New Agents and Emerging Strategies in the Management of Hormone Receptor-Positive (HR+) Advanced Breast Cancer: Inhibiting Cellular Signaling Pathways for Improved Therapeutic Outcomes

A CME/CNE Approved Activity

This activity is supported by educational grants from Novartis Pharmaceuticals and Pfizer
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Instructions for CME/CNE: Activity is valid from February 20, 2018 to February 29, 2020. A score of 70% must be achieved on the post-test to receive continuing education credits. Read the monograph, answer the post-test, complete the evaluation form, and send completed post test and evaluation to:

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Learning Objectives:
1. Describe the biological pathways that drive hormone receptor–positive (HR+), HER2- breast cancer pathogenesis
2. Examine new and emerging CDK 4/6 inhibitor treatment options and their respective mechanisms of action in the management of HR+, HER2- advanced breast cancer
3. Discuss the current advances and challenges of treating HR+, HER2- advanced breast cancer
4. Analyze recent safety and efficacy data of emerging CDK 4/6 inhibitors for HR+, HER2- advanced breast cancer
5. Identify and select combination therapy with CDK 4/6 inhibitors (ribociclib, palbociclib and abemaciclib) and endocrine therapy agents in patients with hormone receptor-positive breast cancer
6. Evaluate optimized strategies specifically for the first-line treatment of HR+, HER2- advanced breast cancer
7. Address challenges to patient quality of life by incorporating effective treatment of HR+, HER2- advanced breast cancer with management of side effects and promotion of adherence

Faculty Disclosure:
Dr. Hurvitz has received grants for clinical research from: Amgen, Bayer, Biogen, Boehringer Ingelheim, Cascadian, Dignatana, Genentech; GlaxoSmithKline, Lilly USA, Medivation, Merrimack, Novartis, OBI Pharma, Pfizer, Puma, Roche, Seattle Genetics and has received travel from: Bayer, Lilly USA, OBI Pharma, Novartis.
Dr. Mayer, MD has disclosed no relevant financial relationships.
Dr. Tolaney has served as an advisor or consultant for: AstraZeneca, Merck & Co., Nanostring, Nektar Therapeutics, Puma Biotechnology and has received grants for clinical research from: AstraZeneca, Genentech, Lilly USA, Merck & Co., Nektar, Novartis, Pfizer.

All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacqueline Cole, RN and Jeremy Williams have no relevant financial relationships to disclose.

Accreditation & Designation
The National Association of Managed Care Physicians (NAMCP) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

NAMCP designates this enduring material for a maximum of 1 AMA PRA Category 1 credits™. Each physician should claim credit commensurate with the extent of their participation in the activity.

The American Association of Managed Care Nurses is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Nurses who complete this activity and achieve a passing score will receive 1 hour in continuing nursing credit.

This activity has been approved by the American Board of Managed Care Nursing for 1.0 contact hours toward CMCN recertification requirements.

This activity is supported by educational grants from Novartis Pharmaceuticals and Pfizer
**Post-Test Questions**

1. Which of the following is NOT one of the ways acquired resistance to hormone therapy occurs?
   a. Activation of growth factor signaling pathways (P13K/AKT/mTOR and MAPK/ERK).
   b. ER Mutations
   c. Loss of EROa
   d. Changes in the tumor microenvironment

2. Chemotherapy is recommended for about 50 percent of patients with HR+, HER2-MBC as initial therapy.
   a. True.  
   b. False.

3. According to this article, what percent of women with breast cancer have hormone responsive disease?
   a. 15%  
   b. 20%  
   c. 52%  
   d. 70%

4. Which of the following agents acts as a pure antagonist to the estrogen receptor with no known agonist effects?
   a. Fulvestrant  
   b. Exemestane
   c. Letrozole  
   d. Everolimus

5. Which of the following is a preferred option for first line treatment of HR+ HER2- MBC?
   a. Fulvestrant plus everolimus  
   b. Letrozole plus palbociclib
   c. Exemestane plus letrozole  
   d. Ribociclib monotherapy

6. Which of the following would be a preferred regimen for a patient who has disease recurrence within 6 months of starting fulvestrant (i.e., second line therapy)?
   a. Fulvestrant continuation  
   b. Palbociclib
   c. Abemaciclib  
   d. Letrozole with everolimus

7. Which of the following is the most common adverse effect with everolimus?
   a. Stomatitus  
   b. Neutropenia
   c. Thrombocytopenia  
   d. QT prolongation

8. Which of the following is an INACCURATE statement about adherence with therapy for MBC?
   a. Patients may not understand the importance of taking these as directed regularly for many years.
   b. Correctly taking the intermittently scheduled palbociclib and ribociclib can be complicated for patients.
   c. Waiting to manage adverse effects rather than anticipating them has no impact on adherence.
   d. Dose holding can be confusing for patients and it is important to communicate clearly when to restart therapy.

9. Which of the following is the primary reason combined CDK 4/6 inhibition with hormone therapy is now a standard option for first or second line treatment of HR+ HER2- MBC?
   a. Longer median overall survival (OS)  
   b. Lack of acquired resistance to therapy with combination
   c. Improved adverse effect profile over either alone  
   d. Prolonged progression free survival (PFS)

10. If ribociclib is used in premenopausal women HR+, HER2- MBC, which of the following should be combined with it?
    a. goserelin and tamoxifen  
    b. exemestane
    c. goserelin and fulvestrant  
    d. letrozole

**Activity Evaluation and Improvement Process**

(Please rate this activity on the following scale:  
4 - Excellent  
3 - Good  
2 - Fair  
1 - Poor)

1. Based on the content presented, I am better able to:
   Describe the biological pathways that drive hormone receptor-positive (HR+), HER- breast cancer pathogenesis.
   a. True.  
   b. False.

2. The activity met my expectations.  
   a. 1, 2, 3, 4

3. The activity and presenters were free of bias.  
   a. 1, 2, 3, 4

4. The activity was applicable to my position.  
   a. 1, 2, 3, 4

5. Do you expect that the information you learned during this activity will help you improve your skills or judgement within the next six months?  
   a. 1, 2, 3, 4

6. How confident are you in managing patients based on this activity?  
   a. 1, 2, 3, 4

7. What other topics interest you?  

8. I plan to implement the following changes based on the content.

9. Did the content of the activity help in meeting your above goal?  
   a. Yes  
   b. No

10. Due to the content of this activity, I will change my practice patterns by:
    a. Identifying opportunities to improve treatment options for patients.
    b. Providing guidelines and resources on new therapies to providers.
    c. My practice patterns will not change.
    d. Other (specify):  

11. Will the content presented increase your abilities in any of the following areas? Please check all that apply.
    a. Management and leadership skills.
    b. Business and/or financial expertise to manage the medical loss ratio.
    c. Exchange ideas and network with colleagues to improve patient outcomes.
    d. Clear knowledge of practice of medicine, especially common disease.
    e. Stay updated on clinical conditions.
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New Agents and Emerging Strategies in the Management of Hormone Receptor-Positive (HR+) Advanced Breast Cancer: Inhibiting Cellular Signaling Pathways for Improved Therapeutic Outcomes

Sara Hurvitz, MD, FACP; Ingrid A. Mayer, MD, MSCI; Sara Tolaney MD

Introduction

TREMENDOUS DEVELOPMENTS HAVE BEEN made in the treatment of hormone (estrogen or progesterone) receptor-positive (HR+) metastatic breast cancer (MBC) since the mid to late 1990s, particularly with the number of available hormonal agents (Exhibit 1). These treatments are changing outcomes in MBC.

When a patient is first diagnosed with MBC, staging scans and tumor biopsies will be done, even if the patient has been treated in the past for the disease. The tumor will be tested for estrogen receptors (ER), progesterone receptors, and human epidermal growth factor receptor 2 (HER2) overexpression. Retesting for these biomarkers is important for someone who had primary treatment in the past for breast cancer because anywhere from 10 to 20 percent of tumors will change biology over time, which will change the recommended therapy. Prior treatment history will be reviewed, including any recent hormonal therapy use. Some patients are initially diagnosed with MBC and thus would not have had prior therapy. Age, menopausal status, comorbidities, performance status, symptoms, and patient preferences/goals also impact treatment selection.

Resistance to Treatment

Before discussing the individual treatments, it is important to understand some of the biology of hormone-responsive breast cancer cells that can lead to resistance to therapy. These cells grow based on interaction of estrogen with its receptors, so the traditional treatments have blocked this interaction or removed the source for the production of estrogen (i.e., oophorectomy, hormonal treatments), but the cells have multiple pathways other than the ER receptors to maintain growth and division.

Eventually, the tumor will escape from hormonal control, which is termed acquired or primary resistance. Acquired resistance is defined as recurrence of disease at least six to 12 months after completion of adjuvant therapy or disease progression at six months or longer after endocrine therapy is initiated in the metastatic setting. Acquired resistance is more common than primary resistance. Some ways acquired resistance may occur are by activation of growth factor signaling pathways (PI3K/AKT/mTOR and MAPK/ERK) that are independent of estrogen based signaling, ER mutations, and changes in the tumor microenvironment. The PI3K/AKT/mTOR pathway, which is also called the survival pathway, confers malignant transformation, tumor invasion, enhanced angiogenesis and cell survival. PI3K pathway activation has been associated with antiestrogen resistance in ER+ breast cancers.

Primary resistance is defined as recurrence either while on adjuvant therapy or within six to 12 months of completion of adjuvant therapy or disease progression at less than six months after treatment in the metastatic setting. Some ways primary resistance may occur include fibroblast growth factor receptor (FGFR) amplifications, loss of ERα (one of two
types of ERs), post-translational modification of ERα, expression of ER co-activation/co-expression factors, cyclin D1 amplification or expression, and MYC amplification and overexpression. These mechanisms of resistance are important in choosing therapies and in drug development for this disease.

Treatment of HR+ HER2-MBC
Chemotherapy is not recommended for the majority of patients with HR+ HER2- MBC as initial therapy because first-line chemotherapy only produces a modest benefit. Endocrine therapy is the preferred option for HR+ HER2- MBC, even in the presence of visceral disease. Treatment with a given agent should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms or intolerable adverse effects occur. The patient should be treated with sequential hormonal therapies until all of these are exhausted before moving to chemotherapy. In the rare case of a patient who presents with visceral crisis, it may be appropriate to start with chemotherapy because there is a rapid response with this treatment. Visceral crisis is severe organ dysfunction and not the mere presence of visceral metastases.

Endocrine Therapy
Approximately 70 percent of women with breast cancer have hormone-responsive disease. Anti-hormonal therapy was actually the first kind of targeted therapy. Removing sources of female hormones as a treatment for breast cancer with bilateral oophorectomy was first recognized in 1896 by George Beatson, a Scottish surgeon. The estrogen receptor was not discovered until 1968. In 1977, tamoxifen, a selective estrogen receptor modulator (SERM), was the first pharmaceutical endocrine therapy to be approved for the treatment of MBC. In the late 1990s nonsteroidal aromatase inhibitors (AIs), such as anastrozole and letrozole, were approved for the first-line or later-line treatment of postmenopausal women with HR+ breast cancer. The steroidal AI, exemestane, was also approved for the later-line treatment of postmenopausal women with HR+ breast cancer. More recently, in the 2000s, the estrogen receptor down-regulator, fulvestrant, was approved for the treatment of postmenopausal women with HR+ advanced breast cancer whose disease has progressed on previous endocrine therapy. Other agents have come along since 2012 that target other pathways in MBC, including mTOR inhibitors (everolimus) and CDK 4/6 inhibitors (palbociclib, ribociclib, abemaciclib). These agents are discussed later.

Hormonal therapy options are chosen on the basis of the type of prior adjuvant treatment, disease-free interval, and extent of disease at time of recurrence. A specific hormonal agent may be used again if recurrence occurs greater than 12 months from the last treatment. For example, a woman has a recurrence of breast cancer two years after finishing five years of adjuvant AI therapy. In this case it would
be appropriate to re-treat with an AI. The use of combined endocrine therapy and chemotherapy is not recommended. Patients should be encouraged to consider enrolling in clinical trials, including patients receiving treatment in the first-line setting.

Endocrine therapies have different mechanisms of action and target different parts of the ER-mediated signaling pathways. SERMs, such as tamoxifen and toremifene, competitively bind to estrogen receptors. Aromatase inhibitors, such as anastrozole, letrozole, and exemestane, block the activity of the enzyme aromatase, which is responsible for estrogen synthesis in peripheral tissues and is the main source of endogenous estrogen in postmenopausal women. Fulvestrant is a selective estrogen receptor down-regulator (SERD) that acts as a pure antagonist to the estrogen receptor with no known agonist effects, and has been shown to bind, block, and increase the degradation of the estrogen receptor. Regardless of the specific mechanism of action, all endocrine therapies ultimately inhibit ER-mediated signaling to prevent growth of tumor cells dependent on the ER pathway. Exhibit 2 shows where the current therapies and some investigational agents for HR+ metastatic cancer work.

First-Line Therapy
In the first-line setting for HR+, HER- MBC, fulvestrant 500 mg intramuscularly once a month produces better responses than AIs in postmenopausal women including progression-free survival (PFS). Using fulvestrant, the median PFS is over 16 months, which is a significant improvement over AIs, tamoxifen, and chemotherapy in the first-line setting.

Cyclin D-dependent kinase 4 and 6 (CDK4/6) inhibitors [abemaciclib (Verzenio®), ribociclib (Kisqali®), palbociclib (Ibrance®)] are the breakthrough therapy that almost did not happen. Palbociclib a potent, selective, reversible inhibitor of CDK4/6 was the first agent to be evaluated. Initially, it did not show anticancer properties, but an evaluation against breast cancer cell lines showed efficacy. Protein kinases are key regulators of sequential progression through the G1, S, G2, and M phases of the cell cycle; these agents inhibit CDK4/6 to halt cell cycling and work in cancers that are ER+ because they express Rb, a master cell cycle regulator (Exhibit 3).

Patients treated with palbociclib and letrozole have a 10-month longer PFS over letrozole alone.
The FDA granted palbociclib accelerated approval in 2015 for first-line treatment in ER+ HER2-MBC. Similar PFS data was seen in a study of ribociclib combined with letrozole compared with letrozole alone (~10 months PFS advantage). This agent was FDA approved in March 2017. The combination of a CDK 4/6 inhibitor and an AI results in the highest PFS of any of the first-line hormonal treatments. The combination of a CDK 4/6 inhibitor and hormonal therapy is becoming the gold standard for first-line treatment of postmenopausal women with ER+, HER2- MBC.

Abemaciclib is the third CDK4/6 inhibitor approved and appears to be the most potent. Although studied in the first-line setting, abemaciclib has not yet been FDA approved for use in the first-line setting. It is FDA approved as monotherapy or with fulvestrant as second-line therapy.

The important adverse effects with the CDK 4/6 inhibitors are neutropenia and leukopenia. Two-thirds of patients on palbociclib or ribociclib will develop Grade 3 or 4 neutropenia or leukopenia. This neutropenia is not as severe as what is seen with chemotherapy. High rates of febrile neutropenia or infections are not seen. Neutropenia does not require growth factors for management. A complete blood count (CBC) with differential should be done every two weeks for two cycles of therapy. Palbociclib and ribociclib are given three weeks on and one week off to allow counts to increase; however, in case of neutropenia, a longer period of time off therapy can be used to allow for the counts to recover.

Abemaciclib is given daily because it causes a much lower rate of neutropenia or leukopenia. A unique adverse effect of ribociclib is QT prolongation, so an EKG is needed prior to starting therapy, at two weeks of therapy, and at the beginning of the second cycle. Abemaciclib causes much more diarrhea compared with the other two in the class. Patients may need concomitant use of Imodium or a dosage reduction to reduce the diarrhea.

With minor differences in adverse effects, the three agents appear to be very comparable in terms of safety and efficacy. Exhibit 4 compares the three available CDK4/6 inhibitors.

Clinicians have questioned whether premenopausal women should be treated the same as postmenopausal women in terms of using the CDK4/6 inhibitors. There is one study of ribociclib in combination with tamoxifen or an AI and goserelin in premenopausal women (MONALEESA-7) which showed about a 10-month improvement in PFS. This study confirmed that clinicians should be treating younger patients with a CDK4/6 inhibitor. There are also good data showing that a CDK4/6 inhibitor in combination with an AI can be used to treat those with visceral disease, so this combination will likely be an alternative to chemotherapy.

Overall, first-line hormone therapy should be the mainstay in patients with ER+ HER2- MBC, including those with visceral disease. Fulvestrant monotherapy, letrozole plus palbociclib or letrozole plus ribociclib are the preferred options. It does not appear to matter which agent/combination is used.
First and which is used in second or third line. Data now supports use of ribociclib in premenopausal women in combination with goserelin and tamoxifen or an AI.

**Second-Line Therapy**

Despite several endocrine therapy options, the majority of patients with advanced breast cancer eventually develop resistance. At disease progression, performance status, prior treatment and response, toxicity, and patient goals and wishes have to be considered. Most of the agents used in second-line therapy and beyond have been shown to increase PFS and not overall survival (OS). In terms of treating ER+ MBC, it is important to note that it is difficult to prove that any individual medication improves OS significantly for several reasons. This population of patients tends to live a long time with their disease compared to other groups, such as triple negative breast cancer, and are thus exposed to multiple different medications. In many of the medication trials, the patients have been heavily pretreated with various classes of agents and even chemotherapy. The composite effect of all the medications appears to be a difference in survival over time for the ER+ MBC patient.

Everolimus, an mTOR inhibitor, is an option for second-line therapy. There is strong preclinical rationale for targeting the PI3K/mTOR/AKT pathway as a method to overcome endocrine resistance. It has been demonstrated to improve PFS by 4.3 to 9 months.\textsuperscript{15-17} This agent works best in those cancers with acquired resistance and has been studied in combination with fulvestrant, tamoxifen, and exemestane. It does not appear to be effective in the first-line setting and presence of PI3K pathway mutations are not predictive of benefit in the second-line setting.

Stomatitis is the most common adverse effect with everolimus and can be prevented with a steroid mouthwash prescribed at the initiation of therapy.\textsuperscript{18} The mouthwash is prescribed as 10 mL of alcohol-free dexamethasone 0.5 mg per 5 mL oral solution swished for two minutes and then spit out four times daily. The rate of Grade 2 or higher mucositis was 2 percent with this regimen in the SWISH trial compared with 8 percent of Grade 3 in other everolimus trials.\textsuperscript{17,18}

CDK4/6 inhibitors can also be used at the time of progression on endocrine therapy. In combination with fulvestrant, palbociclib improved median PFS by five months.\textsuperscript{19} Based on this trial, palbociclib received FDA approval for use in the second- or third-line setting. Abemaciclib was FDA approved

<table>
<thead>
<tr>
<th>Exhibit 4: Comparing the CDK 4/6 Inhibitors\textsuperscript{13}</th>
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<tbody>
<tr>
<td>Palbociclib</td>
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</table>
| **IC\textsubscript{50}** | CDK 4: 9-11 mM  
CDK 6: 15 mM | CDK 4: 2 mM  
CDK 6: 5 mM | CDK 4: 11 mM  
CDK 6: 39 mM |
| **Dosing** | 125 mg daily  
(3 weeks on, 1 week off) | 150 mg twice daily  
(continuously) with endocrine therapy  
OR 200 mg bid | 600 mg daily  
(3 weeks on, 1 week off) |
| **ORR in monotherapy** | 6% | 17% | 3% |
| **CNS penetration** | No | Yes | No |
| **Common adverse events (%)** | All grades  
Grade 3/4 | All grades  
Grade 3/4 | All grades  
Grade 3/4 |
| Neutropenia | 95  
54 | 88  
27 | 46  
29 |
| Thrombocytopenia | 76  
19 | 42  
2 | 37  
10 |
| Fatigue | 68  
0 | 65  
13 | 29  
3 |
| Diarrhea | 16  
0 | 90  
20 | 22  
3 |
| Nausea | 23  
0 | 65  
5 | 46  
2 |
| Vomiting | 5  
0 | 35  
2 | 25  
0 |
| QTc prolongation | NR | NR | NR  
8  
0 |
| **FDA Approval Status** | 2015: 1st line (with letrozole)  
2016: 2nd line (with fulvestrant) | 2017: Monotherapy or  
2nd line with fulvestrant | 2017: 1st line (with letrozole) |
in September 2017 in combination with fulvestrant for women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. It increases PFS about seven months over placebo.\textsuperscript{20} In addition, abemaciclib is the only CDK4/6 inhibitor that has shown activity as monotherapy and is FDA approved as monotherapy for women and men with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.\textsuperscript{21}

Overall, second-line options include fulvestrant (if not used in the first-line setting), palbociclib or abemaciclib with fulvestrant, single-agent abemaciclib, and exemestane or fulvestrant with everolimus. Single-agent chemotherapy is also an option. There are no data to support using a CDK4/6 inhibitor in the second-line setting if the patient progressed on one in the first-line setting. Studies addressing this issue are now enrolling.

Questions to be answered about CDK4/6 Inhibitors
Because the CDK4/6 inhibitors are new, there are still many questions about their optimal use to be answered. At this point, there does not appear to be specific biomarkers that indicate response to CDK4/6 inhibition. Currently, there is not a way to determine which patients will get the most benefit or whether everyone with HR+ MBC should receive one of these agents. Also unanswered is whether there is a role for continuation of CDK 4/6 inhibition beyond disease progression. There are two ongoing trials on this issue. At this time, there is not a role for continuation beyond progression outside of a clinical trial. It has not yet been determined if these agents improve OS. There was not an OS benefit seen in the Phase II trials, but longer term follow-up data from the pivotal Phase III studies will hopefully answer this question.

Improving Clinical Outcomes
Optimizing medication adherence is important for improving clinical outcomes to treat cancer, particularly when oral agents are used. Patients may not understand the importance of taking these as directed regularly for many years. Correctly taking the intermittently scheduled palbociclib and ribociclib and twice daily abemaciclib can be complicated for patients. It is especially important to emphasize to patients to continue their other medications during the week off of the CDK 4/6 inhibitor.

Adverse effects can lead to nonadherence. The dose of the CDK4/6 inhibitors can be reduced to manage some of the adverse effects, but this can cause additional complications. Dose reduction with palbociclib from 125 mg to 100 mg daily will require a new prescription and possibly a new prior authorization which can delay therapy. It is easier to reduce the ribociclib dose because it comes as 200 mg tablets, so the dose can easily be decreased from 600 mg to 400 mg. Dose reduction can be done to help with diarrhea from abemaciclib and is easy to do with the 50 mg tablets. Clinicians need to be proactive in preventing and managing adverse effects with any of the agents used to treat MBC.

Another way to manage adverse effects is withholding doses. For the CDK 4/6 inhibitors, they may need to be held beyond the usual one week off schedule in order to allow blood counts to increase sufficiently. The impact of dose holds can complicate laboratory monitoring schedules. Dose holding can also be confusing for patients, and it is important to communicate clearly when to restart therapy and how the restart impacts their dosing cycles. There are also many other reasons for nonadherence with MBC treatments, including financial challenges, high prescription copayments, lack of social support, poor health care provider communication, and lack of transportation. Clinicians need to be aware of these potential barriers to adherence and proactively address them.

Another way to improve outcomes is with shared decision-making. The SHARE Approach presents a five-step process for decision-making that includes exploring and comparing the benefits, harms, and risks of each option through meaningful dialogue about what matters most to the patient: Seek your patient’s participation, help your patient explore and compare treatment options, assess your patient’s values and preference, reach a decision with your patient, and evaluate your patient’s decision.\textsuperscript{22,23} Patients and their families/caregivers who are engaged in a decision-making process are more likely to arrive at a treatment decision that works best for all those involved. This type of approach can be used to improve quality outcomes in oncology practices.

Investigational Therapies
Numerous targeted therapies are currently under investigation. A pan-PI3K inhibitor (buparlisib) has been investigated and found to be modestly effective but caused major adverse effects. Investigation on it has halted for now. Early trials of PI3K specific inhibitors (taselisib, alpelisib) have shown potential. These agents appear to be more effective in those with PI3K mutations.

Several trials are investigating the CDK4/6 inhibitors in the early adjuvant disease setting in pa-
tients with high risk of recurrence. Other trials are investigating how to overcome CDK4/6 inhibitor resistance. It also appears that CDK4/6 inhibition makes breast cancer cells more sensitive to immunotherapy, so using them in combination is being studied. CDK4/6 inhibition triggers anti-tumor immunity, increases antigen presentation and appears to be synergistic with checkpoint inhibition. Studies of immunotherapy alone have not been very successful in breast cancer because the tumor cells are not very immunogenic. In HR+ MBC resistance to endocrine therapy, total mutational burden increases, but these tumors are still generally immunologically ‘cold.’ There may be a role for the CDK 4/6 inhibitors in other breast cancer subtypes. Some tumors that are HER2+ appear to respond to abemaciclib, and a trial is ongoing to evaluate in this population in combination with trastuzumab. Synergistic combination of CDK 4/6 inhibitors with other targeted therapies is being evaluated. Combinatorial drug screen on PIK3CA mutant cancers with decreased sensitivity to PI3K inhibitors revealed CDK 4/6 and PI3K inhibition was synergistic.

There is also a great deal of work ongoing in identifying and targeting additional genetic mutations in breast cancer. Some of these include ESR1, FGFR1, and HER2 mutations.

Because ERα plays a critical role in resistance, additional SERDs are under investigation. HR+ breast cancer continues to rely on the ER in the endocrine resistant state. Targeting ERα in the endocrine resistant state requires a dual mechanism of blocking ER activity by binding to ER to antagonize transcriptional activity and reducing the ER protein level to induce conformational changes. Several SERDs are in Phase I and II trials, including RAD1901, bazedoxifene, GDC-810/ARN-810, and GDC-927/SRN-927.

Entinostat, a histone deacetylase (HDAC) inhibitor, is under development for breast and several other types of cancer. HDAC is an enzyme that regulates chromatin structure and gene transcription.

**Conclusion**

Combining CDK4/6 inhibition with hormonal therapy is now the standard option for first- or second-line metastatic therapy given significant increase in PFS (though no OS benefit yet seen). It is important that patients be educated on the importance of adherence with these agents and any other therapy for MBC. Currently, the three agents in this class appear to be equally effective, with minor differences in adverse effects. It is still unclear which patients may do just as well with endocrine therapy alone. There are ongoing studies addressing many of the unanswered questions about the optimal use of these agents.

**References**


