National Comprehensive Cancer Network®

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Program Overview/Statement of Need

Recently updated guidelines for HR+/HER2- advanced or metastatic breast cancer include treatment recommendations for the use of inhibitors of CDK 4/6 and the PI3K/Akt/mTOR signal cascade. The emergence and approval of several CDK 4/6 inhibitors and everolimus, an mTOR inhibitor, warrant an assessment of new and emerging data to determine which agents should be used in specific patients with differing menopausal status and treatment outcomes goals.

Use of Novel Combination Therapies in the Treatment of Advanced HR+/HER2- Breast Cancer will frame treatment decisions within the context of patient cases to facilitate care that is consistent with clinical guidelines and consensus recommendations. Guidance will also be provided to appropriately integrate PI3K/Akt/mTOR and CDK 4/6 targeted therapies into clinical practice for optimal personalized medicine for pre-, peri-, and post-menopausal HR+/HER2- breast cancer patients.

Target Audience

This activity is intended for community-based medical oncologists and other clinicians involved in the care of patients with advanced or metastatic breast cancer.

Accreditation

ACCME ACCREDITED

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Potomac Center for Medical Education and Rockpointe Oncology. The Potomac Center for Medical Education is accredited by the ACCME to provide continuing medical education for physicians.

For information about the accreditation of this activity, please email: contact@potomacme.org.

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Credit Designation

The Potomac Center for Medical Education designates this enduring material for a maximum of *1.0 AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Instructions for Obtaining Credit

To receive credit, learners must complete an online post-test and evaluation located at: www.rockpointe.com/breastcancersupplement.

Fee information

There is no fee for this educational activity.

Educational Objectives

This program is designed to address the following IOM competencies: provide patient-centered care and employ evidence-based practice.

At the conclusion of this activity, participants should be able to demonstrate the ability to:

- Evaluate the updated clinical guidelines for combination therapies in the treatment of HR+/HER2- advanced breast cancer patients
- Integrate clinical data regarding the use of CDK 4/6 inhibitors and mTOR inhibitors to treat HR+/HER2- advanced breast cancer, including appropriate subpopulations
- Mitigate toxicities associated with multi-drug treatment regiments to improve patient outcomes
- Recognize potential drug-drug interactions to plan effective and safe treatment regimens for each patient

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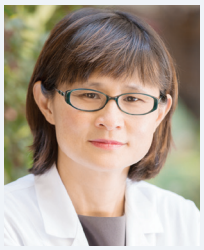
Faculty



Jenny C. Chang, MD
Director
Houston Methodist Cancer Center
Houston, TX

Jenny C. Chang, MD, is Director of the Cancer Center at Houston Methodist Hospital and a Professor at Weill Cornell Medical School. She obtained her medical degree at Cambridge University in England, and then completed fellowship training in medical oncology at the Royal Marsden Hospital/Institute for Cancer Research in the United Kingdom. She was awarded a research doctorate from the University of London. Her recent work has focused on the intrinsic therapy resistance of cancer stem cells (CSCs), which has led to several publications and international presentations. In addition, she has been awarded several federal grants to evaluate novel biologic agents and holds patents on new technologic advances and therapeutic agents.

Dr. Chang has worked in the field of CSCs for more than 10 years. After her discovery that CSCs are chemo-resistant, and that targeting the EGFR/HER2 pathway can decrease this subpopulation, Dr. Chang has played a key role in demonstrating some of the limitations and mechanisms of CSCs. Her work is now focused on the mechanisms that regulate CSCs, as well as initiating and planning clinical trials that target this critical tumor-initiating subpopulation. She is also interested in characterizing the cross-talk between these different pathways that may lead to mechanisms of resistance, and has identified some of the chief regulatory pathways, including inducible nitric oxide (iNOS) and JAK/STAT3 signaling involved in CSC self-renewal. She is a world-renowned clinical investigator, credited as one of the first to describe intrinsic chemo-resistance of CSCs.

Ruth O'Regan, MD
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Disclosure Statement

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Use of Novel Combination Therapies in the Treatment of Advanced HR+/HER2– Breast Cancer

Abstract

Endocrine therapy remains the backbone for treatment of hormone receptor-positive breast cancer in the metastatic setting. Despite the effectiveness of endocrine therapy, primary and acquired endocrine resistance continue to be important clinical challenges. The landscape of metastatic breast cancer treatment has changed considerably with the incorporation of novel agents, including cyclin-dependent kinase 4/6 and mammalian target of rapamycin inhibitors. This article reviews current endocrine treatment strategies and recent and ongoing studies of combination therapies in metastatic hormone receptor-positive, HER2-negative breast cancer.

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Introduction

Endocrine therapy (ET) remains the backbone for treatment of hormone receptor-positive (HR+) breast cancer in the metastatic setting. Despite the effectiveness of ET, primary and acquired endocrine resistance continue to be important clinical challenges. The landscape of metastatic breast cancer treatment has changed considerably with the incorporation of novel agents, including cyclin-dependent kinase (CDK) 4/6, and mammalian target of rapamycin (mTOR) inhibitors. This article reviews current endocrine treatment strategies and recent and ongoing studies of combination therapies in metastatic HR+, HER2-negative (HER2−) breast cancer.

ET

The estrogen receptor (ER) plays a fundamental role in the development and progression of HR+ breast cancer. ET is targeted toward inhibiting activation of ER via several different mechanisms. These include direct inhibition of ER by selective estrogen receptor modulators (SERMs), selective ER degraders (SERDs), and deprivation of the receptor's ligand by blocking estrogen production via aromatase enzymatic inhibition.

Tamoxifen is a nonsteroidal triphenylethylene derivative that acts as a SERM, with antagonist properties in mammary tissue. Tamoxifen has demonstrated efficacy and a favorable toxicity profile compared with chemotherapy as first-line treatment for HR+ breast cancer. A systematic review of 86 clinical trials has shown an objective response rate (ORR) of 34%, with an additional 19% experiencing stable disease for at least 6 months.[1] Subsequently in 1977, the FDA approved tamoxifen for treatment of breast cancer with a standard dose of 20 mg by mouth once daily.

Aromatase inhibitors (AIs) have shown significant improvements in survival and remain part of a first-line strategy for postmenopausal patients per current guidelines.[2,3] AIs are subdivided into steroidal and nonsteroidal inhibitors, which interact with the aromatase enzyme differently. Nonsteroidal AIs bind non-covalently and reversibly to the aromatase protein, whereas steroidal AIs may bind covalently and irreversibly to the aromatase enzyme. Nonsteroidal AIs include anastrozole and letrozole, and exemestane is classified as a steroidal AI. Ferreti et al[4] pooled 6 phase III clinical trials comparing AIs versus tamoxifen, which showed an improvement in ORR, time to progression (TTP), and disease control rate (DCR) of AIs over tamoxifen.[4] Notably, no difference was found in overall survival (OS).

Fulvestrant is a SERD approved for treatment of HR+ metastatic breast cancer in postmenopausal patients. It is similar to tamoxifen in that fulvestrant competitively binds to ER, but with a higher affinity.[5] In the CONFIRM trial, patients were randomized to receive fulvestrant 500 mg versus 250 mg dosing strategies in the second-line setting.[6] Progression-free survival (PFS) was significantly longer for the 500 mg dosing strategy (6.5 vs 5.5 months;

P=.006). However, ORR and DCR were similar in both arms. The final data analysis showed that median OS (mOS) was 26.4 versus 22.3 months with 500 mg versus 250 mg of fulvestrant (*P*=.016). Based on these data, current treatment guidelines recommend using the 500 mg dose with a loading schedule (treatment start, day 15, day 28, then once per month).[2,3]

To assess the efficacy of fulvestrant in the first-line setting, the FIRST trial compared fulvestrant (500 mg) with anastrozole.[7] Of note, patients in this study could have received previous ET in the adjuvant setting for early HR+ breast cancer if last dose was >1 year prior. Fulvestrant was at least as effective as anastrozole in terms of DCR and ORR, but was associated with longer mOS (54.1 vs 48.4 months; *P*=.041). FALCON is a phase III trial studying fulvestrant (500 mg) versus anastrozole in postmenopausal patients with de novo metastatic HR+ breast cancer with no previous exposure to ET.[8] This study showed that fulvestrant improved mPFS by 2.8 months compared with anastrozole (16.6 vs 13.8 months; *P*=.049).

Research continues to examine whether using more than one endocrine agent can improve response rates and clinical outcomes over single-agent therapy. The FACT trial compared combined fulvestrant (250 mg) and anastrozole versus anastrozole alone in patients with recurrent disease after treatment for early HR+ breast cancer.[9] Both postmenopausal and premenopausal patients on gonadotropin-releasing hormone (GnRH) agonist were eligible. No difference was found in outcomes between the study arms, with a mOS of 37.8 versus 38.2 months (*P*=1.00) in the combination and control arms, respectively.

SWOG S0226 is a phase III trial that also compared fulvestrant (250 mg) in combination with anastrozole versus anastrozole alone.[10] This patient population included those who had no prior therapy for metastatic disease. The original protocol excluded women who received adjuvant AIs or fulvestrant, but adjuvant tamoxifen was allowed. In an early amendment, patients who received adjuvant AIs were eligible if therapy had been completed >1 year before enrollment. It showed that combination therapy significantly improved mPFS (15.0 vs 13.5 months; *P*=.049) and mOS (47.7 vs 41.3 months; *P*=.049). Given the difference in study populations, the percentages of ET-naïve patients were higher in SWOG S0226 (59.7%) versus FACT (34.4%), which may have contributed to the discordant results. Currently, combination ET in postmenopausal women is not routinely recommended in the first-line setting.[2]

Novel Agents for HR+ Breast Cancer: CDK4/6 Inhibitors

Cyclin-dependent kinases (CDKs) are a group of serine/threonine kinases that play a key regulatory role in cell cycle progression. Preclinical studies have identified alterations of cell cycle regulators in HR+ breast cancer and provided the rationale for the potential therapeutic role for CDK4/6 inhibition. Several oral, selective CDK 4/6 inhibitors have been approved for HR+ metastatic breast cancer. These include palbociclib, ribociclib, and abemaciclib (Table 1).[11]

CDK 4/6 Inhibition in Postmenopausal Patients

Several studies have validated the role of CDK 4/6 inhibition in combination with ET (Table 2). The PALOMA-1 phase II trial studied palbociclib with or without letrozole in postmenopausal patients as upfront treatment for advanced disease.[12] A statistically significant improvement was seen in mPFS with the addition of palbociclib (20.2 vs 10.2 months; *P*=.0004). The most frequent treatment-related adverse events in the combination arm included

Table 1. CDK 4/6 Inhibitors

Characteristics	Palbociclib	Ribociclib	Abemaciclib
Inhibitory Concentration 50 (IC50)[11]			
CDK 4	9–11 nM	10 nM	2 nM
CDK 6	15 nM	39 nM	5 nM
Dose	125 mg daily[a]	600 mg daily[a]	200 mg twice daily[b]
Major dose-limiting toxicity	Neutropenia[14] (79.5%)	Neutropenia[15] (76.9%)	Diarrhea[19] (81.3%)

Abbreviation: CDK, cyclin-dependent kinase.
[a]3 weeks on/1 week off
[b]Continuously

neutropenia, anemia, and fatigue. No cases of febrile neutropenia were observed. However, an increased rate of grade 3/4 infections and pulmonary embolism was seen in the palbociclib/letrozole arm (5% vs 0% for both adverse events). This study lead to the approval of letrozole and palbociclib for the first-line treatment of HR+ metastatic breast cancer in postmenopausal patients by the FDA in 2013. This regimen is a category 1 recommendation for first-line treatment in postmenopausal and premenopausal patients with ovarian ablation/suppression per the NCCN Guidelines.[2] Interestingly, updated survival data presented at ASCO in 2017 did not show a mOS benefit (37.5 vs 34.5 months in the combination and control arms, respectively; *P*=.281).[13]

PALOMA-2 is the larger phase III study to confirm the findings of PALOMA-1. This study verified the benefit of adding palbociclib to letrozole, with improvement in mPFS (24.8 vs 14.5 months; *P*<.001).[14] Subgroup analysis of PFS according to other characteristics confirmed a consistent benefit of palbociclib/letrozole across all subgroups. This included patients with visceral disease and history of prior ET. The ORR was improved in the

Table 2. Clinical Studies of CDK 4/6 Inhibitors with Endocrine Therapy in Patients with Advanced HR+, HER2– Breast Cancer

Trial Name	Treatment	Population	N	ORR, %	Median TTP/PFS, mo	Median OS, mo
CDK 4/6 Inhibitors + ET in Postmenopausal Patients						
PALOMA-1[12]	Palbociclib + letrozole vs letrozole	No prior treatment for advanced disease	165	43 vs 33 *P*=.13	20.2 vs 10.2 *P*=.0004	Not reported
PALOMA-2[14]	Palbociclib + letrozole vs letrozole	No prior treatment for advanced disease	666	42.1 vs 34.7[a]	24.8 vs 14.2 *P* <.001	37.5 vs 34.5 *P*=.211
MONALEESA-2[15]	Ribociclib + letrozole vs letrozole	No prior treatment for advanced disease	668	42.5 vs 28.7 *P*=9.18 x 10^{-5}	25.3 vs 16.0 *P*=9.63 x 10^{-8}	Not reported
MONARCH-3[19,20]	Abemaciclib + NSAI vs NSAI	No prior treatment for advanced disease	493	61.0 vs 45.5 *P*=.003	28.2 vs 14.8 *P*=.000002	Not reported
MONALEESA-3[21,22]	Ribociclib + fulvestrant vs fulvestrant	Treatment naïve and ET-resistant disease	726	32.4 vs 21.5 *P*=.0009	NR vs 18.3[a] (1st line cohort)	Not reported
CDK 4/6 Inhibitors + ET in Premenopausal Patients						
MONALEESA-7[23]	Ribociclib + NSAI/ tamoxifen + goserelin vs NSAI/tamoxifen + goserelin	No previous ET, up to 1 line of systemic chemotherapy for advanced disease allowed	672	41 vs 30 *P*=.00098	23.8 vs 13.0 *P*<.0001	Not reported
CDK 4/6 Inhibitors in ET-Resistant Disease						
PALOMA-3[26]	Palbociclib + fulvestrant vs fulvestrant	ET-resistant disease, up to 1 line of systemic chemotherapy for advanced disease allowed	521	24.6 vs 10.9 *P*=.0012	9.5 vs 4.6 *P*<.0001	Not reported
MONARCH-1[28]	Abemaciclib	ET-resistant disease with progression after 1 line of systemic chemotherapy for advanced disease	132	19.7	6.0	17.7
MONARCH-2[29]	Abemaciclib + fulvestrant vs fulvestrant	ET-resistant disease	669	35.2 vs 16.1 *P*<.001	16.4 vs 9.3 *P*<.001	Not reported
MONALEESA-3[21,22]	Ribociclib + fulvestrant vs fulvestrant	Treatment naïve and ET-resistant disease	726	32.4 vs 21.5 *P*=.0009	14.6 vs 9.1[a] (ET-resistant cohort)	Not reported

Abbreviations: CDK, cyclin-dependent kinase; ET, endocrine therapy; HR+, hormone receptor-positive; NR, not reached; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.
[a]Statistically significant

palbociclib/letrozole group compared with letrozole alone (42.1% vs 34.7%). Data on OS were immature at time of publication and will be presented in the future. Similar to in PALOMA-1, neutropenia was the most common adverse event in the combination group, with a grade 3/4 rate of 66.4%.

Ribociclib has shown similar efficacy in postmenopausal patients with HR+ metastatic breast cancer. MONALEESA-2 is the phase III trial studying ribociclib plus letrozole versus letrozole monotherapy in postmenopausal patients in the first-line setting.[15] The addition of ribociclib lead to an improvement in mPFS (25.3 vs 16.0 months; P=9.63 x 10^{-8}). The ORR of ribociclib/letrozole versus letrozole alone was 42.5% versus 28.7%, respectively (P=9.18 x 10^{-5}). The most common adverse event in the ribociclib arm was neutropenia (59.3%). Other grade 3/4 adverse events included hypertension, transaminitis, and QTc prolongation. Interruptions or dose reduction of ribociclib were noted in more than half of the patients and allowed most patients to remain on treatment. This combination is also a category 1 recommendation in the NCCN Guidelines for first-line treatment of HR+ metastatic breast cancer in postmenopausal and premenopausal patients with ovarian suppression/ablation.[2]

Abemaciclib is another orally bioavailable inhibitor of CDK 4/6 with low nanomolar potency and greater selectivity of CDK4.[11] This agent is active against multiple other CDK/cyclin complexes; this activity is thought to lead to its greater cytotoxic activity compared with palbociclib and ribociclib.[16,17] Additionally, abemaciclib has been shown to cross the blood-brain barrier.[18] MONARCH-3 is a phase III study comparing aromatase inhibitor therapy with or without abemaciclib. Again, mPFS was significantly improved in the abemaciclib arm (28.2 in abemaciclib arm vs 14.8 months; P=.000002).[19,20] The ORR was 61.0% in the abemaciclib arm compared with 45.5% in the control arm (P=.003). Abemaciclib in combination with an AI can also be considered in the first line setting, according to current NCCN Guidelines.[2] Notably, the toxicity profile with abemaciclib differs from that of palbociclib and ribociclib. In this study, most frequent adverse events were diarrhea, fatigue, nausea, and neutropenia.

Several trials are also studying the utility of combining CDK 4/6 inhibitors with other types of ET. The MONALEESA-3 trial compared fulvestrant in combination with ribociclib in postmenopausal patients with HR+ metastatic breast cancer.[21] Eligibility criteria included the following cohorts: (1) de novo advanced disease, (2) relapsed disease >12 months from completion of previous ET with no prior treatment for advanced disease, (3) relapsed disease on or within 12 months of ET with no treatment for advanced disease, (4) relapsed disease >12 months from adjuvant ET with subsequent progression on first line ET for advanced disease, and (5) advanced disease at diagnosis that has progressed on 1 line of ET. At data cut off, mPFS was improved with ribociclib/fulvestrant compared with fulvestrant alone across all cohorts (20.5 vs 12.8 months; P<.001). In the treatment-naïve subset (cohorts 1 and 2), mPFS was also improved with the addition of ribociclib (not reached vs 18.3 months; hazard ratio [HR], 0.577; 95% CI, 0.415–0.802).[22] The most common all-grade adverse events in the ribociclib arm included neutropenia (69.6%), nausea (45.3%), and fatigue (31.5%), consistent with past ribociclib studies. The only grade 4 event reported in ≥5% of patients was neutropenia, with a febrile neutropenia rate of 1.0%. QTc prolongation occurred 6.2% of patients, with no occurrence of torsades de pointes.

CDK 4/6 Inhibition in Premenopausal Patients

Treatment recommendations for premenopausal patients with HR+ metastatic disease has largely been extrapolated from studies in the postmenopausal population. Ongoing trials are looking at the role of adding CDK 4/6 inhibitors to ET in the premenopausal population. MONALEESA-7 is a phase III clinical trial studying pre- or perimenopausal patients with HR+ metastatic breast cancer to be randomized to ET (tamoxifen or AI) with GnRH agonist therapy with or without ribociclib.[23] Approximately 40% of patients were previously treated with ET for early HR+ breast cancer, most of which had progression less than 12 months after completion of ET. Consistent with the previous trials, the ribociclib arm showed a significant improvement in mPFS compared with ET with ovarian suppression alone (23.8 vs 13.0 months; P<.0001). Median PFS in the subgroup of patients treated with tamoxifen (n=177) as the combination partner was 22.1 months in the ribociclib arm and 11.0 months in the control arm (HR, 0.58; 95% CI, 0.39–0.88). In the subgroup treated with AI (n=495), mPFS was 27.5 months in the ribociclib arm compared with 13.8

months (HR, 0.57; 95% CI, 0.44–0.74). Toxicity was similar to past ribociclib trials, with grade 3/4 adverse events including neutropenia (61%), febrile neutropenia (2%), and QTc prolongation (7%). Despite the increased toxicity, quality of life measures showed a clinically meaningful improvement from patient baseline with the addition of ribociclib. Improvement in the EORTC QLQ-C30 pain score was observed as early as 8 weeks in the ribociclib arm. Median time to definitive deterioration as measured by the global health status/quality-of-life scale score of the EORTC QLQ-C30 was not reached (95% CI, 22.2 months–not reached) in the ribociclib group compared with 21.2 months (95% CI, 15.4–23.0 months) in the control arm (HR, 0.70; 95% CI, 0.53–0.92; *P*=.004). The activity of CDK 4/6 inhibitors has been validated in premenopausal patients regardless of the ET partner in studies of ET-resistant disease and is now incorporated as a category 1 first-line treatment recommendation in the NCCN Guidelines for postmenopausal patients or premenopausal patients treated with ovarian suppression/ablation.[2]

CDK 4/6 Inhibition in Endocrine-Resistant Disease

Breast tumors can have primary resistance to ET or may acquire resistance over time. The EFECT study is a phase III trial comparing fulvestrant and exemestane in postmenopausal patients who either relapsed within 6 months of discontinuation of adjuvant nonsteroidal AI or whose disease progressed during treatment with nonsteroidal AI. No difference was seen in time to progression, with a mTTP of 3.7 months in both arms (*P*=.65).

Dysregulation in cell cycle progression via alterations of key cell cycle checkpoints can contribute to loss of endocrine responsiveness.[24] Preclinical data has shown constitutive activation of cyclin D1-mediated pathways in the presence of ER inhibition as a contributing mechanism.[25] Therefore, targeting the cyclin D1–CDK 4/6 pathway is of increasing interest in ET-resistant disease. PALOMA-3 was a phase III trial studying the role of palbociclib in combination with fulvestrant in patients with endocrine-resistant disease.[26] Both postmenopausal and pre/perimenopausal patients on GnRH agonist therapy were considered eligible. Endocrine resistance was defined as disease relapse or progression after previous ET while on or within 1 month after treatment in the advanced setting, or while on or within 12 months of completion of adjuvant ET. Eligible patients could have progressed on several lines of ET and 1 line of systemic chemotherapy. The addition of palbociclib improved mPFS to 9.6 months compared with 4.6 months (*P*<.0001). The ORR of palbociclib/fulvestrant was 19% compared with 9% in the control arm (*P*=.0019). Subgroup analysis showed both pre/perimenopausal and postmenopausal patients benefit from the addition of palbociclib. NCCN Guidelines include palbociclib/fulvestrant as a treatment option for both pre- and postmenopausal patients who have progressed on prior ET.[2]

Hormone-receptor expression level did not significantly correlate with treatment response. To explore potential biomarkers, cell free DNA (cfDNA) analysis was performed, which detected *PIK3CA* mutations in 33% of patient samples. *PIK3CA* status did not significantly affect the magnitude of benefit associated with the addition of palbociclib to fulvestrant. Toxicity of this regimen is consistent with past palbociclib trials, with neutropenia being the most common adverse event in 65% of patients in the palbociclib arm. Febrile neutropenia was rare (n=3).

Other CDK 4/6 inhibitors have been studied in ET-resistant disease. Phase I data studying abemaciclib monotherapy in several solid tumors showed an ORR of 26% in patients with ET-resistant metastatic breast cancer.[27] The MONARCH-1 study is a single-arm phase II trial studying abemaciclib in patients who progressed on or after previous ET and up to 2 lines cytotoxic chemotherapy in the metastatic setting.[28] Abemaciclib showed single-agent activity with an ORR of 19.7% and a clinical benefit rate of 42.4%. Median PFS was 6.0 months.

MONARCH-2 was a phase III study of patients of any menopausal status (with pre/perimenopausal patients on GnRH agonist therapy) with ET-resistant disease to be treated with fulvestrant with or without abemaciclib.[29] Patients were required to have disease that progressed while on neoadjuvant or adjuvant ET, that progressed fewer than 12 months after adjuvant ET, or progressed while receiving ET for advanced disease. Eligible patients could only have shown progression on 1 line of ET with no history of cytotoxic chemotherapy for advanced disease. The addition of abemaciclib significantly extended mPFS (16.4 vs 9.3 months; *P*<.001). In addition, the ORR in the abemaciclib/fulvestrant arm was more than twice that of the fulvestrant monotherapy arm (35.2% vs 16.1%;

P<.001). Pre/perimenopausal patients (n=114) also benefited from the addition of abemaciclib, with statistically significant improvement in mPFS (not reached vs 10.5 months; *P*=.002). As seen with other abemaciclib trials, diarrhea was a predominant side effect (86.4%). Due to this safety evidence, the protocol was amended to reduce the starting dose of abemaciclib from 200 mg twice a day to 150 mg twice a day, with improvement in rates of grade 2/3 diarrhea.[30] Other adverse events included neutropenia (46.0%), nausea (45.1%), and fatigue (39.9%). Thromboembolic events were the most frequently reported serious adverse event. Abemaciclib in combination with fulvestrant is another treatment option recommended by the NCCN Guidelines for patients who have experienced progression on previous ET.[2]

As reviewed previously, the MONALEESA-3 trial compared fulvestrant in combination with ribociclib in postmenopausal patients with HR+ metastatic breast cancer. Eligible patients included those who received ET with subsequent relapse or progressive disease (cohorts 3–5).[21] Notably, this trial did not include patients who received prior cytotoxic chemotherapy for metastatic disease. At data cut off, mPFS was improved in the ribociclib/fulvestrant arm compared with fulvestrant alone across all cohorts (20.5 vs 12.8 months; *P*<.001). In patients with ET-resistant disease, mPFS was improved with the combination of ribociclib and fulvestrant compared with fulvestrant alone (14.6 vs 9.1 months, respectively).[22]

Biomarkers for CDK 4/6 Inhibition

Great interest exists in identifying biomarkers to expand the clinical utility of CDK 4/6 inhibition beyond metastatic HR+, HER2− breast cancer. Thus far, the most predictive biomarker for CDK 4/6 inhibition is ER positivity. An FDA analysis pooled raw data from 5 phase III randomized trials of CDK 4/6 inhibitors to explore subsets that may have different degrees of endocrine sensitivity.[31] Exploratory subset analyses focused on patients with de novo metastatic disease, bone-only metastases, disease-free interval >12 months, progesterone-receptor negative, and lobular cancer. Interestingly, the addition of CDK 4/6 inhibition confered benefit for all studied subsets, including those who thought to have more indolent disease biology.

To explore other potential biomarkers, it is important to understand the role of CDKs in cell cycle progression (Figure 1). Transition from G1 to the S phase is controlled by the tumor suppressor retinoblastoma (Rb) protein.[32] Inactivation of Rb via phosphorylation allows for cellular division to continue. During G1, growth signals allow cyclin D to complex with either CDK 4 or CDK 6 to phosphorylate Rb, which releases the transcription factor E2F to drive transcription and promote cell cycle progression.

High expression CDK 4 is not common in breast cancer, making this a poor biomarker for CDK 4/6 inhibition. However, high CDK 6 expression has been associated with shorter PFS in patients with ER-positive metastatic breast cancer treated with fulvestrant.[33] Preclinical data show that tumor cells with high CDK 6 expression undergo apoptosis after treatment with CDK 4/6 inhibition, whereas low expression demonstrated cell cycle arrest.[34] Further prospective study of CDK 6 expression as a biomarker is warranted.

Based on preclinical data, experts have hypothesized that overexpression of cyclin D1 or loss of p16 could predict response to CDK 4/6 inhibition.[35] Biomarker analysis of patient tumor samples from PALOMA-2 were analyzed for ER, Rb, p16, cyclin D1, and Ki-67 (a proliferative index) via immunohistochemistry (IHC).[36] Improvement in PFS with palbociclib and letrozole was observed in any level of ER expression and Rb-positive tumors. Interestingly, the benefit of palbociclib in cyclin D1 positive tumor did not vary with degree of positivity on IHC. Additionally, patients with p16-negative disease did not have a statistically significant benefit with the addition of palbociclib. The role of cyclin D1 amplification and/or loss of p16 in patient selection remains to be further studied.

Because CDK 4/6 inhibitors primarily exert influence on suppressing Rb phosphorylation, Rb expression may be a potential predictive factor. Patnaik et al[27] demonstrated that early changes in phosphorylation of Rb may be an indicator of clinical benefit in a phase I study of abemaciclib. Additionally, the biomarker analysis of PALOMA-2 showed that patients with Rb-positive tumors benefit from the addition of palbociclib to letrozole.[36] A phase II study enrolled patients with advanced breast cancer that was positive for Rb by IHC, regardless of HR and HER2 status.[37] In contrast, Rb positivity did not predict response or clinical benefit. Notably, this study is limited by small sample size in a cohort of

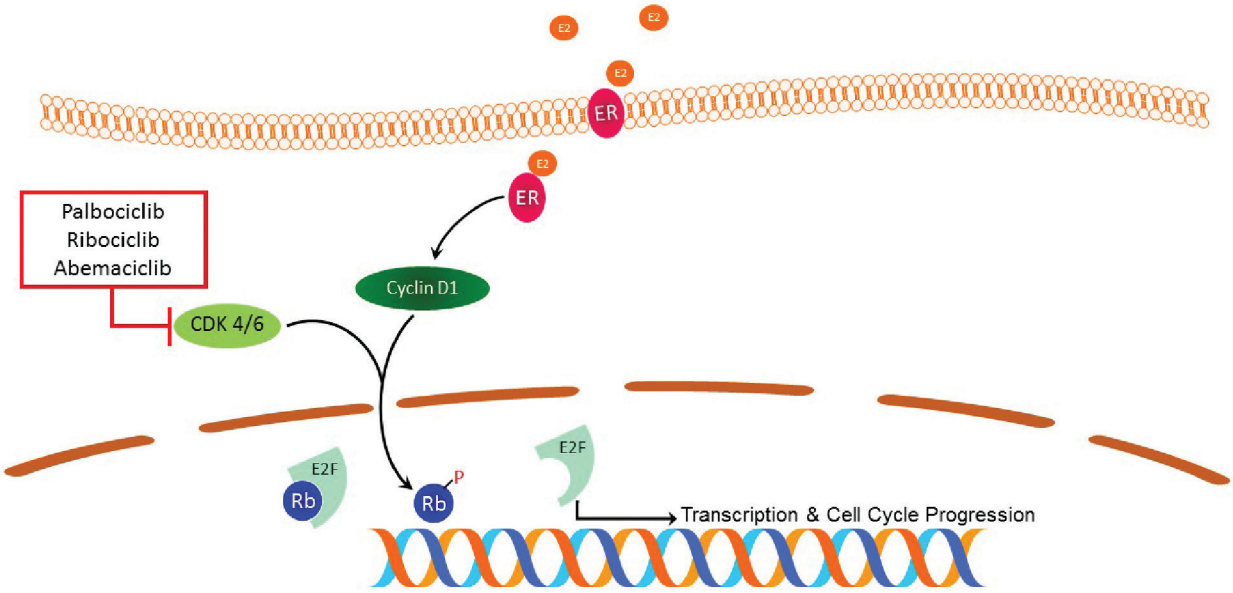

Figure 1. Estrogen Receptor Signaling and Cell Cycle Regulation
Abbreviations: CDK, cyclin-dependent kinase; ER, estrogen receptor; E2, estradiol; E2F, transcription factor; Rb, retinoblastoma protein.

patients who were heavily pretreated.

The cyclin E–CDK2 kinase complex is an alternative pathway that regulates Rb phosphorylation and cell cycle progression.[38] Amplification of C*CNE1* may play predict for primary resistance to CDK 4/6 inhibition. As part of the PALOMA-3 trial, pretreatment samples were analyzed with mRNA gene expression profiling.[39] Patients with low cyclin E before treatment with palbociclib had almost double the PFS of those who had high cyclin E expression (14.1 vs 7.6 months; *P*=.00238). Notably, this effect was more pronounced in metastatic tissues than in primary tissue, emphasizing the role of analyzing metastatic sites to direct therapy.

Investigation is ongoing to understand and identify mechanisms of acquired resistance to CDK 4/6 inhibition. Turner et al[40] studied circulating tumor DNA (ctDNA) samples from patients enrolled on the PALOMA-3 clinical trial to identify potential markers of resistance to palbociclib and fulvestrant. PALOMA-3 was a phase III randomized study of fulvestrant with or without palbociclib. As part of the trial, plasma samples for ctDNA analysis were banked at baseline and at the end of treatment for analysis. Driver mutations were acquired in both treatment arms and included *PIK3CA*, *ESR1* (Y537S), *ERBB2*, and *FGFR2/3*. Mutations uniquely acquired in the palbociclib arm include *RB1* mutations, though infrequent (4.8%). Regardless of treatment regimen, this study demonstrates the mutational changes that can occur over time. Hopefully, this modality can provide future biomarkers to guide clinicians on how to modify therapy

Targeting Mechanisms of Endocrine Resistance: MTOR and PI3K

Numerous and complex mechanisms underlie resistance to ET. Known mechanisms include dysregulation of ER signaling pathways, alterations in cell cycle progression, and cross talk between different growth factor and ER pathways. Resistance can be separated into 2 basic patterns of drug failure. Primary resistant tumors show no response to ET and are clinically defined as recurrent disease during adjuvant ET or progression within 6 months of ET for metastatic disease. Tumors that show initial response to therapy but then progress or recur reflect acquired resistance. This is clinically defined as progression while on ET for at least 6 months for metastatic disease or recurrent disease that develops at least 1 year after the completion of adjuvant ET.

Gain-of-function mutations in the gene encoding ERα (*ESR1*) have been identified in up to 40% of patients with metastatic ERα+ breast cancer.[41] These mutations cluster in the portion of the recep-

tor responsible for binding estrogen and result in a constitutively active receptor signaling and transcriptional regulation that is always "turned on" despite the absence of estrogen. These mutations arise predominately in patients with metastatic disease who have received previous aromatase inhibitors and are associated with reduced patient survival.[42] The SoFEA study looked at the efficacy of fulvestrant versus exemestane in patients with metastatic HR+ breast cancer.[43] Patients with wild-type *ESR1* did well with either agent. However, *ESR1*-mutation cancers had worse mPFS on exemestane compared with fulvestrant (2.6 vs 5.7 months; *P*=.02). Thus, *ESR1* mutations may be predictive of benefit from more novel ET agents over AIs. In the PALOMA-3 study, approximately 27% of patient samples had detectable *ESR1* mutations.[44] Interestingly, *ESR1* mutations were not predictive of benefit from CDK 4/6 inhibition with palbociclib in combination with fulvestrant. Other alterations in ER have been implicated, including loss of ERα, post-translational modification of ERα, and expression of ER cofactors.[45,46]

Growth factor signaling can affect ET responsiveness through the ability to stimulate survival and proliferation independent of ER activation. Alterations in fibroblast growth factor receptor (FGFR) and its downstream signaling are of interest in ET-resistant disease. Multiple genetic aberrations in FGFRs lead to increased pathway activation in breast cancer, the most common being *FGFR1* gene amplification.[47] Additionally, downstream activation of several targets, including *c-Myc* can lead to cell cycle progression independent of ER signaling. In vitro studies suggest that *c-Myc* amplification can decrease endocrine responsiveness.[48] However, few data are available evaluating the effect of *c-Myc* amplification on response to ET in patients with breast cancer, and those that exist are inconsistent with observations from preclinical studies.[49]

One of the more widely studied pathways in ET-resistant disease is the PI3K/AKT/mTOR pathway. Preclinical data have shown hyperactivation of this pathway as a mechanism of endocrine resistance.[50] Several clinical trials with PI3K and mTOR inhibitors have recently been completed in ET-resistant disease. Everolimus, a potent oral inhibitor of mTORC1, has been studied in combination with exemestane in postmenopausal women with AI-resistant disease in the phase III BOLERO-2 trial.[51] Median PFS improved to 6.9 months in the combination arm compared with 2.8 months in the exemestane monotherapy arm (*P*<.001). However, this benefit came at the cost of increased toxicity. The most common any-grade adverse events in the everolimus arm were stomatitis (56%), rash (36%), and diarrhea (30%). Other more-frequent grade 3/4 adverse events include hyperglycemia (4%), dyspnea (4%), and pneumonitis (3%). The TAMRAD trial compared tamoxifen with combination therapy with everolimus in postmenopausal patients with AI-resistant disease.[52] TTP was increased from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus everolimus.

Finally, everolimus has been studied in combination with fulvestrant in AI-resistant disease.[53] Median PFS improved from 5.1 to 10.3 months with the addition of everolimus (*P*=.02). Based on these data, the NCCN Guidelines note that everolimus in combination with ET (exemestane, tamoxifen, or fulvestrant) can be considered for patients who previously progressed on nonsteroidal AIs.[2] Interest in combining CDK and mTOR inhibition to overcome endocrine resistance has been shown. TRINITI-1 was a phase II trial combining ribociclib with everolimus and exemestane in patients who experienced progression on CDK 4/6 inhibition with AI.[54] An appreciable clinical benefit rate of 39.5% was seen. Further randomized trials studying this strategy are ongoing.

Inhibition of mTORC1 alone with everolimus can lead to activation of a feedback mechanism via AKT signaling, possibly leading to resistance.[55] Vistusertib (AZD2014) is a novel, dual inhibitor of mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin insensitive) that has been studied with the hypothesis that this agent may be superior to everolimus by allowing for complete blockade of the signaling pathway. Additionally, preclinical models suggest a relationship between higher exposure of mTOR inhibition and increased efficacy. The short half-life of vistusertib allows for the study of high-dose intermittent scheduling to be compared with continuous scheduling.

The MANTA study was a randomized trial to compare the efficacy of dual inhibition of vistusertib (both intermittent and continuous dosing schedules) and fulvestrant with everolimus/fulvestrant and fulvestrant monotherapy. Eligible patients were postmenopausal with AI-resistant disease. Interestingly, dual inhibition with vistusertib/fulvestrant had

worse PFS compared with everolimus/fulvestrant (7.6 vs 12.3 months, respectively; *P*=.01). No difference was seen between the 2 different dosing schedules of vistusertinib. Additionally, the everolimus arm had a higher ORR compared with continuously dosed vistusertinib (41.2% vs 30.4%). Although the mechanism behind the benefit seen with everolimus is still unclear, the feedback activation loop via mTORC2/AKT could possibly resensitize tumor cells to ET.

A plethora of compounds were developed to inhibit PI3K in breast cancer. They are classified according to specificity for each PI3K isoform as a pan-PI3K inhibitor, isoform-specific PI3K inhibitor, and dual-PI3K/mTOR inhibitors. Buparlisib is a pan-PI3K inhibitor that has the potential advantage of broadly targeting multiple oncogenic PI3K isoforms but also narrows the therapeutic window due to increased toxicity. The BELLE-2 study was a phase III trial studying fulvestrant with or without buparlisib in postmenopausal patients with ET-resistant disease.[56] The study met its primary endpoint for significant improvement in mPFS of 6.8 months compared with 4.0 months with the addition of buparlisib (*P*=.014). In a cohort of patients with *PIK3CA* mutations identified using ctDNA, the benefit of buparlisib was more substantial, with a mPFS of 7.0 months compared with 3.2 months (*P*<.001). In those with wild-type *PIK3CA* shown via ctDNA, no difference was observed between the 2 arms (6.8 months in both arms; *P*=.642). Across the full population, the ORR with buparlisib/fulvestrant was 12% compared with 8% with fulvestrant alone. Grade 3/4 adverse events occurred in 77.3% of patients in the buparlisib arm. The most frequent any-grade toxicities with buparlisib were nausea (37%), diarrhea (31%), hyperglycemia (28%), fatigue (27%), rash (24%), depression (22%), and stomatitis (20%). Of note, suicidal ideation was reported in 3 patients on buparlisib versus 2 in the control arm. Fortunately, no suicide attempts were made. Because of this toxicity, the buparlisib arm had a higher incidence of dose interruptions (51%), reductions (45%), and treatment discontinuation (39%). The most common adverse event leading to discontinuation of buparlisib was transaminitis.

BELLE-3 is another phase III trial studying the combination of buparlisib and fulvestrant. However, this study selected for more resistant disease, as patients had to have ET-resistant disease with progression on an mTOR inhibitor to be eligible.[57] The most common mTOR inhibitor before study enrollment was everolimus. Modest improvement was seen in mPFS (2.1 months; 3.9 vs 1.8 months; *P*=.0003). Patients with *PIK3CA* mutations seen via ctDNA had greater improvement in mPFS (4.2 vs 1.6 months; *P*=.00031) whereas those with wild-type *PIK3CA* seen via ctDNA did not (3.9 vs 2.7 months; *P*=.026). As seen in BELLE-2, the addition of buparlisib comes at the cost of increased toxicity. Grade 3/4 adverse events occurred in 62% of patients treated with buparlisib, most frequently including increased alanine transaminase (22%), increased aspartate amino transferase (18%), and hyperglycemia. Medical review confirmed that one patient in the buparlisib arm met criteria for Hy's law. Other all-grade adverse events of importance included depression (21%) and anxiety (18%). Three suicide attempts were reported in the buparlisib arm. Given the low benefit/toxicity ratio of buparlisib, it is unlikely this drug will be further developed or recommended for use in clinical practice.

PI3Kα is the primary isoform mutated in cancer. Its selective inhibition has been shown to block PI3K/AKT signaling.[58] The rationale for development of PIK3α-specific inhibitors is to maximize inhibition of the more oncogenic isoform, while sparing the patient from the increased toxicity of pan-inhibition. Taselisib is a potent inhibitor of PI3Kα with greater selectivity for *PIK3CA* mutant isoforms.[59] SANDPIPER was a phase III trial studying fulvestrant in combination with taselisib in patients with ET-resistant breast cancer harboring a *PIK3CA* mutation.[60] Modest clinical benefit was seen, with improvement in mPFS to 7.4 versus 5.4 months (*P*=.0037). The ORR with the taselisib combination was 28% compared with 11.9% with fulvestrant alone (*P*=.0002). As seen with other PI3K inhibitors, the combination is challenging in terms of tolerability. Grade 3/4 adverse events were seen in 32% of patients receiving taselisib. The most common toxicities reported in the taselisib arm were diarrhea (60.1%) and hyperglycemia (40.4%). This lead to increased rates of treatment discontinuation with taselisib.

Alpelisib is another PI3Kα isoform inhibitor with preferential activity against tumors with *PIK3CA* mutations. Early studies of alpelisib in combination with ET demonstrate a more favorable toxicity profile compared with other PI3K inhibitors. In a phase I dose-escalation study of alpelisib with le-

trozole, most common adverse events were diarrhea (80%), hyperglycemia (62%), fatigue (54%), and rash (42%).[61] Dose-limiting toxicity was grade 3 rash that was medically managed with supportive care and drug interruption. Alpelisib is also being studied in combination with fulvestrant.[62] In the *PIK3CA*-altered cohort, the clinical benefit rate (ORR plus stable disease > 24 weeks) was 45%. No patients with wild-type *PIK3CA* showed a response. The most frequently reported all-grade adverse events were diarrhea (56%), hyperglycemia (48%), and rash (48%). Based on these findings, the phase III SOLAR-1 trial is currently enrolling postmenopausal patients with ET-resistant disease with a planned analysis for *PIK3CA* mutation status using ctDNA.

Given the modest benefit shown with PI3K inhibition, great interest has been shown in combination therapy to sensitize tumor cells to PI3K inhibitors. A combinatorial drug screen on multiple *PIK3CA*-mutant cancers showed that dual CDK 4/6 and PI3K inhibition can improve initial responses to PI3K inhibitors and overcome acquired resistance in *PIK3CA*-mutated breast cancers.[63] Trials looking at the clinical activity of this combination include a phase I study of triplet therapy with exemestane, everolimus, and ribociclib in ET-resistant breast cancer.[64] Preliminary results demonstrate an ORR of 9% with stable disease seen in 51% of patients. Responses were even seen in patients treated with previous CDK 4/6 and/or mTOR inhibition. Another phase I study is looking at the combination of letrozole, alpelisib, and ribociclib.[65] Patients with previous CDK 4/6, mTOR, and PI3K inhibition were not eligible. This combination shows some preliminary efficacy, with an ORR of 16% and a clinical benefit rate of 26%. Studies are ongoing to determine the role of triplet therapy in ET-resistant disease.

Supportive Care With Targeted Therapy

CDK 4/6 Inhibitors

As reviewed, the PALOMA and MONALEESA studies demonstrate the risk of myelosuppression and infection with these CDK 4/6 inhibitors. Close monitoring of patients' blood counts is important to prevent severe neutropenia and to minimize the risk of infectious complications. Abemaciclib has a slightly different toxicity profile, with increased risk of diarrhea over myelosuppression compared with the other CDK 4/6 inhibitors. Approximately 13% of patients can experience grade 3 gastrointestinal toxicity. It is important to institute anticipatory management with supportive antiemetic and antidiarrhea medications.

Everolimus: Everolimus-associated stomatitis can significantly inhibit a patient's ability to continue therapy and maintain quality of life. The SWISH trial studied the role of dexamethasone mouthwash (0.5 mg/5 mL solution, swish for 2 minutes and spit, 4 times daily) to prevent stomatitis in patients treated with exemestane and everolimus on the BOLERO-2 study.[66] The study showed that by 8 weeks, prophylactic use of dexamethasone mouthwash substantially decreased the incidence of grade 2 or worse stomatitis to 2% compared with 33%. This is now considered standard supportive care for everolimus-based regimens.

Other toxicities that require close monitoring and management include hyperglycemia, rash, and, diarrhea. Though rare, pneumonitis has been reported in 8% to 14% of patients treated with everolimus. Baseline interstitial lung disease appears to be a risk factor.[67] Most common symptoms include dyspnea, cough, fatigue, and fever. The most common radiographic findings are focal areas of consolidation at the lung bases or ground glass opacities, but some radiographs show diffuse ground glass or consolidative opacities. Management is based on the severity of pneumonitis; severe pneumonitis may require permanent discontinuation of therapy and initiation of systemic glucocorticoids.

Emerging Strategies in HR+ Breast Cancer

Understanding the mutational evolution and crosstalk of other signaling pathways in HR+ breast cancer is important for developing new therapeutic targets. As previously stated, preclinical models suggest FGFR1 inhibition could reverse endocrine resistance. *FGFR1* is amplified in 10% to 15% of ER+ breast cancers.[68] This subgroup of ER+ breast cancer is clinically associated with higher-grade disease and worse prognosis.[47,69] A randomized phase II trial evaluated the safety and efficacy of dovitinib (inhibitor of FGFR1 and other tyrosine kinases) combined with fulvestrant in postmenopausal patients with ET-resistant disease.[70] The frequency of FGF pathway amplification was lower than an-

ticipated, so the study was terminated early due to slow recruitment. The addition of dovitinib did not increase mPFS (5.5 vs 5.5 months) across the whole population. However, in the FGF-amplified cohort (n=31), an improvement in mPFS was shown with the addition of dovitinib (10.9 vs 5.5 months). The RADICAL trial was a phase I study evaluation the safety and efficacy of AZD4547 (FGFR inhibitor) in combination with nonsteroidal AI in ET-resistant breast cancer.[71] This regimen demonstrated a clinical benefit rate of 36.5% and a mPFS of 3.1 months in a very heavily pretreated population. Several trials to further study the role of FGFR inhibition in combination with ET in *FGFR1* amplified, HR+ breast cancer are ongoing.

Great interest has been shown in applying immunotherapy in HR+ breast cancer. Thus far, check point inhibition has shown little success, with response rates ranging between 6% and 12%.[72,73] This poor response to immune check point blockade is thought to be due to the low mutational burden of these tumors. Current immunotherapy strategies are targeted toward increased immune recognition through enhanced antigen presentation and increased T-cell activation. Abemaciclib has been shown to increase the T-cell inflammatory signature in preclinical models of HR+ breast cancer via both increased activation of T-cells and upregulated expression of antigen presentation genes in breast cancer cells.[74] Additionally, data from the phase II, preoperative neoMONARCH trial showed treatment with abemaciclib correlated with an increase in total T-cells and a greater ratio of cytotoxic/suppressor T cells in the tumor microenvironment.[75] Based on these data, a clinical trial evaluating the combination of abemaciclib and pembrolizumab in advanced HR+ breast cancer is ongoing (NCT 02779751).

There is increasing evidence to implicate epigenetic gene regulatory mechanisms in the development of endocrine resistance. Several inhibitors of enzymes controlling epigenetic modifications, specifically histone deacetylase (HDAC) inhibitors, have been developed and show promising antitumorigenic effects. ENCORE 301 was a phase II study of the combination of exemestane and entinostat (HDAC inhibitor) in ET-resistant disease.[76] A noted improvement was seen in mPFS in the subset of patients with evidence of hyperacetylation treated in the entinostat arm (8.55 vs 2.76 months). The phase III ECOG 2112 trial (NCT 02115282) studying etinostat with exemestane is ongoing. Measurement of target gene expression and identification of other potential epigenetic biomarkers is a critical task for ongoing and future trials with HDAC inhibitors.

Identifying and developing future therapeutic targets requires understanding of molecular changes that occur in response to ET. Cohen et al[77] studied metastatic tumor biopsies in patients with ET-resistant disease via whole exome sequencing, comparing the genetic alterations present between the primary tumor and metastatic lesions. Their findings showed several changes that occur at a genetic level. These include acquired *ERBB2* mutations, *ESR1* mutations, PI3K pathway mutations, and loss of *RB1*. Clearly, the future of targeted therapy will involve identifying molecular alterations in metastatic biopsies to dictate next choice of systemic therapy. As technology behind assessing ctDNA improves, the "liquid biopsy" will increasingly play a role in assessing mechanisms of resistance and predicting response to therapy.

Conclusions

Unfortunately, metastatic HR+/HER2– breast cancer remains incurable. However, great strides have been made to improve clinical outcomes for patients with this cancer. The addition of CDK 4/6 inhibition has demonstrated impressive activity in combination with ET, with disease control for up to 2 years. The role of CDK4/6 inhibition beyond progression remains unclear. Primary and secondary resistance to upfront therapy remains a clinical challenge. There is ongoing study of using novel agents targeting PI3K/AKT/mTOR to overcome inevitable endocrine resistance. Future directions include optimizing combination targeted therapy and immunotherapy, and identifying biomarkers for personalized treatment decision making.

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Posttest Questions

1. 70-year-old female presents with hip pain. Past history is significant for stage 2 breast cancer diagnosed 20 years ago, at which time she received 5- years of tamoxifen. Imaging demonstrates multiple areas consistent with probable bone metastases. Bone biopsy shows adenocarcinoma consistent with breast primary, ER-positive 95%, PR-negative, HER2-negative. She receives anastrozole and has stable disease for 24- months, at which point she develops progressive disease in her bones. All of these are reasonable second-line therapeutic options EXCEPT:
    a. Tamoxifen
    b. Letrozole
    c. Fulvestrant plus palbociclib or abemaciclib
    d. Exemestane plus everolimus
    e. Fulvestrant

2. 65-year-old post-menopausal female presents with a palpable right breast mass. Imaging confirms a mass in the right breast, as well as several enlarged lymph nodes. Breast biopsy demonstrates invasive ductal cancer, grade 1, ER-positive, PR-positive, HER2-negative. Systemic staging demonstrates enlarged nodes in the mediastinum, as well as bone metastases. She undergoes a bone biopsy that confirms metastatic breast cancer, ER-positive, PR-positive, HER2-negative. All of these are reasonable first-line therapeutic options EXCEPT:
    a. Fulvestrant
    b. Fulvestrant plus anastrozole
    c. Letrozole plus a CDK inhibitor
    d. Exemestane plus everolimus

3. 65-year-old postmenopausal woman from previous question was treated with exemestane and everolimus. Twelve weeks into therapy, she complained of generalized rash and mild dyspnea on exertion. CXR showed apical changes consistent with pneumonia or pneumonitis. Treatment options would include all EXCEPT:
    a. CT chest
    b. Continue current medications
    c. Oral antibiotics or steroids
    d. Pulmonary consult

4. The patient received CDK4/6 inhibitor and letrozole. Three weeks into treatment she develops fever, diarrhea, and an episode of syncope. At presentation in ER, her vitals were: temp, 101°F; pulse, 60/min; BP, 90/60. Possible causes related to CDK4/6 inhibitor causing her symptoms include:
    a. Neutropenic fever
    b. Heart block
    c. Diarrhea
    d. All of the above