = 0.045$).[33] Both toremifene and exemestane were well tolerated, with no serious AEs. The most common AEs were nausea, fatigue, and hot flashes.[33]

Although endocrine therapies are recommended over chemotherapy for the treatment of patients with advanced or metastatic breast cancer, intrinsic and acquired resistance is a major problem. The sequential use of different endocrine therapies or combining endocrine therapies with targeted therapies is currently the most viable option to prevent endocrine resistance without compromising patient QOL.

Mammalian target of rapamycin inhibitors. Agents that inhibit multiple signaling pathways and targets are in various stages of development, and identifying different subtypes of breast cancer allows for targeted treatment (Fig. 1).[7,34–36] A major mechanism of endocrine resistance is the activation of the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) intracellular signaling pathway. mTOR inhibitors have subsequently

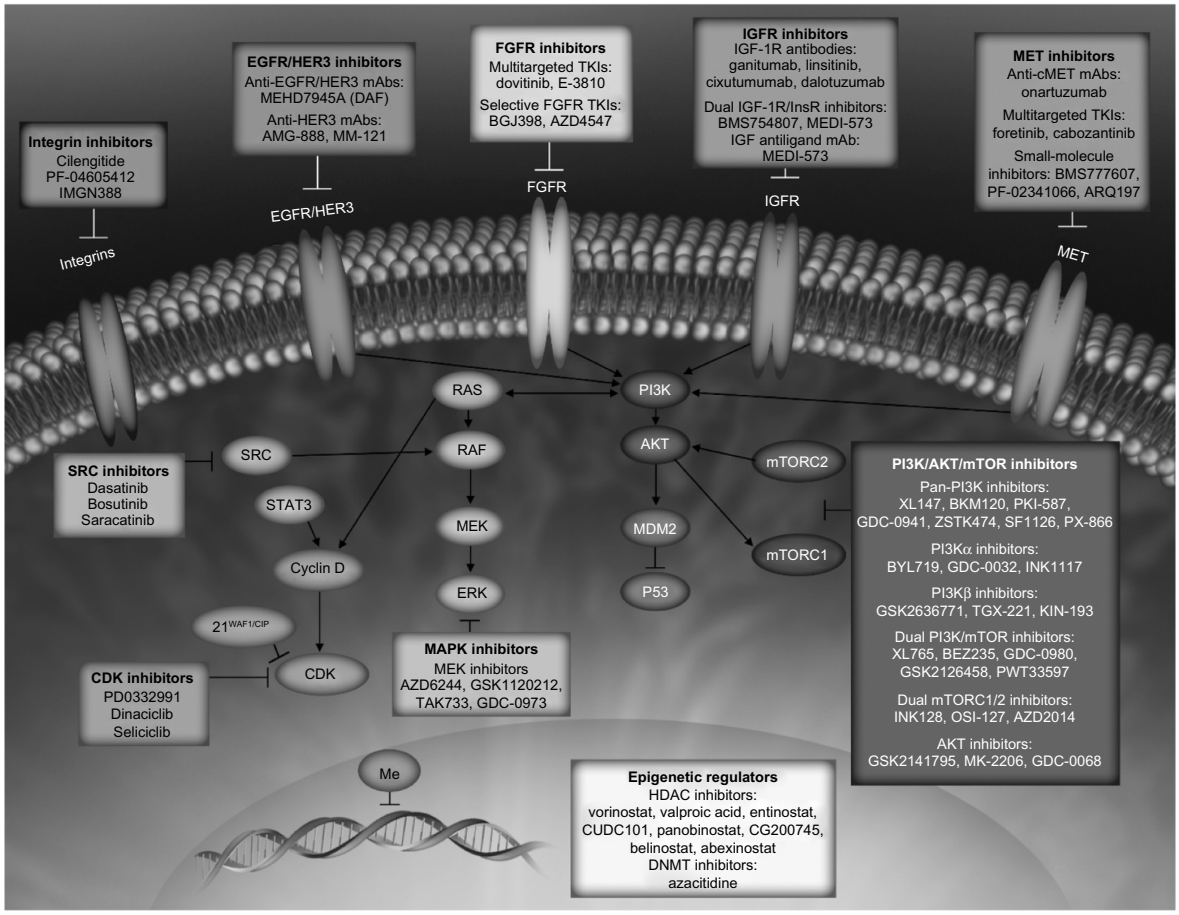

Figure 1. Emerging targeted agents against breast cancer under clinical development. Reprinted with permission from Ref 36.

been developed to overcome resistance, with promising results observed in patients with advanced HR-positive, HER2-negative breast cancer. Indeed, studies have shown that adding the mTOR inhibitor everolimus to exemestane significantly improves PFS versus exemestane alone in postmenopausal patients with HR-positive breast cancer who experienced recurrence or progression while receiving NSAI therapy.[37] In the phase 3 BOLERO-2 trial, 724 patients were randomly assigned 2:1 to treatment with everolimus plus exemestane or exemestane plus placebo.[38] In the final PFS analysis, median PFS (assessed by the investigator) was 7.8 months with everolimus plus exemestane versus 3.2 months with exemestane plus placebo (hazard ratio for progression or death, 0.45; 95% CI, 0.38–0.54; log rank $P < 0.0001$).[38] Median PFS (determined via central assessment) was 11.0 months versus 4.1 months for everolimus plus exemestane versus exemestane plus placebo, respectively (hazard ratio, 0.38; 95% CI, 0.31–0.48; log rank $P < 0.0001$).[38] PFS was improved in both elderly and younger patients.[39] However, everolimus plus exemestane did not significantly reduce the risk of death.[40] Median OS was 31.0 months for everolimus plus exemestane versus 26.6 months for exemestane plus placebo (hazard ratio, 0.89; 95% CI, 0.73–1.10; $P = 0.14$).[40] Poststudy treatments were received by 84% of patients in the everolimus plus exemestane arm versus 90% of patients in the exemestane plus placebo arm.[40] In patients who had previously received only neoadjuvant treatment, everolimus plus exemestane nearly tripled PFS (as assessed by the investigator) to 11.5 months versus 4.1 months (hazard ratio, 0.39; 95% CI, 0.25–0.62).[41] Adding everolimus to exemestane increased median PFS by 4 months in patients with HR-positive, HER2-negative advanced breast cancer, regardless of the presence of visceral metastases.[42] In the everolimus plus exemestane treatment arm, bone marker levels decreased after 6 and 12 weeks, whereas in the exemestane plus placebo arm, bone marker levels increased.[43] The everolimus plus exemestane arm also had a lower cumulative incidence rate of progressive bone disease than the exemestane plus placebo arm (13.0% vs 18.8%; $P = 0.04$, Gray's test), despite the less frequent use of bisphosphonates in the everolimus plus exemestane (43.9%) versus the exemestane plus placebo arm (54.0%).[41]

Overall, the most common AEs in the everolimus plus exemestane arm (reported in >25% of patients) were stomatitis, rash, fatigue, diarrhea, nausea, decreased appetite, weight loss, and cough versus nausea and fatigue in the exemestane plus placebo arm.[38] The most common grade 3/4 toxicities with the everolimus plus exemestane combination

were stomatitis, fatigue, dyspnea, anemia, hyperglycemia, and increase in gamma-glutamyl transferase levels.[38]

In addition to its use in combination with exemestane, everolimus is being investigated in combination with other endocrine therapies, such as tamoxifen and fulvestrant.[44] In a randomized, open-label, phase 2 study, the combination of everolimus plus tamoxifen resulted in a higher CBR than tamoxifen alone in patients with HR-positive, HER2-negative metastatic breast cancer resistant to AI therapy.[45] The CBR at 6 months was 61% (95% CI, 47–74) with tamoxifen plus everolimus versus 42% (95% CI, 29–56) with tamoxifen alone.[45] Median TTP was 8.6 months with tamoxifen plus everolimus versus 4.5 months with tamoxifen alone (46% reduction in the risk of progression; hazard ratio, 0.54; 95% CI, 0.36–0.81).[45] The tamoxifen plus everolimus combination was also associated with a survival benefit, with the risk of death reduced by 55% versus tamoxifen alone (hazard ratio, 0.45; 95% CI, 0.24–0.81).[45] The most common nonhematologic AEs that occurred at a substantially higher rate with the tamoxifen plus everolimus combination versus tamoxifen alone were fatigue (72% vs 53%), stomatitis (56% vs 7%), rash (44% vs 7%), anorexia (43% vs 18%), and diarrhea (39% vs 11%).[45] The most common hematologic AEs with the tamoxifen plus everolimus combination and tamoxifen alone, respectively, were decreases in hemoglobin (69% vs 35%), lymphocytes (48% vs 21%), and leukocytes (54% vs 18%).[45] This regimen, as with the exemestane plus everolimus combination, may soon find a place in the first-line setting.

In a small phase 2 study of 31 patients with HR-positive metastatic breast cancer who progressed or relapsed within 6 months of AI therapy, the combination of fulvestrant (loading dose of 500 mg followed by 250 mg in subsequent injections) plus everolimus was associated with a TTP of 7.4 months, ORR of 13%, and CBR of 49%.[46] Most AEs were grade 1/2, and the most common were liver enzyme elevations, anemia, metabolic changes (eg, hyperglycemia, hypercholesterolemia, and hypokalemia), mucositis, and thrombocytopenia.[46] Of note, 32% of the patients in the study were classified as having AI-resistant disease at baseline.[46] The identification of biomarkers that correlate with treatment benefit may help improve the benefit-to-risk ratio of this combination.[46] The use of high-dose fulvestrant (500 mg for all injections) may also improve outcomes with the fulvestrant plus everolimus combination.

Clinical studies with everolimus indicate that mTOR inhibitors are a promising class of targeted therapy. The BOLERO-2 trial showed substantial improvement in PFS without compromising patient QOL. As such, the combination of everolimus and exemestane has been approved for first-line use in the treatment of postmenopausal women with HR-positive, HER2-negative breast cancer. The results generated from everolimus trials have led to the development of second-generation mTOR inhibitors.

Cyclin-dependent kinase 4/6 inhibitors. Therapies targeting cyclin D1 and cyclin-dependent kinase (CDK) 4/6 have recently been developed for patients with advanced breast cancer. Cyclin D1 and CDK 4 and 6 are critical components of the cell cycle regulatory machinery; in the setting of endocrine resistance they can maintain cell cycle activity independent of the ER.[47] Palbociclib is a highly selective inhibitor of CDK 4/6, which is downstream of signaling pathways that lead to cellular proliferation.[48] In preclinical studies, palbociclib inhibited the growth of ER-positive human breast cancer cells *in vitro* and restored sensitivity to tamoxifen in resistant cells.[49] In a phase 2 study in 37 patients with histologically confirmed metastatic breast cancer positive for retinoblastoma protein and measurable disease, treatment with palbociclib was associated with a CBR of 19% (two patients with partial responses and five patients with stable disease).[50] The median overall PFS was 3.7 months, but it was significantly longer for those with HR-positive versus HR-negative disease (4.5 months vs 1.5 months; $P = 0.03$) and for those who had previously received two or more lines of endocrine therapy versus fewer than two prior lines (5 months vs 2 months; $P = 0.02$).[50] Grade 3/4 toxicities were all due to myelosuppression and included neutropenia (51%), thrombocytopenia (22%), and anemia (5%).[50] The efficacy of palbociclib was evaluated further in the PALOMA-1/TRIO-18 trial, a randomized, multicenter, phase 2 study comparing palbociclib plus letrozole versus letrozole alone in 165 patients with ER-positive, HER2-negative previously untreated advanced breast cancer.[51] Median PFS was 20.2 months (95% CI, 13.8–27.5) for the palbociclib plus letrozole group versus 10.2 months (95% CI, 5.7–12.6) for the letrozole group (hazard ratio, 0.488; 95% CI, 0.319–0.748; $P = 0.0004$).[51] The most common AEs in the palbociclib plus letrozole group were neutropenia, leukopenia, and fatigue.[51] The incidence of anemia ($P < 0.0001$) and alopecia ($P = 0.0002$) was significantly higher in the palbociclib plus letrozole arm than in the letrozole arm.[51] More patients in the palbociclib plus letrozole group (13%) than in the letrozole group (2%) discontinued the study because of AEs.[51] Palbociclib in combination with letrozole recently received accelerated US Food and Drug Administration approval for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as the initial endocrine-based therapy for their metastatic disease.[52] The combination of palbociclib and letrozole is being studied further in an ongoing phase 3 trial (PALOMA-2; NCT01740427).[51] Recently, the PALOMA-3 trial, a phase 3 trial of palbociclib plus fulvestrant versus fulvestrant alone in HR-positive, HER2-negative advanced breast cancer (NCT01942135), demonstrated a significant improvement in PFS with the palbociclib plus fulvestrant combination versus fulvestrant alone (9.2 months vs 3.8 months; hazard ratio, 0.42; 95% CI, 0.32–0.56; $P < 0.001$).[53] The most common AEs (≥25%) reported for the palbociclib plus fulvestrant group were neutropenia (78.8%), leukopenia (45.5%), fatigue (38.0%), nausea (29.0%), and anemia (26.1%).[53]

In addition to palbociclib, other CDK 4/6 inhibitors are in development, including abemaciclib and ribociclib (LEE011).[34] Abemaciclib is being evaluated in several trials both as

monotherapy and in combination with various endocrine agents (eg, AIs, fulvestrant) for advanced ER-positive breast cancer in the first-line setting and after progression on endocrine therapy or chemotherapy.[34] Ribociclib is an investigational CDK 4/6 inhibitor being evaluated in combination with letrozole as first-line treatment for patients with metastatic HR-positive, HER2-negative disease in the phase 3 MONALEESA-2 trial.[54] Preclinical studies have shown that combining ribociclib with PI3K inhibitors may result in synergistic inhibition of tumor cell growth.[55,56] As a result, triplet combinations with an AI, PI3K inhibitor, and CDK 4/6 inhibitor are being investigated in the ongoing randomized trials.[54]

Similar to everolimus, palbociclib has the potential to be an exciting new therapy in the treatment of advanced breast cancer. A study of the use of palbociclib in combination with endocrine therapies such as letrozole is under way, and the results from the phase 3 PALOMA-2 trial were expected by the end of 2015. The promising results for palbociclib will likely pave the way for the investigation of other CDK 4/6 therapies.

Tyrosine kinase inhibitors. Tyrosine kinase inhibitors (TKIs) are another class of targeted therapy being developed for patients with metastatic breast cancer. Cross-talk between the ER and intracellular growth factor signaling pathways (ie, epidermal growth factor receptor [EGFR], HER2, and insulin-like growth factor 1 [IGF-1]) may lead to endocrine resistance in metastatic breast cancer and provide a rationale for adding TKIs that block these specific pathways. However, studies that have evaluated the addition of TKIs (ie, gefitinib, lapatinib, and bosutinib) to endocrine therapy in patients with HR-positive metastatic breast cancer have shown only modest, if any, benefit and increased toxicities compared to either mode alone. In a phase 2 study of the EGFR TKI gefitinib in combination with anastrozole or fulvestrant in postmenopausal patients with metastatic HR-positive breast cancer, both combination regimens were associated with similar CBR and PFS; however, these rates were not higher than those obtained with single-agent endocrine therapy.[57] In another phase 2 study of postmenopausal patients with metastatic HR-positive disease who had not been treated with endocrine therapy, anastrozole plus gefitinib was associated with longer median PFS than anastrozole plus placebo (14.7 months vs 8.4 months; hazard ratio, 0.55; 95% CI, 0.32–0.94).[58] The CBR for anastrozole plus gefitinib versus anastrozole plus placebo was 49% versus 34%, respectively, but the ORR was 2% versus 12%.[58] The rate of treatment-related AEs was nearly doubled with the anastrozole plus gefitinib combination versus anastrozole plus placebo, with substantially higher rates of diarrhea (63% vs 18%), fatigue (40% vs 26%), rash (37% vs 10%), pruritus (26% vs 10%), dry skin (14% vs 2%), and acne (12% vs 0%).[58]

A phase 3 study comparing fulvestrant 500 mg plus the EGFR TKI lapatinib with fulvestrant plus placebo in patients with HR-positive advanced breast cancer treated with prior AI therapy found no difference in OS or PFS between the two regimens.[59] In addition, the lapatinib plus fulvestrant combination was associated with a greater incidence of diarrhea, fatigue, and rash.[59] In an analysis of a phase 3 trial, the addition of lapatinib to letrozole was found to significantly improve PFS compared to letrozole plus placebo (13.6 months vs 6.7 months; $P = 0.01$) in patients with HR-positive, HER2-negative disease with weak ER expression, but there was no benefit in patients with higher ER expression.[60] Another single-arm study of lapatinib plus letrozole in patients with AI-resistant advanced or metastatic breast cancer suggested some antitumor activity (CBR, 21%) with a good safety profile and found that the combination could overcome resistance to letrozole.[61] In the neoadjuvant setting, adding lapatinib to letrozole has demonstrated feasibility in a clinical setting but limited clinical benefit beyond letrozole alone.[62]

The combination of the dual Src/Abl TKI bosutinib plus letrozole was evaluated as first-line therapy in a phase 2 study of 16 postmenopausal patients with locally advanced or metastatic HR-positive, HER2-negative breast cancer but proved to be too toxic, resulting in the early termination of the study.[63]

Studies involving gefitinib, lapatinib, and bosutinib in combination with endocrine therapies have not been as successful as those studies involving everolimus or palbociclib in combination with endocrine therapy. Moreover, the incidence of treatment-related AEs and associated toxicities with TKIs has been high. Thus far, data from these studies suggest that other classes of targeted therapies are more effective treatments for patients with metastatic breast cancer.

PI3K inhibitors. PI3K inhibitors are another type of targeted therapy under current investigation. Preclinical modeling studies have shown that estrogen deprivation increased the apoptotic effects of PI3K and dual PI3K/mTOR inhibitors in ER-positive disease, providing a rationale for using PI3K plus AI combinations as first-line therapy for HR-positive advanced breast cancer.[64,65] Buparlisib (BKM120) is a pan-PI3K inhibitor with a tolerable AE profile that is being studied primarily in combination with other antitumor agents.[66,67] In a phase 1b study, buparlisib plus letrozole was found to be well tolerated; the most common AEs were gastrointestinal disorders, transaminitis, hyperglycemia, and reversible mood disorders.[68] A CBR (defined in this study as a lack of disease progression for ≥6 months) of 30% was observed.[68] This combination is being explored further in an ongoing phase 3 trial. In an early phase 1b trial, the investigational agent alpelisib (BYL719), a PI3Kα inhibitor, was evaluated in combination with letrozole in postmenopausal patients with ER-positive, HER2-negative metastatic breast cancer refractory to previous endocrine therapies (18/21 patients had progressed on an AI).[69] The majority of these patients had bone or visceral metastases.[69] The alpelisib plus letrozole combination was found to be tolerable at 300 mg/day and had preliminary clinical benefits: three of 18 patients had partial response and six of 18 patients had stable disease.[69]

The results from these early clinical studies using buparlisib and alpelisib in combination with letrozole suggest that

Table 1. Approved and investigational treatment options for HR-positive advanced breast cancer.

TYPE OF THERAPY	CLASS OF THERAPY	AGENT	THERAPY STATUS
Endocrine	SERMs	Tamoxifen	Approved
		Toremifene	Approved
	Estrogen downregulator	Fulvestrant	Approved
	AI	Letrozole	Approved
		Anastrozole	Approved
		Exemestane	Approved
	Ovarian ablation	Goserelin	Approved
		Leuprorelin	Approved
	mTOR inhibitors	Everolimus	Approved
		Temsirolimus	Investigational
	CDK 4/6 inhibitors	Palbociclib	Approved
		Abemaciclib	Investigational
		Ribociclib	Investigational
	Tyrosine kinase inhibitors	Gefitinib	Investigational
		Lapatinib	Investigational
		Bosutinib	Investigational
	PI3K inhibitors	Buparlisib	Investigational
	HDAC inhibitors	Entinostat	Investigational
		Vorinostat	Investigational
	Monoclonal antibodies	Ganitumab	Investigational
	VEGF inhibitor	Bevacizumab	Investigational
	ER receptor inhibitors	GDC-0810 RAD1901	Investigational Investigational
	Cell cycle regulators	LY2606368	Investigational
	MicroRNAs	Not available	Not available

PI3K inhibitors have the potential to be a highly effective class of targeted therapy. However, further investigation in phases 2 and 3 is required to confirm the efficacy and safety of these drugs. It is expected that results from additional studies will provide support for the suitability of these agents in the treatment of patients with metastatic breast cancer.

Histone deacetylase inhibitors. Histone deacetylases (HDACs) are the critical regulators of gene expression, and aberrant HDAC expression patterns have been reported in ER-positive breast cancer patients.[70] In preclinical studies, the HDAC inhibitor entinostat has been found to inhibit ER-positive tumor growth and restore hormone sensitivity by downregulating estrogen-independent growth factor signaling pathways, normalizing ER levels, and increasing aromatase enzyme levels.[71] A randomized, double-blind, phase 2 study compared entinostat plus exemestane versus exemestane plus placebo in patients with locally advanced or metastatic breast cancer who had progressed on an AI.[71] The entinostat plus exemestane combination improved median PFS to 4.3 months versus 2.3 months with exemestane plus placebo (hazard ratio, 0.73; 95% CI, 0.50–1.07; $P = 0.055$ [predefined significance level of 0.10]) and improved median OS to 28.1 months versus 19.8 months (hazard ratio, 0.59; 95% CI, 0.36–0.97; $P = 0.036$).[71] The most common AEs (≥10%) with the entinostat plus exemestane combination were fatigue, nausea, neutropenia, peripheral edema, vomiting, anemia, dyspnea, thrombocytopenia, decreased weight, diarrhea, and pain.[71] Phase 3 primary results for the entinostat and exemestane combination are expected in early 2017 (NCT02115282).[72,73]

Vorinostat, an HDAC inhibitor approved for the treatment of cutaneous T-cell lymphoma, was studied in combination with tamoxifen in a phase 2 study of patients with ER-positive metastatic breast cancer progressing on endocrine therapy.[74] The results showed that the combination was well tolerated, with an ORR of 19% and CBR of 40%, indicating promising activity in reversing hormone resistance.[74] The main toxicities with vorinostat were fatigue, anorexia, neutropenia, lymphopenia, and thrombocytopenia.[74] Vorinostat is also being evaluated in combination with paclitaxel plus bevacizumab chemotherapy.[75]

The results from clinical studies involving HDAC inhibitors have been promising. Phase 3 investigations using these agents will confirm whether or not they will be suitable to treat patients with advanced breast cancer.

Other strategies. Several other strategies to overcome endocrine resistance have been explored. Ganitumab is a fully

human monoclonal IgG1 antibody that inhibits the binding of IGF-1 and IGF-2 to the IGF-1 receptor.[76] However, adding ganitumab to either exemestane or fulvestrant in patients with advanced or metastatic HR-positive breast cancer previously treated with endocrine therapy failed to improve clinical outcomes compared with endocrine therapy alone.[76] Median PFS and ORR were not significantly different between the groups, and OS was significantly lower among those treated with ganitumab.[76] The incidence of most AEs was the same across groups, but thrombocytopenia, neutropenia, hyperglycemia, and fatigue occurred at substantially higher rates among those receiving ganitumab.[76]

The combination of fulvestrant plus bevacizumab, a vascular endothelial growth factor inhibitor, was tolerable but did not demonstrate clinical benefit over existing options for patients with metastatic breast cancer previously treated with AIs.[77] Among the 33 evaluable patients, the median PFS was 6.2 months and median OS was 26.9 months.[77]

Since the identification of mutations in the *BRCA1* gene in patients with breast cancer, significant research has focused on DNA damage, DNA repair, and the cell cycle and their links to breast cancer.[78] Checkpoint kinases 1 and 2 (CHK1/2) are cell cycle regulators that can stop cell division to allow any DNA damage to be repaired.[78,79] A phase 2 clinical trial (NCT02203513) to investigate the ability of the CHK1/2 inhibitor LY2606368 to shrink tumors in women with breast and ovarian cancer is currently recruiting patients.[79]

The binding of microRNAs (miRNAs) to mRNAs that encode tumor suppressor proteins have been implicated in the transformation of a normal cell to a malignant cell. As such, miRNA inhibitors, which disrupt the interaction between miRNA and mRNA to allow the translation of tumor suppressor proteins, could provide a useful strategy to overcome endocrine therapy resistance.[80]

Conclusion

The range of therapies used to treat patients with metastatic breast cancer has increased significantly in recent years. The development of a variety of targeted agents will provide patients with alternative options to chemotherapy. To date, the strategy of adding targeted treatments to first-line therapy in order to delay endocrine resistance and chemotherapy in HR-positive, HER2-negative metastatic breast cancer has not improved OS despite increasing ORR.[81] However, considering the promising results seen with everolimus, palbociclib, and some of the investigational agents in clinical trials, new combinations of targeted agents and endocrine therapies may yield improved results in patients with HR-positive, HER2-negative metastatic breast cancer.

Although current US, European, and Canadian institutional guidelines recommend multiple lines of endocrine therapy for ER-positive, HER2-negative advanced or metastatic breast cancer, many patients are instead treated with chemotherapy first and many others receive only a single endocrine therapy before being switched to chemotherapy. Evidence suggests that multiple lines of endocrine therapy can be effective, particularly if additional targeted agents are added to overcome or delay the development of endocrine resistance. Continuing endocrine therapy through multiple lines of treatment allows the clinician to delay chemotherapy in patients with HR-positive, HER2-negative advanced or metastatic breast cancer and maintain patient QOL by minimizing treatment toxicities. In the future, the approval of more targeted drug therapies will provide clinicians with a greater variety of nonchemotherapy-based treatments to choose from. As the overall number of therapies approved to treat metastatic HR-positive, HER2-negative breast cancer increases, it is anticipated that the need to use chemotherapy will be significantly reduced.

Acknowledgments

The author thanks Viji Anantharaman and Matthew Grzywacz for their writing and editorial assistance.

Author Contributions

Involved in the conception, design, writing, review, and approval of the final manuscript: ABM.

REFERENCES

1. International Agency for Research on Cancer. *GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012*. 2012. http://globocan.iarc.fr/Default.aspx. Accessed September 21, 2015.
2. American Cancer Society. *Cancer Facts and Figures 2015*. 2015. Available at: http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc–044552.pdf. Accessed September 22, 2015.
3. American Cancer Society. *Breast Cancer Facts and Figures 2013–2014*. 2013. Available at: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-042725.pdf. Accessed September 21, 2015.
4. Cardoso F, Harbeck N, Fallowfield L, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(suppl 7):vii11–9.
5. National Cancer Institute. *SEER Stat Fact Sheets*: *Breast*. 2015. Available at: http://seer.cancer.gov/statfacts/html/breast.html. Accessed September 21, 2015.
6. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist*. 2005;10(suppl 3):20–9.
7. Cadoo KA, Traina TA, King TA. Advances in molecular and clinical subtyping of breast cancer and their implications for therapy. *Surg Oncol Clin N Am*. 2013;22(4):823–40.
8. Fang L, Barekati Z, Zhang B, et al. Targeted therapy in breast cancer: what's new? *Swiss Med Wkly*. 2011;141:w13231.
9. National Comprehensive Cancer Network, Inc. NCCN clinical practice guidelines in oncology. *Breast Cancer*. Version 3.2014.
10. Anderson WF, Chatterjee N, Ershler WB, et al. Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End Results database. *Breast Cancer Res Treat*. 2002;76:27–36.
11. Mohd Sharial MS, Crown J, Hennessy BT. Overcoming resistance and restoring sensitivity to HER2-targeted therapies in breast cancer. *Ann Oncol*. 2012;23:3007–16.
12. Onitilo AA, Engel JM, Greenlee RT, et al. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. *Clin Med Res*. 2009;7:4–13.
13. Mauri D, Pavlidis N, Polyzos NP, et al. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst*. 2006;98:1285–91.
14. Riemsma R, Forbes CA, Kessels A, et al. Systematic review of aromatase inhibitors in the first-line treatment for hormone sensitive advanced or metastatic breast cancer. *Breast Cancer Res Treat*. 2010;123:9–24.
15. Llombart-Cussac A, Ruiz A, Anton A, et al. Exemestane versus anastrozole as front-line endocrine therapy in postmenopausal patients with hormone receptor-positive, advanced breast cancer: final results from the Spanish Breast Cancer Group 2001–03 phase 2 randomized trial. *Cancer*. 2012;118(1):241–7.

16. Ellis MJ, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: overall survival analysis from the phase II FIRST study. Abstract presented at: 2014 San Antonio Breast Cancer Symposium; December 9–13, 2014; San Antonio, TX.
17. Carrick S, Parker S, Thornton CE, et al. Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev*. 2009;(2):CD003372.
18. Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2014;32:3307–29.
19. Pritchard KI, Gelmon KA, Rayson D, et al. Endocrine therapy for postmenopausal women with hormone receptor-positive her2-negative advanced breast cancer after progression or recurrence on nonsteroidal aromatase inhibitor therapy: a Canadian consensus statement. *Curr Oncol*. 2013;20:48–61.
20. DeVita VT Jr, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer Principles and Practice of Oncology*. Vol 2. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins and Wolters Kluwer; 2008:1292–452.
21. Macalalad AR, Hao Y, Lin PL, et al. Treatment patterns and duration in postmenopausal women with HR+/HER2- metastatic breast cancer in the US: a retrospective chart review in community oncology practices (2004–10). *Curr Med Res Opin*. 2015;31:263–73.
22. Gupta S, Zhang J, Jerusalem G. The association of chemotherapy versus hormonal therapy and health outcomes among patients with hormone receptor-positive, HER2-negative metastatic breast cancer: experience from the patient perspective. *Expert Rev Pharmacoecon Outcomes Res*. 2014;14:929–40.
23. Andre F, Neven P, Marinsek N, et al. Disease management patterns for postmenopausal women in Europe with hormone-receptor-positive, human epidermal growth factor receptor-2 negative advanced breast cancer. *Curr Med Res Opin*. 2014;30:1007–16.
24. Mayer M, Hunis A, Oratz R, et al. Living with metastatic breast cancer: a global patient survey. *Community Oncol*. 2010;7:406–12.
25. Gluck S. Extending the clinical benefit of endocrine therapy for women with hormone receptor-positive metastatic breast cancer: differentiating mechanisms of action. *Clin Breast Cancer*. 2014;14:75–84.
26. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol*. 2008;26:1664–70.
27. Chlebowski RT. Strategies to overcome endocrine therapy resistance in hormone receptor-positive advanced breast cancer. *Clin Invest*. 2014;4:19–33.
28. Cardoso F, Senkus-Konefka E, Fallowfield L, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(suppl 5):v15–9.
29. di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol*. 2010;28:4594–600.
30. di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM Trial. *J Natl Cancer Inst*. 2014;106(1):djt337.
31. Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. *Lancet Oncol*. 2013;14:989–98.
32. Mrozek E, Layman R, Ramaswamy B, et al. Phase II trial of exemestane in combination with fulvestrant in postmenopausal women with advanced, hormone-responsive breast cancer. *Clin Breast Cancer*. 2012;12:151–6.
33. Yamamoto Y, Ishikawa T, Hozumi Y, et al. Randomized controlled trial of toremifene 120 mg compared with exemestane 25 mg after prior treatment with a non-steroidal aromatase inhibitor in postmenopausal women with hormone receptor-positive metastatic breast cancer. *BMC Cancer*. 2013;13:239.
34. Fedele P, Orlando L, Schiavone P, et al. Recent advances in the treatment of hormone receptor positive HER2 negative metastatic breast cancer. *Crit Rev Oncol Hematol*. 2015;94:291–301.
35. Chlebowski RT. Changing concepts of hormone receptor-positive advanced breast cancer therapy. *Clin Breast Cancer*. 2013;13:159–66.
36. Zardavas D, Baselga J, Piccart M. Emerging targeted agents in metastatic breast cancer. *Nat Rev Clin Oncol*. 2013;10:191–210.
37. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366:520–9.
38. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR breast cancer: BOLERO-2 final progression-free survival analysis. *Adv Ther*. 2013;30:870–84.
39. Pritchard KI, Burris HA III, Ito Y, et al. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. *Clin Breast Cancer*. 2013;13:421–32.
40. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. *Ann Oncol*. 2014;25:2357–62.
41. Beck JT, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane as first-line therapy in HR, HER2 advanced breast cancer in BOLERO-2. *Breast Cancer Res Treat*. 2014;143:459–67.
42. Campone M, Bachelot T, Gnant M, et al. Effect of visceral metastases on the efficacy and safety of everolimus in postmenopausal women with advanced breast cancer: subgroup analysis from the BOLERO-2 study. *Eur J Cancer*. 2013;49(12):2621–32.
43. Gnant M, Baselga J, Rugo HS, et al. Effect of everolimus on bone marker levels and progressive disease in bone in BOLERO-2. *J Natl Cancer Inst*. 2013;105:654–63.
44. Yardley DA. Combining mTOR inhibitors with chemotherapy and other targeted therapies in advanced breast cancer: rationale, clinical experience, and future directions. *Breast Cancer*. 2013;7:7–22.
45. Bachelot T, Bourgier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: A GINECO study. *J Clin Oncol*. 2012;30(22):2718–24.
46. Massarweh S, Romond E, Black EP, et al. A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure. *Breast Cancer Res Treat*. 2014;143:325–32.
47. Cadoo KA, Gucalp A, Traina TA. Palbociclib: an evidence-based review of its potential in the treatment of breast cancer. *Breast Cancer (Dove Med Press)*. 2014;6:123–33.
48. Fry DW, Harvey PJ, Keller PR, et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther*. 2004;3:1427–38.
49. Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines *in vitro*. *Breast Cancer Res*. 2009;11:R77.
50. DeMichele A, Clark AS, Tan KS, et al. CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. *Clin Cancer Res*. 2015;21:995–1001.
51. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol*. 2015;16:25–35.
52. Pfizer Labs. *Ibrance (Palbociclib) Capsules, for Oral Use [Package Insert]*. New York, NY: Pfizer Labs; 2015.
53. Turner NC, Ro J, Andre F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2015;373:209–19.
54. Mayer EL. Targeting breast cancer with CDK inhibitors. *Curr Oncol Rep*. 2015;17:443.
55. Kim S, Loo A, Chopra R, et al. LEE011: an orally bioavailable, selective small molecule inhibitor of CDK4/6 – reactivating Rb in cancer. *Mol Cancer Ther*. 2013;12(11 suppl):abstract R02.
56. Bardia A, Modi S, Chavez Mac Gregor M, et al. Phase Ib/II study of LEE011, everolimus, and exemestane in postmenopausal women with ER+/HER2- metastatic breast cancer. *J Clin Oncol*. 2014;32:abstract 535.
57. Carlson RW, O'Neill A, Vidaurre T, et al. A randomized trial of combination anastrozole plus gefitinib and of combination fulvestrant plus gefitinib in the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer. *Breast Cancer Res Treat*. 2012;133:1049–56.
58. Cristofanilli M, Valero V, Mangalik A, et al. Phase II, randomized trial to compare anastrozole combined with gefitinib or placebo in postmenopausal women with hormone receptor-positive metastatic breast cancer. *Clin Cancer Res*. 2010;16:1904–14.
59. Burstein HJ, Cirrincione CT, Barry WT, et al. Endocrine therapy with or without inhibition of epidermal growth factor receptor and human epidermal growth factor receptor 2: a randomized, double-blind, placebo-controlled phase III trial of fulvestrant with or without lapatinib for postmenopausal women with hormone receptor–positive advanced breast cancer – CALGB 40302 (Alliance). *J Clin Oncol*. 2014;32:3956–66.
60. Finn RS, Press MF, Dering J, et al. Quantitative ER and PgR assessment as predictors of benefit from lapatinib in postmenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer. *Clin Cancer Res*. 2014;20:736–43.
61. Villanueva C, Romieu G, Salvat J, et al. Phase II study assessing lapatinib added to letrozole in patients with progressive disease under aromatase inhibitor in metastatic breast cancer-Study BES 06. *Target Oncol*. 2013;8:137–43.
62. Guarneri V, Generali DG, Frassoldati A, et al. Double-blind, placebo-controlled, multicenter, randomized, phase IIb neoadjuvant study of letrozole-lapatinib in postmenopausal hormone receptor-positive, human epidermal growth factor receptor 2-negative, operable breast cancer. *J Clin Oncol*. 2014;32:1050–7.

63. Moy B, Neven P, Lebrun F, et al. Bosutinib in combination with the aromatase inhibitor letrozole: a phase II trial in postmenopausal women evaluating first-line endocrine therapy in locally advanced or metastatic hormone receptor-positive/HER2-negative breast cancer. *Oncologist*. 2014;19:348–9.
64. Brufsky AM. Managing postmenopausal women with hormone receptor-positive advanced breast cancer who progress on endocrine therapies with inhibitors of the PI3K pathway. *Breast J*. 2014;20:347–57.
65. Sanchez CG, Ma CX, Crowder RJ, et al. Preclinical modeling of combined phosphatidylinositol-3-kinase inhibition with endocrine therapy for estrogen receptor-positive breast cancer. *Breast Cancer Res*. 2011;13:R21.
66. Maira SM, Pecchi S, Huang A, et al. Identification and characterization of NVP-BKM120, an orally available pan-class I PI3-kinase inhibitor. *Mol Cancer Ther*. 2012;11:317–28.
67. Geuna E, Milani A, Martinello R, et al. Buparlisib, an oral pan-PI3K inhibitor for the treatment of breast cancer. *Expert Opin Investig Drugs*. 2015;24:421–31.
68. Mayer IA, Abramson VG, Isakoff SJ, et al. Stand up to cancer phase Ib study of pan-phosphoinositide-3-kinase inhibitor buparlisib with letrozole in estrogen receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2014;32:1202–9.
69. Mayer IA, Abramson VG, Balko JM, et al. Su2C phase Ib study of the P13Ka inhibitor BYL19 with letrozole in ER+/HER2-metastatic breast cancer (MBC). *J Clin Oncol*. 2014;32(5s suppl):abstract 516.
70. West AC, Johnstone RW. New and emerging HDAC inhibitors for cancer treatment. *J Clin Invest*. 2014;124:30–9.
71. Yardley DA, Ismail-Khan RR, Melichar B, et al. Randomized phase ii, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. *J Clin Oncol*. 2013;31:2128–35.
72. Connolly RM, Zhao F, Miller KD, et al. E2112: a randomized phase III trial of endocrine therapy plus entinostat or placebo in patience with hormone receptor-positive advanced breast cancer. *J Clin Oncol*. 2015;33:abstract TS636.
73. National Cancer Institute. Exemestane with or without entinostat in treating postmenopausal patients with recurrent hormone receptor-positive breast cancer that is locally advanced or metastatic. *ClinicalTrials.gov*. Bethesda (MD): National Library of Medicine (US); 2000. [cited 2015 Sep 21]. Available at: https://clinicaltrials.gov/ct2/show/NCT02115282 NLM Identifier: NCT02115282.
74. Munster PN, Thurn KT, Thomas S, et al. A phase II study of the histone deacetylase inhibitor vorinostat combined with tamoxifen for the treatment of patients with hormone therapy-resistant breast cancer. *Br J Cancer*. 2011;104:1828–35.
75. Ramaswamy B, Fiskus W, Cohen B, et al. Phase I-II study of vorinostat plus paclitaxel and bevacizumab in metastatic breast cancer: evidence for vorinostat-induced tubulin acetylation and Hsp90 inhibition in vivo. *Breast Cancer Res Treat*. 2012;132(3):1063–72.
76. Robertson JF, Ferrero JM, Bourgeois H, et al. Ganitumab with either exemestane or fulvestrant for postmenopausal women with advanced, hormone-receptor-positive breast cancer: a randomised, controlled, double-blind, phase 2 trial. *Lancet Oncol*. 2013;14:228–35.
77. Tan WW, Dueck AC, Flynn P, et al. N0539 phase II trial of fulvestrant and bevacizumab in patients with metastatic breast cancer previously treated with an aromatase inhibitor: a North Central Cancer Treatment Group (now Alliance) trial. *Ann Oncol*. 2013;24:2548–54.
78. Davis JD, Lin SY. DNA damage and breast cancer. *World J Clin Oncol*. 2011;2:329–38.
79. National Cancer Institute. Chk1/2 inhibitor (LY2606368) in women with BRCA1/2 mutation associated breast or ovarian cancer, non-high risk triple negative breast cancer, and high grade serous ovarian cancer at low genetic risk. *ClinicalTrials.gov*. Bethesda (MD): National Library of Medicine (US); 2000. [cited 2015 Sep 21]. Available at: https://clinicaltrials.gov/ct2/show/NCT02203513 NLM Identifier: NCT02203513.
80. Rothschild SI. microRNA therapies in cancer. *Mol Cell Ther*. 2014;2:7.
81. Kawalec P, Lopuch S, Mikrut A. Effectiveness of targeted therapy in patients with previously untreated metastatic breast cancer: a systematic review and meta-analysis. *Clin Breast Cancer*. 2015;15:90–100.