

Precision Endocrine-Based Combinations After CDK4/6 Inhibitor Progression in HR-Positive Metastatic Breast Cancer

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Abstract: CDK4/6 inhibitors combined with endocrine therapy (ET) has significantly improved progression-free (PFS) and overall survival (OS) in patients with hormone receptor-positive (HR+), HER2-negative breast cancer, however, most patients ultimately develop acquired resistance and experience disease progression. Historically, this transition marked the point at which chemotherapy was initiated; however, advances in molecular profiling and drug development have fundamentally altered this paradigm. Resistance to endocrine therapy is mediated by distinct and therapeutically actionable mechanisms, most notably *ESR1* mutations, activation of the PI3K/AKT/mTOR signaling pathway, and cell-cycle deregulation. These insights have led to the development of a new generation of targeted endocrine therapies that restore or prolong endocrine sensitivity. Oral selective estrogen receptor degraders (SERDs), particularly elacestrant and imlunestrant, have demonstrated clinically meaningful efficacy in patients with *ESR1*-mutant tumors progressing after CDK4/6 inhibitors. Additionally, targeted inhibitors of the PI3K and AKT pathways, such as alpelisib and capivasertib, when combined with appropriate endocrine backbones, have been shown to overcome resistance mechanisms. The emergence of circulating tumor DNA (ctDNA) testing has further refined therapeutic decision-making by enabling real-time detection of resistance mutations and guiding directed treatment selection. Several prospective trials have demonstrated that molecularly guided switching of endocrine therapy can delay clinical progression and extend disease control, highlighting a shift toward precision-based, adaptive strategies. Collectively, these advances support a new treatment paradigm in which endocrine-based combinations remain the preferred approach after progression, delaying the need for chemotherapy while maintaining efficacy and quality of life. This review summarizes the biology of endocrine resistance, evaluates current targeted endocrine therapies, and provides a practical framework for biomarker-driven sequencing in patients with HR+/HER2– advanced breast cancer following progression on prior endocrine therapy.

Keywords: metastatic breast cancer, endocrine therapy, CDK4/6 inhibitors, precision therapy, *ESR1*, ctDNA, PI3K/AKT/mTOR

Introduction

Hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) breast cancer accounts for approximately 70% of all metastatic breast cancers and remains largely driven by estrogen receptor (ER) signaling.^{1,2} Over the past decade, the integration of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors with endocrine therapy (ET) has transformed the management of metastatic breast cancer (MBC), producing unparalleled improvements in progression-free survival (PFS) and overall survival (OS) compared with ET alone.³ Large Phase III trials, including MONALEESA-2/3/7^{4–6} PALOMA-2,⁷ and MONARCH-3,⁸ have established CDK4/6 inhibitor-based regimens as the standard first-line therapy for HR+/HER2– MBC, achieving median PFS ranging approximately from 20–33 months and overall survival ranging from approximately 45 months to beyond 60 months in selected studies.^{4–8}

Despite these major advances, most patients ultimately experience disease progression due to the development of endocrine resistance.⁹ Once resistance emerges, the therapeutic challenge shifts from simple endocrine substitution, or initiation of chemotherapy, to the rational deployment of molecularly targeted strategies that suppress escape pathways

and restore ER sensitivity. Advances in genomic profiling, particularly circulating tumor DNA (ctDNA) analysis, have revealed that acquired resistance is driven by clonal evolution involving ER mutations (*ESR1*),¹⁰ activation of PI3K/AKT/mTOR signaling, and alterations in cell-cycle control.¹¹ These insights have led to the development of novel oral selective estrogen receptor degraders (SERDs), PI3K and AKT inhibitors, and other targeted combinations that extend endocrine sensitivity beyond progression on first-line therapy.¹²

The current management of HR+/HER2– advanced breast cancer therefore requires a systematically informed approach to post-progression therapy, in which endocrine backbones are combined with targeted agents selected according to tumor biology.^{13,14} This review focuses on the evolving endocrine strategies for patients who progress after prior CDK4/6 inhibitors.

Biology of Endocrine Resistance After Endocrine Therapy

Advances in genomic profiling, particularly serial ctDNA analysis, have demonstrated that endocrine resistance is a dynamic and heterogeneous process involving both acquired subclonal alterations and pre-existing truncal genomic events.¹⁵ *ESR1* mutations frequently emerge under selective therapeutic pressure and may expand during treatment, representing a classic mechanism of acquired endocrine resistance.¹⁶ In contrast, alterations such as *PIK3CA* mutations are often early truncal events that may persist throughout tumor evolution rather than arise exclusively at progression. Furthermore, activation of resistance pathways including PI3K/AKT/mTOR signaling may occur through non-mutational mechanisms such as signaling crosstalk, epigenetic adaptation, or compensatory pathway activation, which are not always fully captured by ctDNA-based genomic profiling alone.¹⁷ These observations highlight both the biological complexity of endocrine resistance and the limitations of relying solely on genomic mutation profiling to characterize functional pathway activation. Table 1 summarizes these mechanisms of endocrine resistance.^{18–23}

The persistence of partial ER dependency in some resistant tumors supports the continued use of endocrine-based combinations after progression, particularly in biomarker-selected patients with actionable alterations such as *ESR1* mutations or PI3K/AKT pathway activation. However, endocrine responsiveness generally diminishes with successive lines of therapy, especially in endocrine-refractory disease.²⁴

ESR1 Mutations

Mutations in the *ESR1* gene, which encodes the estrogen receptor α , represent one of the most important mechanisms of acquired resistance to endocrine therapy. These mutations, most commonly occurring in the ligand-binding domain, lead to constitutive, ligand-independent activation of ER signaling. *ESR1* mutations are rare in primary breast cancer but emerge in approximately 40% of patients following prolonged exposure to AIs in patients with advanced stage disease.¹⁸

Functionally, *ESR1* mutations confer resistance to estrogen deprivation by AIs, while retaining partial sensitivity to ER antagonists. Preclinical and clinical data demonstrate that SERDs, particularly oral SERDs, are more effective than AIs or tamoxifen in suppressing mutant ER signaling. The detection of *ESR1* mutations in ctDNA has therefore become an essential biomarker guiding therapy selection following disease progression on AI.¹⁹

Table 1 Mechanisms of Endocrine Resistance

Mechanism	Frequency/Prevalence	Clinical Relevance	Therapeutic Implications
<i>ESR1</i> mutations ^{18,19}	30–40%	Ligand-independent ER signaling	SERDs (Elacestrant, Imlunestrant, Camizestrant)
<i>PIK3CA</i> mutations ²⁰	40%	PI3K pathway activation	Alpelisib + ET
AKT activation/PTEN loss ²¹	15–20%	Downstream survival signaling	Capivasertib + ET
Cell-cycle deregulation (RB loss, cyclin E1 amplification) ^{22,23}	10–15%	CDK4/6 inhibitor resistance	Alternative CDK inhibition/novel strategies

Abbreviations: AI, Aromatase Inhibitors, SERDs, Selective Estrogen Receptor Degraders, ET, Endocrine Therapy.

PI3K–AKT–mTOR Pathway Activation

Activation of the PI3K/AKT/mTOR signaling cascade is another major driver of endocrine resistance. *PIK3CA* mutations, which occur in approximately 30–45% of HR+/HER2– breast cancers promote estrogen-independent cell growth and survival.²⁵

Resistance to CDK4/6 inhibitors is increasingly recognized as a biologically heterogeneous process involving both direct alterations of the cyclin D–CDK4/6–RB pathway and activation of compensatory signaling networks. Proposed resistance mechanisms include *RB1* loss or dysfunction, cyclin E/CDK2 activation, CDK6 amplification, and adaptive activation of parallel pathways such as PI3K/AKT/mTOR, FGFR, and MAPK signaling.^{26,27} In addition, endocrine resistance may arise through *ESR1* mutations, epigenetic reprogramming, and signaling crosstalk that promote estrogen-independent tumor growth. Importantly, not all resistance mechanisms are fully captured by genomic profiling alone, as functional pathway activation may occur through non-mutational processes.²⁸

These biologic insights have important therapeutic implications in the post-CDK4/6 inhibitor setting. Selected patients may continue to benefit from endocrine-based strategies when combined with biomarker-directed targeted therapies, including oral SERDs for *ESR1*-mutant disease and PI3K/AKT/mTOR inhibitors for tumors harboring actionable pathway alterations.²⁹ Other emerging approaches include continuation or switching of CDK4/6 inhibitors, development of CDK2-targeted therapies to overcome cyclin E-mediated resistance, and rational combination strategies designed to delay or reverse endocrine escape. These evolving treatment paradigms further support the growing role of precision medicine in guiding therapy selection after CDK4/6 inhibitor progression.

Cell-Cycle Deregulation

Resistance to CDK4/6 inhibition is increasingly recognized as a contributor to post-progression disease. Mechanisms include loss of retinoblastoma (RB) protein, amplification of cyclin E1 (*CCNE1*), and activation of CDK2, all of which allow tumor cells to bypass CDK4/6 blockade and continue proliferating.³⁰ These alterations often coexist with endocrine resistance mechanisms, further underscoring the need for combination strategies that target both ER signaling and cell-cycle escape pathways.³¹

Targeted Endocrine Combinations After Progression on Endocrine Therapy

The therapeutic landscape of HR-positive/HER2-negative metastatic breast cancer following progression on CDK4/6 inhibitor-based therapy has evolved substantially in recent years. While antibody drug conjugates (ADCs), including sacituzumab govitecan and trastuzumab deruxtecan, have emerged as important standards of care for patients with endocrine-refractory disease and in later treatment lines, many patients retain partial endocrine sensitivity and may still benefit from biomarker-driven endocrine-based strategies.³² Consequently, increasing emphasis has been placed on identifying actionable molecular alterations such as *PIK3CA*, *ESR1*, *AKT*, and *PTEN* abnormalities to guide personalized treatment selection.^{33,34} This section focuses primarily on precision endocrine-based therapeutic approaches after CDK4/6 inhibitor progression, particularly in patients with preserved endocrine responsiveness, while acknowledging the growing role of ADCs and chemotherapy in endocrine-resistant disease.

Targeting *ESR1* Mutations: Oral SERDs

Multiple studies have shown that *ESR1* mutations detected in peripheral blood are strongly associated with resistance to AIs but retained sensitivity to SERDs.³⁵ In the PADA-1 trial, patients receiving first-line AI plus palbociclib underwent serial ctDNA monitoring. Those who developed *ESR1* mutations without radiological or clinical progression were randomized to switch to fulvestrant plus palbociclib or continue their regimen. Early switching significantly improved median PFS (11.9 vs 5.7 months), demonstrating for the first time that molecular progression can guide endocrine therapy adaptation and improve outcomes.³⁶ Similarly, in the EMERALD trial as detailed below, the benefit of elacestrant was largely driven by patients with *ESR1*-mutant tumors, further validating *ESR1* mutation status as a predictive biomarker rather than merely a prognostic factor.

Elacestrant (EMERALD Trial)

Elacestrant is the first oral selective estrogen receptor degrader (SERD) to demonstrate superiority over standard endocrine therapy in a randomized phase III trial. The EMERALD trial enrolled 478 patients with ER-positive, HER2-negative metastatic breast cancer whose disease had progressed after prior endocrine therapy and mandatory CDK4/6 inhibitor exposure. Patients were randomized to receive elacestrant or investigator’s choice of standard endocrine therapy (fulvestrant or an aromatase inhibitor). *ESR1* mutation status was prospectively assessed using circulating tumor DNA (ctDNA) and used as a stratification biomarker for treatment evaluation.³⁷

In the overall study population, elacestrant significantly improved progression-free survival (PFS) compared with standard endocrine therapy (HR 0.70; P=0.0018). The greatest benefit was observed in patients harboring *ESR1* mutations, in whom median PFS was 3.8 months with elacestrant versus 1.9 months with standard therapy (HR 0.55; P=0.0005). Importantly, outcomes appeared particularly favorable among patients with prolonged prior exposure to CDK4/6 inhibitors. In the subgroup receiving ≥12 months of prior CDK4/6 inhibition, median PFS reached 8.6 months with elacestrant versus 1.9 months with standard therapy among patients with *ESR1*-mutant tumors (HR 0.41), Table 2.³⁸ These findings suggest that patients with retained endocrine sensitivity may derive the greatest benefit from elacestrant-based therapy after CDK4/6 inhibitor progression. Elacestrant was generally well tolerated, with nausea, fatigue, and vomiting representing the most commonly reported adverse events. Treatment discontinuation rates due to toxicity were low.

Collectively, EMERALD established elacestrant as an important biomarker-driven endocrine treatment option for patients with *ESR1*-mutated HR-positive/HER2-negative metastatic breast cancer following progression on CDK4/6 inhibitor-based therapy. The study also reinforced the clinical utility of ctDNA-based *ESR1* mutation detection for therapeutic selection in endocrine-resistant disease. Based on these findings, elacestrant received regulatory approval in 2023 for ER-positive, HER2-negative, *ESR1*-mutated advanced breast cancer after progression on endocrine therapy.³⁹

Imlunestrant (EMBER-3 Trial)

More recently, the EMBER-3 study has established imlunestrant, another oral SERD, as an effective drug in endocrine-pretreated ER+/HER2-negative MBC, particularly in tumors with *ESR1* mutations. In this trial, 874 patients were randomized to receive single agent imlunestrant (n= 331), standard ET (investigator’s choice of fulvestrant or exemestane; n= 330), or imlunestrant in combination with abemaciclib (n= 213). Among the 256 patients with *ESR1*-mutated tumors, imlunestrant monotherapy significantly improved median PFS compared with standard therapy, 5.5 months vs 3.8 months, corresponding to a 38% reduction in the risk of progression or death (HR 0.62; 95% CI 0.46–0.82; P= 0.0008). Importantly, the imlunestrant–abemaciclib combination demonstrated even greater efficacy in the overall population, with median PFS of 10.9 versus 5.5 months (HR 0.59, 95% CI 0.47–0.74, nominal P< 0.0001) indicating a robust activity irrespective of prior CDK4/6 inhibitor exposure or *ESR1* status. Updated analyses also suggest a clinically meaningful extension in median OS for imlunestrant monotherapy in *ESR1*-mutant disease (34.5 months vs 23.1 months; HR 0.60), although formal statistical boundaries were not met.^{40–42} These results reinforce imlunestrant as a potent oral SERD with significant clinical benefit in a biomarker-defined subset and support continued evaluation of combination strategies with CDK4/6 inhibitors. Based on these findings, the U.S. Food and Drug Administration (FDA)

Table 2 EMERALD Trial, Elacestrant vs Standard Endocrine Therapy

Population	Median PFS		HR (95% CI) P-value	12-Month PFS (%) (95% CI)		12-Month OS, % (95% CI)	
	Elacestrant	Standard ET		Elacestrant	Standard ET	Elacestrant	Standard ET
Overall ITT population (N=477)	2.8 months	1.9 months	0.70 (0.55–0.88) 0.0018	22.3 (15.2–29.4)	9.4 (4.0–14.8)	79.3 (73.8–84.7)	73.3 (67.2–79.4)
<i>ESR1</i> -mutated subgroup (n=228)	3.8 months	1.9 months	0.55 (0.39–0.77) 0.0005	26.8 (16.2–37.4)	8.2 (1.3–15.1)	82.6 (75.3–90.0)	73.6 (64.8–82.4)
<i>ESR1</i> -mutated + ≥12 months prior CDK4/6i	8.6 months	1.9 months	0.41 (0.26–0.63) NR	NR	NR	NR	NR

Abbreviations: ITT, Intention to treat; PFS, Progression-Free Survival; HR, Hazard Ratio; OS, Overall Survival; ET, Endocrine Therapy; NR, Not Reported.

approved imlunestrant in September 2025 for patients with ER+, HER2-negative and *ESR1*-mutated advanced breast cancer whose disease has progressed after at least one line of ET. Detailed of Imlunestrant therapy in all patients and those with or without *ESR1* mutation are summarized in Table 3.

Amcenestrant (AMEERA-3 Trial)

The AMEERA-3 was a randomized, open-label Phase II trial that evaluated amcenestrant, another oral SERD, versus physician's choice of standard ET (fulvestrant, AI, or tamoxifen) in patients with ER+, HER2-negative advanced breast cancer who had progressed after prior ET, including CDK4/6 inhibitors. The primary endpoint was PFS assessed by independent central review. In the overall population, amcenestrant did not significantly improve PFS compared with standard ET (median PFS 3.6 vs 3.7 months; HR 1.05). However, a numerical PFS advantage was observed in patients with *ESR1*-mutant tumors (3.7 vs 2.0 months; HR, 0.9) suggesting potential biological activity in this molecularly defined subgroup. The safety profile of amcenestrant was consistent with endocrine therapy and generally well tolerated. Although AMEERA-3 did not meet its primary endpoint, its results provided important insights into the role of oral SERDs and highlighted the need for biomarker-driven strategies in endocrine-resistant ER+ breast cancer.⁴³

Targeting the PI3K Pathway

The phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR pathway is one of the most frequently dysregulated signaling cascades in HR+, HER2-negative breast cancer, with activating *PIK3CA* mutations present in approximately 40% of tumors and strongly implicated in endocrine resistance.

The pivotal phase III SOLAR-1 trial evaluated the PI3K α -selective inhibitor alpelisib in combination with fulvestrant in 572 patients with advanced HR+/HER2- MBC progressing on or after AI therapy, stratified by *PIK3CA* mutation status. In the *PIK3CA*-mutant cohort (n= 341), alpelisib significantly improved PFS compared with fulvestrant alone (11.0 vs 5.7 months; HR 0.65, $p < 0.001$), with higher objective response (26.6% vs 12.8%) and clinical benefit rates, whereas no benefit was observed in *PIK3CA*-wild-type tumors, confirming mutation-specific pathway dependence.⁴⁴

Because few SOLAR-1 patients had prior CDK4/6 inhibitor exposure, the phase II BYLieve study specifically examined alpelisib plus fulvestrant in a real-world, post-CDK4/6 setting. In Cohort A (n = 121), which enrolled patients with *PIK3CA*-mutant tumors progressing on CDK4/6 inhibitor plus AIs, the combination achieved a 6-month PFS rate of 50.4% and a median PFS of 7.3 months, with an objective response rate of 17% and clinical benefit in 46%, confirming preserved PI3K pathway dependency after CDK4/6 inhibitor failure, Table 4.⁴⁵ More recently, the phase III EPIK-B5 trial evaluated alpelisib plus fulvestrant in patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer progressing after prior CDK4/6 inhibitor therapy. The study demonstrated a significant improvement in PFS with alpelisib–fulvestrant (7.4 months) compared with placebo–fulvestrant (2.8 months), HR: 0.52, 95% CI: 0.37,0.72, $P<0.0001$. These studies support continued targeting of the PI3K pathway in the post-CDK4/6 setting. However, the clinical utility of alpelisib is tempered by its toxicities, particularly hyperglycemia, rash, and diarrhea, necessitating careful metabolic screening, patient selection, and proactive toxicity management.⁴⁶

Table 3 EMBER-3 Trial, Imlunestrant vs Standard Endocrine Therapy

Population/Outcome		Imlunestrant Monotherapy	Standard-of-Care	HR (95% CI)	P-value
<i>ESR1</i> -mutant	Median PFS (months)	5.5 (3.9–7.4)	3.8 (3.7–5.5)	0.62 (0.47–0.82)	0.0007
	Median OS (months)	34.5 (25.4–NR)	23.1 (18.4–28.9)	0.60 (0.43–0.86)	0.0043
<i>ESR1</i> -wild	Median PFS (months)	5.6 (4.4–9.1)	5.7 (5.5–7.4)	0.97 0.78–1.22	0.7942
	Median OS (months)	37.1 (32.6–NR)	NR	1.12 0.80–1.58	NA
All Patients	Median PFS (months)	5.6 (5.3–7.2)	5.5 (4.6–5.6)	0.89 0.75–1.05	0.1669
	Median OS (months)	37.1 (32.0–NR)	32.3 (29.1–43.5)	0.86 0.68–1.10	0.2343

Abbreviations: PFS, Progression-Free Survival; OS, Overall Survival; NR, Not reached; NA, Not available.

Table 4 Difference Between SOLAR-I and BYLieve Trial Evaluating the Use of Alpelisib

Characteristic	SOLAR-I	BYLieve Cohort A
Design	Phase III, randomized, double-blind, placebo-controlled	Phase II, open-label, single-arm, non-comparative
Population	HR+/HER2- advanced breast cancer progressing after AI therapy	HR+/HER2- advanced breast cancer progressing after CDK4/6 inhibitor + AI
<i>PIK3CA</i> status	Required stratification, benefit in mutant cohort	Required central confirmation of <i>PIK3CA</i> mutation
Treatment	Alpelisib + fulvestrant vs placebo + fulvestrant	Alpelisib + fulvestrant
Primary endpoint	Investigator-assessed PFS (<i>PIK3CA</i> -mutant cohort)	6-month PFS rate (local assessment)
Median PFS	11.0 months vs 5.7 months (Hazard Ratio 0.65; $P < 0.001$)	7.3 months (post-CDK4/6i)
6-month PFS rate	Not primary endpoint	50.4%
Objective response rate	26.6% vs 12.8%	17%
Safety	Hyperglycemia, rash, diarrhea common; managed with monitoring	Similar toxicity profile; manageable with guidance

Abbreviations: AI, Aromatase Inhibitors; HR, Hormone receptor; HER2, Human epidermal growth factor receptor 2; PFS, Progression-Free Survival.

Targeting AKT Signaling

AKT represents a key station in PI3K pathway signaling and provides an alternative target that may overcome some of the limitations of PI3K inhibition.

Capivasertib + Fulvestrant (CAPItello-291)

The phase III CAPItello-291 trial evaluated the addition of capivasertib, a selective AKT inhibitor, to fulvestrant compared with placebo plus fulvestrant in patients with HR+, HER2-negative advanced breast cancer who progressed during or after AI-based endocrine therapy, including a high proportion (69%) previously treated with CDK4/6 inhibitors. In this randomized, double-blind study of 708 patients, capivasertib plus fulvestrant produced a clinically meaningful and statistically significant improvement in PFS in the overall population, with a median PFS of 7.2 months versus 3.6 months for placebo plus fulvestrant (HR 0.60; 95% CI 0.51–0.71; $P < 0.001$), demonstrating nearly a 40% reduction in the risk of progression or death. In the prespecified AKT pathway–altered subgroup (defined by *PIK3CA*, *AKT1*, or *PTEN* alterations), the benefit was even more pronounced, with median PFS of 7.3 months versus 3.1 months (HR 0.50; 95% CI 0.38–0.65; $P < 0.001$), confirming that activation of the PI3K/AKT pathway confers enhanced sensitivity to AKT inhibition, Table 5.⁴⁷ Importantly, benefit was observed across biomarker strata, including patients without documented alterations, although the magnitude was greatest in the altered cohort, positioning capivasertib as a broadly applicable targeted therapy in endocrine-resistant HR+ disease. The safety profile was consistent with AKT inhibition, with diarrhea, rash, and hyperglycemia among the most frequently reported toxicities, and adverse events leading to discontinuation occurring more often in the capivasertib arm. The median time to deterioration in quality of life as measured by QLQ-C30 score (defined as a sustained decrease of ≥ 10 points in the score from baseline) was 24.9 months in the capivasertib–fulvestrant group, as compared with 12.0 months in the placebo-fulvestrant group (HR, 0.70; 95% CI, 0.53–0.92). Based on these data, the combination has FDA approval in November 2023 for patients with AKT pathway alterations, with ongoing debates about its utility in unselected populations.⁴⁸

Therapeutic Sequencing After Progression on Endocrine Therapy

The increasing availability of targeted endocrine therapies has transformed the post-progression landscape of HR+/HER2 – advanced breast cancer from a linear sequence of treatments into a molecular-driven algorithm. Rather than viewing progression on endocrine therapy as endocrine failure, modern management emphasizes continued ER targeting combined with inhibition of resistance pathways, guided by molecular profiling. The optimal sequencing strategy

Table 5 CAPItello-291, Progression-Free Survival by PI3K/AKT Pathway Biomarker Status

Biomarker Subgroup	Median PFS (95% CI), Months		Hazard Ratio (95% CI) P-value	18 Months Overall Survival (95% CI) %		Hazard Ratio (95% CI)
	Capivasertib + Fulvestrant	Placebo+ Fulvestrant		Capivasertib + Fulvestrant	Placebo+ Fulvestrant	
AKT pathway–altered (n=289) *	7.3 (5.5–9.0)	3.1 (2.0–3.7)	0.50 (0.38–0.65) <0.001	73.2% (64.8–80.0)	62.9% (53.1–71.2)	0.69 (0.45–1.05)
AKT pathway–non-altered (n=313) ^	5.3 (3.6–7.3)	3.7 (3.5–5.1)	0.79 (0.61–1.02)	Not Reported	Not Reported	Not Reported
Overall population (N=708)	7.2 (5.5–7.4)	3.6 (2.8–3.7)	0.60 (0.51–0.71) <0.001	73.9% (68.3 –78.7)	65.0% (58.7–70.6)	0.74 (0.56–0.98)

Note: * Tumors with *PIK3CA*, *AKT1*, or *PTEN* alterations as detected by next-generation sequencing (NGS) ^ 106 patients with unknown results on NGS.

depends primarily on prior therapies, *ESR1* mutation status, PI3K/AKT pathway alterations, and clinical factors such as disease pace and patient comorbidities.⁴⁹

First Progression After CDK4/6 Inhibitor-Based Therapy

For most patients, disease progression ultimately occurs after first-line therapy with an AI or fulvestrant combined with a CDK4/6 inhibitor. At this stage, ctDNA testing should be performed to identify actionable mutations. In patients with *ESR1* mutations, AIs are no longer effective, and oral SERDs represent the preferred endocrine backbone. Elacestrant and imlunestrant are the only approved oral SERDs with phase III evidence in this setting. However, fulvestrant remains an option when oral SERDs are unavailable, though its efficacy is inferior in *ESR1*-mutant tumors. In the absence of *ESR1* mutations, fulvestrant remains the standard endocrine partner for targeted therapy combinations.

Integration of PI3K and AKT Pathway Inhibitors

Patients with *PIK3CA*-mutant disease derive the greatest benefit from PI3K pathway inhibition. Alpelisib plus fulvestrant is appropriate when hyperglycemia and dermatologic adverse events can be managed. However, capivasertib plus fulvestrant is an attractive alternative, offering efficacy with improved tolerability and broader applicability.⁴⁷

Later-Line Endocrine Strategies

After failure of SERDs and PI3K/AKT-directed therapy, additional endocrine-based combinations may still provide meaningful disease control. Everolimus plus exemestane remains a valid option, particularly in patients with indolent disease.^{50,51} Rechallenge with alternative endocrine backbones may be considered when chemotherapy is not yet indicated.

Transition to Chemotherapy

Chemotherapy should be reserved for patients with rapidly progressive disease, visceral crises or endocrine-refractory tumors. Multiple studies show that effective targeted endocrine therapy preserves quality of life and delays chemotherapy without compromising overall survival.⁵²

Endocrine Therapy versus Chemotherapy After Endocrine Progression

Comparative Efficacy of Chemotherapy and Endocrine-Based Therapy

For decades, progression on endocrine therapy in HR+/HER2– metastatic breast cancer was viewed as a signal to switch to cytotoxic chemotherapy. However, recent data have challenged this concept as most patients retain endocrine sensitivity after progression, and that recently designed endocrine-based combinations can achieve disease control comparable to chemotherapy with substantially better tolerability and quality of life.^{53–56}

Although direct randomized comparisons between targeted endocrine therapy and chemotherapy are limited, historical data indicate that single-agent chemotherapy in endocrine-resistant HR+ MBC typically produces median PFS of 3–5 months.^{57–59} In contrast, modern endocrine-based regimens such as capivasertib plus fulvestrant and elacestrant in biomarker-selected populations achieve similar or superior PFS with lower toxicity profile.⁵¹

Quality of Life and Toxicity Considerations

A key advantage of endocrine-based therapy is its favorable safety profile compared with chemotherapy. Cytotoxic regimens are associated with myelosuppression and infection risk, alopecia, neuropathy and fatigue; all of which negatively impact quality of life. In contrast, targeted endocrine combination therapy are generally manageable with dose modifications and supportive care.^{60,61}

Analyses of patient-reported outcomes from trials of CDK4/6 inhibitors, SERDs, and AKT inhibitors consistently show better preservation of quality of life compared with chemotherapy, making prolonged endocrine-based treatment particularly important in this typically indolent disease.^{62,63}

Clinical Implications

In the absence of visceral crisis or rapidly progressive disease, targeted endocrine therapy should remain the preferred treatment strategy after endocrine progression. Chemotherapy should be reserved for patients who have exhausted endocrine-based options or who require rapid tumor control due to life-threatening organ involvement. This approach maximizes disease control, minimizes toxicity, and aligns treatment with the biological reality that HR+/HER2– metastatic breast cancer remains fundamentally hormone driven even after multiple lines of therapy.^{64,65}

Emerging Therapies

The rapid evolution of molecular understanding in HR+/HER2– advanced breast cancer has catalyzed the development of next-generation targeted and endocrine therapies with the purpose of prolonging endocrine sensitivity and overcoming resistance. Several innovative approaches have reshaped the treatment landscape beyond currently approved agents.

Next-Generation Oral SERDs

While imlunestrant and elacestrant validated oral SERDs as a therapeutic class, multiple next-generation drugs are in late-phase development with the goal of achieving greater activity against *ESR1* mutations, deeper ER degradation, and better tolerability.^{66,67}

Camizestrant

Camizestrant has demonstrated potent and deeper ER degradation and activity against *ESR1*-mutant tumors. In the phase II SERENA-2 trial, in patients previously treated with ET, camizestrant significantly improved PFS compared with fulvestrant with enhanced benefit observed in *ESR1*-mutant disease.⁶⁸

The SERENA-6 trial is randomized, double-blind phase III landmark study designed to evaluate whether early switching from an AI to the next-generation oral SERD camizestrant, upon detection of emergent *ESR1* mutations in ctDNA, can extend clinical benefit over continued standard endocrine therapy in patients whose disease remains stable on first-line AI plus CDK4/6 inhibitor therapy.

In this study, patients receiving first line AIs plus a CDK4/6 inhibitor underwent serial ctDNA monitoring; those found to have an emerging *ESR1* mutation without radiographic progression were randomized to switch to camizestrant (75 mg once daily) with continued CDK4/6 inhibition versus continuing AI plus CDK4/6 inhibitor. At a median follow-up of approximately 12.6 months, camizestrant significantly improved PFS, with a median PFS of 16.0 months (95% CI, 12.7–18.2), compared with 9.2 months (95% CI, 7.2–9.5) for the continued AI arm, (HR 0.44; 95% CI, 0.31–0.60; $P < 0.0001$). The benefit was consistent across subgroups and was reflected in PFS rates at 12 months (60.7% vs 33.4%) and at 24 months (29.7% vs 5.4%), underscoring the durability of disease control with camizestrant-based therapy.^{69,70} Importantly, patient-reported outcomes indicated a significant extension in quality of life, with the median time to deterioration in global health status delayed to 21–23 months versus 6.4 months in the AI arm with low

discontinuation rates due to adverse events (1.3%).⁷¹ These outcomes support the notion that HR+/HER2– metastatic breast cancer can be more effectively managed with treatment adapted to evolving tumor biology rather than conventional imaging alone.

Giredestrant

Giredestrant, another SERD, has shown promising pharmacodynamic activity and clinical efficacy in multiple clinical settings. The lidERA adjuvant trial tested the use of giredestrant in patients with early-stage ER+/HER2-negative breast cancer. At the first prespecified analysis, giredestrant significantly improved invasive disease-free survival (iDFS) compared with standard-of-care endocrine therapy, reducing the risk of recurrence or death by approximately 30%, with favorable iDFS rates at 12, 24, and 36 months and trends toward better overall survival and distant recurrence-free interval. Safety was consistent with known profiles and discontinuation rates were modestly lower than standard endocrine treatment.⁷²

In the advanced disease setting, updated phase III evERA demonstrated that giredestrant plus everolimus significantly improved PFS in patients with ER+/HER2-negative breast cancer previously treated with CDK4/6 inhibitors, including those with *ESR1*-mutated tumors. Overall survival data remain immature but suggest positive trends, and no new safety signals have emerged.⁷³

Other ongoing phase III studies are evaluating giredestrant in combination with CDK4/6 inhibitors and also as monotherapy in early and resistant disease settings, seeking to define its role across lines of therapy and potentially position it as a new standard of care in ER-positive breast cancer.^{74,75}

Estrogen Receptor Degraders Beyond SERDs: PROTACs and CERANs

Proteolysis-targeting chimeras (PROTACs) and complete estrogen receptor antagonists (CERANs) represent novel strategies to induce rapid and sustained ER degradation through the ubiquitin–proteasome system.⁷⁶ These agents have demonstrated potent activity against both mutant and wild-type ER in early-phase clinical trials.⁷⁷ By eliminating ER protein rather than merely inhibiting its activity, these compounds may overcome resistance even to current SERDs.

The Phase III VERITAC-2 trial of the oral PROTAC ER degrader vepdegestrant, compared daily oral vepdegestrant to intramuscular fulvestrant in adults with ER+/HER2-negative metastatic breast cancer post-CDK4/6 inhibitor and ET, with PFS as the primary. In this study, the *ESR1*-mutated subgroup achieved a significant PFS benefit (median 5.0 vs 2.1 months; HR 0.58, $P < 0.001$) while the ITT analysis did not reach statistical significance, and OS data remain immature.^{78,79}

Meanwhile, the OPERA-01 Phase III study of the oral CERAN/SERD palazestrant is designed as a randomized, open-label trial comparing palazestrant monotherapy to standard-of-care endocrine therapy (eg., fulvestrant or AI) in patients with ER+, HER2-negative locally advanced or metastatic breast cancer after progression on at least one CDK4/6 inhibitor plus ET, with PFS as its primary endpoint and OS, duration of response, safety, and patient-reported outcomes as secondary endpoints.⁸⁰

ctDNA-Guided Adaptive Endocrine Therapy

The use of ctDNA to guide proactive treatment plans is perhaps the most transformative future direction. Trials such as SERENA-6 and PADA-1 demonstrated that switching endocrine therapy at the time of molecular progression, before radiographic progression, can significantly extend disease control. This innovative adaptive approach may allow continuous suppression of evolving resistant clones, effectively converting metastatic breast cancer into a chronically managed disease.

Conclusions and Future Directions

The management of HR-positive, HER2-negative advanced breast cancer following progression on endocrine therapy has fundamentally evolved significantly in recent years. Disease progression is now considered a biologically adaptive and therapeutically targetable process, with most tumors retaining estrogen dependence despite prior CDK4/6 inhibition and endocrine therapy. The introduction of mTOR-targeted therapies, oral SERDs, PI3K and AKT inhibitors has extended

endocrine sensitivity and delayed the need for more aggressive chemotherapy. The integration of ctDNA enables real-time detection of resistance mechanisms and supports biomarker-guided treatment adaptation.

Together, these advances move endocrine-based precision therapy to the center of post-progression breast cancer management, offering preserved quality of life with durable disease control, while underscoring the importance of aligning economic sustainability with clinical innovation. This approach represents the preferred pathway specifically for patients with retained endocrine sensitivity, whereas those with endocrine-refractory disease generally require treatment with antibody-drug conjugates (ADCs) or chemotherapy.

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