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Review Article

Optimizing Post-CDK4/6i Strategies In HR +/HER2− Advanced Breast Cancer: A Contemporary Evidence-Based Framework

Teena Rajan[1] Amol Akhade[2,3]

[1] Department of Medical Oncology, N. Sreedharan Memorial Institute of Medical Sciences, Kollam, Kerala, India
[2] Department of Medical Oncology, Nair Hospital, Mumbai, Maharashtra, India
[3] Department of Medical Oncology, Bethany Hospital, Thane, Maharashtra, India

Address for correspondence Teena Rajan, MD, DM, Department of Medical Oncology, N. Sreedharan Memorial Institute of Medical Sciences, Kollam 691020, Kerala, India (e-mail: teenarajan97@gmail.com).

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Abstract

The advent of CDK4/6 inhibitors has transformed the frontline management of HR +/HER2− metastatic breast cancer. However, resistance to these agents is inevitable, leading to a growing need for evidence-based post-progression strategies. This review synthesizes data from major trials—SONIA, PALMIRA, MAINTAIN, postMONARCH, and EMBER-3—exploring both rechallenge and class-switching strategies. We evaluate the clinical impact of switching versus continuing CDK4/6 inhibitors, mechanisms of resistance, and emerging agents such as oral SERDs (selective estrogen receptor degraders) and PROTACs. The evidence suggests limited benefit for same-agent rechallenge and supports the use of novel combinations in biomarker-selected populations. Personalized sequencing guided by molecular profiling may define the next frontier in HR +/HER2− metastatic breast cancer management.

Keywords
- HR+ breast cancer
- CDK4/6 inhibitors
- SERDs
- endocrine resistance
- imlunestrant
- biomarker-driven treatment

Refining Sequencing Decisions in the Post-CDK4/6 Era

The treatment paradigm of hormone receptor-positive (HR +), HER2 negative advanced breast cancer (ABC) has been revolutionized with the advent of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors. Incorporation of agents such as palbociclib, ribociclib, and abemaciclib in the frontline setting alongside endocrine therapy (ET) has resulted in profound improvements in progression-free survival (PFS) and, in select trials, overall survival (OS). These landmark benefits have firmly entrenched CDK4/6 inhibitors as the cornerstone of initial therapy for metastatic HR+ breast cancer.

However, despite these advances, resistance to CDK4/6 inhibition is inevitable in nearly all patients, typically within 2 to 3 years of treatment initiation.[1] This has led to an important clinical dilemma: what constitutes the optimal treatment strategy following progression on a CDK4/6 inhibitor? In recent years, several pivotal studies including SONIA, PALMIRA, PACE, MAINTAIN, postMONARCH, and EMBER-3 have provided valuable insights. Understanding the nuances of these trials is key to crafting a personalized, evidence-informed treatment sequence in this setting.

Revisiting First-Line CDK4/6: Insights from the SONIA Study

The SONIA trial is one of the first large-scale randomized trials to directly interrogate the necessity of upfront CDK4/6 inhibition in all patients.[2] Conducted in the Netherlands, this phase III study randomized HR +/HER2− ABC patients to either receive CDK4/6i plus aromatase inhibitor (AI) followed

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by fulvestrant, or a deferred strategy where patients received AI alone initially followed by CDK4/6i plus fulvestrant upon progression.

The primary endpoint of PFS2, defined as time to progression on second-line therapy, showed no statistically significant difference between the two strategies (31.0 vs. 26.8 months; hazard ratio [HR]: 0.87; $p = 0.10$). While these results do not refute the benefit of CDK4/6i, they raise the possibility of de-escalation in low-risk patients, particularly those with indolent disease biology. The study was limited by predominant use of palbociclib (which lacks an OS signal) and reliance on fulvestrant monotherapy as second-line ET, which may not reflect contemporary practice. Nonetheless, SONIA underscores the importance of individualized decision-making in front-line therapy.

PALMIRA Trial: Evaluating Same-Class Rechallenge

PALMIRA was a randomized phase II study designed to test the hypothesis that rechallenge with the same CDK4/6 inhibitor (palbociclib) following a prior response could retain clinical efficacy.[3] Patients who had progressed after an initial benefit from palbociclib were randomized in a 2:1 ratio to receive palbociclib plus ET versus ET alone.

While the clinical benefit rate favored the combination arm (41.9 vs. 27.4%), the primary endpoint of median PFS showed only a modest, statistically nonsignificant improvement (4.9 vs. 3.6 months; HR: 0.84; $p = 0.149$). Objective response rates and OS outcomes were also not significantly different. These findings suggest that rechallenge with the same CDK4/6 inhibitor, even in patients with previous benefit, offers limited utility and may be best reserved for highly selected cases.

Comparative Evidence: PACE, MAINTAIN, postMONARCH

Beyond PALMIRA, several additional studies have interrogated various strategies following progression on CDK4/6 inhibition. The PACE trial evaluated whether continued use of palbociclib in combination with a new ET partner (fulvestrant) could offer additional benefit post-progression.[4] The study failed to show a PFS advantage, with a HR of 1.11 ($p = 0.62$), suggesting that simple continuation of the same CDK4/6i is not effective.

In contrast, the MAINTAIN trial explored a different approach—switching the CDK4/6 inhibitor.[5] In this study, patients who progressed on palbociclib were switched to ribociclib in combination with a new ET backbone. This strategy yielded a significant PFS improvement (5.3 vs. 2.8 months; HR: 0.57; $p = 0.006$), demonstrating that switching agents within the same drug class can recapture therapeutic benefit.

Similarly, the postMONARCH trial evaluated abemaciclib in combination with fulvestrant versus fulvestrant alone, again in a post-CDK4/6i setting.[6] Here, abemaciclib retained efficacy with a PFS improvement of 6.0 versus 5.3 months (HR: 0.73; $p = 0.01$). These findings collectively underscore that while same-agent rechallenge is largely ineffective, a class switch—especially to a CDK4/6 inhibitor with different pharmacodynamics—may offer meaningful benefit (►**Tables 1** and **2**).

Mechanisms of Resistance and Implications for Sequencing

As resistance to CDK4/6 inhibitors emerges as a near-universal phenomenon, understanding the underlying biological mechanisms becomes essential to guide rational sequencing. Several well-characterized pathways have been implicated in mediating resistance. Loss of the retinoblastoma protein (RB1) is a pivotal driver, given that intact RB1 is necessary for CDK4/6i-mediated cell cycle arrest. CDK6 amplification and overexpression of cyclin E1, both of which can bypass CDK4/6 control, are also important contributors. Activation of the PI3K/AKT/mTOR signaling axis can promote cellular proliferation independent of the CDK4/6-RB1 pathway.

Probable pharmacodynamic reasons supporting a switch from palbociclib to either ribociclib or abemaciclib include differences in CDK4/6 selectivity, with abemaciclib and ribociclib exhibiting stronger CDK4 inhibition. Abemaciclib offers continuous inhibition, in contrast to the intermittent dosing of palbociclib, and also demonstrates broader kinase inhibition—particularly of CDK9. Its superior tissue and central nervous system penetration further enhance its therapeutic reach. Ribociclib, on the other hand, has shown a profound effect on RB phosphorylation and cell cycle arrest, alongside notable impacts on the tumor microenvironment and immune modulation. Additionally, ribociclib may help bypass several resistance mechanisms that can emerge during palbociclib treatment, making it a rational post-progression strategy.

Endocrine resistance mechanisms often co-occur, particularly mutations in the estrogen receptor gene (ESR1), which are observed in up to 30 to 40% of tumors post-CDK4/6i therapy.[7] These mutations confer ligand-independent receptor activation and reduced sensitivity to AIs. Importantly, ESR1 mutations remain targetable with selective estrogen receptor degraders (SERDs) such as elacestrant and imlunestrant, offering a rationale for incorporating these agents into post-progression regimens (►**Table 3**).[8–16]

EMBER-3: Oral SERDs post CDK4/6i Progression

The EMBER-3 trial marks a new chapter in the post-CDK4/6 treatment landscape. This phase III study evaluated the combination of imlunestrant, a novel oral SERD, with abemaciclib in patients who had progressed on prior CDK4/6 inhibitor therapy.[8] The combination achieved a statistically significant improvement in PFS compared with imlunestrant monotherapy (9.4 vs. 5.5 months; HR: 0.57).

Subgroup analyses revealed that patients harboring ESR1 mutations or PI3K pathway alterations derived particularly strong benefit. Notably, a subset analysis in patients with prior exposure to abemaciclib showed attenuated benefit, raising important questions about cross-resistance.

Table 1 CDK4/6 rechallenge and switch trials—combined summary

Trial	*N*	Inclusion	Setting	Endpoint	HR (95% CI)	*p*	Grade 3+ toxicity	Crossover	Drawbacks	Key points
PALMIRA[3]	198	HR+/HER2− ABC, prior palbociclib, ≥24 week benefit	Post-palbociclib progression (same CDK4/6 rechallenge)	PFS	0.84 (0.66–1.07)	0.149	47.4% (neutropenia, anemia)	No	Same drug rechallenge, underpowered	CBR improved, but not PFS/OS
PACE[4]	220	HR+/HER2− ABC, post-CDK4/6i	Post-CDK4/6i progression (mostly palbociclib)	PFS	1.11 (0.79–1.55)	0.62	46.6% (neutropenia)	No	Small sample, heterogeneous population	No benefit adding palbociclib post-progression
MAINTAIN[5]	120	HR+/HER2− ABC, post-palbociclib	Switch to ribociclib after palbociclib failure	PFS	0.57 (0.39–0.95)	0.006	High but manageable	No	Small sample size, mostly palbociclib, few ribo-switch	Ribociclib switch showed benefit
postMONARCH[6]	463	HR+/HER2− ABC, post-CDK4/6i	Switch to abemaciclib after prior CDK4/6i	PFS	0.73 (0.57–0.95)	0.01	49.2% (neutropenia, diarrhea)	No	Some heterogeneity in prior CDK4/6i use	Abemaciclib retained efficacy in this setting

Abbreviations: ABC, advanced breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase4/6 inhibitor; HER2neu, human epidermal growth factor receptor; HR, hazard ratio; HR, hormone receptor; PFS, progression-free survival.

Table 2 CDK4/6 switch trials: MAINTAIN versus postMONARCH

Trial	CDK4/6 switch	Median PFS (combo vs. control)	HR (95% CI)	*p*-Value	ESR1 mutation rate	ESR1 impact
MAINTAIN[5]	Yes (ribociclib)	5.3 vs. 2.8 months	0.57 (0.39–0.95)	0.006	Not reported	Not specified
postMONARCH[6]	Yes (abemaciclib)	6.0 vs. 5.3 months	0.73 (0.57–0.95)	0.02	~47% (ctDNA subset)	No loss of benefit

Abbreviations: CI, confidence interval; ctDNA, circulating tumor DNA; ESR, estrogen receptor gene; HR, hazard ratio.

Table 3 Oral SERDs and PROTACs in ER +/HER2− metastatic breast cancer

Drug	Trial	Company	Line	PFS (all-comers)	PFS (ESR1-mutant)	Toxicity	Status
Elacestrant[9]	EMERALD	Menarini	2nd+ line	2.8 vs. 1.9 months (HR 0.70)	3.8 vs. 1.9 months (HR 0.55)	Mild	Approved
Amcenestrant[10]	AMEERA-3	Sanofi	2nd+ line	No benefit	No benefit	Well tolerated	Terminated
Giredestrant[11]	acelERA	Roche	2nd+ line	No benefit	Trend toward benefit	Well tolerated	Ongoing
Camizestrant[12]	SERENA-2	AstraZeneca	2nd+ line	7.2 vs. 3.7 months (HR 0.58)	Benefit seen	Well tolerated	Ongoing
Camizestrant[13]	SERENA-4	AstraZeneca	1st line	Ongoing	Ongoing	Expected similar	Ongoing
Camizestrant[14]	SERENA-6	AstraZeneca	1st line (switch)		16 m vs. 9.2 m, (HR 0.44)	Acceptable	Positive
Imlunestrant[8]	EMBER-3	Eli Lilly	2nd+ line	9.4 vs. 5.5 months (HR 0.57)	11.1 vs. 5.5 months (HR 0.55)	Acceptable	Positive
Vepdegestrant[15]	VERITAC-2	Arvinas/Pfizer	2nd+ line	3.8 m vs. 3.6 m (HR 0.83)	5 m vs. 2.1 m (HR 0.58)	Favorable	Positive
Palazestrant[16]	OPERA-1	Olema	2nd+ line	TBD	TBD	TBD	Data due 2026
AC0682	Phase 1	Accutar	2nd+ line	Preliminary	ER degrader activity	Favorable (early)	Ongoing
ZD12	Preclinical	Not disclosed	Preclinical	In vitro potent	Yes	Unknown	Preclinical

Abbreviations: ER, estrogen receptor; TBD, to be determined.
Note: Vepdegestrant's two phase 3 trials halted in January and May 2025 due to strategic reprioritization. AC0682 and ZD12 are PROTACs.

However, it is crucial to recognize that this subset was small and the trial was not powered to evaluate outcomes specifically in post-abemaciclib patients. Therefore, while the data suggest potential limitations of sequencing abemaciclib before and after progression, further studies are needed to validate these observations.

SERENA-6 Trial

The SERENA-6 trial demonstrated that early switching to camizestrant upon detection of ESR1 mutations via serial ctDNA (circulating tumor DNA) monitoring prolonged PFS (16.0 vs. 9.2 months; HR: 0.44) and improved patient-reported outcomes.[14] However, the trial design raises critical concerns: continuing AIs in the control arm despite known ESR1 resistance is biologically suboptimal and may have inflated the observed benefit. Moreover, the intervention hinges on access to frequent liquid biopsy testing—an expensive and logistically intensive strategy not widely available. Post-progression treatment imbalance further complicates interpretation: patients in the camizestrant arm received more chemotherapy after first progression, while 10% in the control arm received oral SERDs, diluting comparability. Additionally, the lack of crossover to camizestrant in the control group precludes a fair assessment of the strategy's total clinical impact. This design flaw limits the ability to compare early versus delayed introduction of camizestrant and may artificially enhance first-line PFS differences. With OS and PFS2 data still immature, the true clinical utility and cost-effectiveness of this early-switch approach remain uncertain.

VERITAC-2 Trial

The VERITAC-2 trial evaluated vepdegestrant, a novel oral PROTAC ER degrader, against fulvestrant in patients with HR +/HER2− ABC post-CDK4/6 inhibitor therapy.[15] In the ESR1-mutant subgroup, vepdegestrant improved PFS (5.0 vs. 2.1 months; HR: 0.58; $p < 0.001$), but the overall population did not meet significance (HR: 0.83; $p = 0.07$). Despite this, treatment discontinuation due to adverse events remained low (<5%), underscoring favorable tolerability. However, exclusion of prior fulvestrant or chemotherapy limits applicability to real-world settings. Moreover, the modest absolute PFS gain and absence of mature OS data suggest that the drug's role may be confined to biomarker-selected niches.

Controversies in Post-CDK4/6 Sequencing

Despite the growing body of evidence, several areas of controversy persist in post-CDK4/6i sequencing. Notably, the conflicting outcomes among trials evaluating CDK4/6 inhibitor continuation versus switch strategies—such as PALMIRA, PACE, MAINTAIN, and postMONARCH—highlight inherent complexities. While PALMIRA and PACE failed to demonstrate PFS benefit with palbociclib continuation, MAINTAIN and postMONARCH showed that switching to ribociclib or abemaciclib can offer meaningful efficacy. These discrepancies may stem from differences in trial design, CDK4/6 pharmacologic profiles, endocrine backbone

selection, and inclusion criteria. Abemaciclib's continuous dosing schedule and broader kinase inhibition profile may explain its favorable outcomes in the postMONARCH trial.

A second area of ambiguity relates to the potential for cross-resistance, particularly concerning sequencing of abemaciclib. In EMBER-3, the subset of patients previously exposed to abemaciclib derived attenuated benefit when re-treated with the same agent. Also, if one looks at the Kaplan Meier curves of all these trials, we see steep drop in initial few months and curve separation occurs after 2 to 3 months, this suggests that some of these patients may have endocrine resistance due to mechanism that we do not know yet and probable such patients can be salvaged by early introduction of cytotoxic chemotherapy. But as of today, we do not have biomarkers to identify these patients. However, given the small size of this subgroup and the lack of statistical powering, these findings must be interpreted with caution. Prospective data are needed to assess whether prior abemaciclib use should influence future selection.

Finally, the distinction between pharmacologic failure and true biologic resistance remains poorly defined. Some patients progressing on CDK4/6 inhibitors may still harbor endocrine-responsive disease, suggesting that ET backbone or resistance mechanisms such as ESR1 mutation, rather than CDK4/6i inefficacy, may drive progression. These nuances underscore the need for biomarker-integrated strategies to guide clinical decision-making.

Managing Relapses after Adjuvant CDK4/6i

With the approval of abemaciclib and ribociclib in the adjuvant setting, patients who relapse after receiving adjuvant CDK4/6, treatment in the metastatic setting should be guided by mutational profile and prior treatment-free interval. If the relapse occurs within 12 months of stopping adjuvant CDK4/6i, most guidelines consider it as "CDK4/6-refractory." In such cases, CDK4/6 rechallenge (even with a different agent) is not routinely recommended outside trials. Instead, ET with targeted agents based on mutation status (e.g., alpelisib or capivasertib for PIK3CA-mutant tumors, elacestrant for ESR1-mutant disease) is preferred. For PIK3CA-mutant tumors, the inavolisib–palbociclib–fulvestrant triplet also shows promise.[17] In patients without targetable mutations or with rapid progression, chemotherapy may be required. PostMONARCH showed that continuing abemaciclib beyond progression may delay further progression, but data specifically in post-adjuvant settings are limited.

Patients with early progression (i.e., within 12 months of CDK4/6i initiation) are more likely to harbor intrinsic resistance mechanisms and may be less suitable for rechallenge. Conversely, late progressors—those deriving benefit beyond 1 year—may still respond to a class switch or combination strategies involving novel endocrine agents or targeted therapies.

Future Directions and Conclusions

The management of HR +/HER2− metastatic breast cancer following progression on CDK4/6 inhibitors is increasingly complex and rapidly evolving. Current evidence indicates that same-agent rechallenge offers limited benefit and should be discouraged. Switching to a different CDK4/6 inhibitor—such as ribociclib or abemaciclib—or combining with a novel endocrine agent like imlunestrant appears to be a more effective strategy.

Looking ahead, biomarker-driven treatment algorithms that incorporate genomic and transcriptomic profiling will be essential. Resistance mechanisms such as RB1 loss, ESR1 mutations, and PI3K/AKT activation must inform clinical decisions. Additionally, the emergence of new SERDs, PROTACs, and AKT inhibitors opens exciting avenues for overcoming resistance and extending disease control (►**Table 3**).

Ultimately, the post-CDK4/6 landscape demands nuanced, individualized treatment strategies. Future trials should aim to integrate biomarker stratification, consider prior drug exposure patterns, and explore rational combination strategies to optimize outcomes in this patient population.

In resource-constrained settings, particularly in low- and middle-income countries, access to novel oral SERDs, PROTACs, and liquid biopsy–based ctDNA monitoring remains highly limited. High costs, lack of availability, and infrastructural challenges make routine implementation difficult. Therefore, class-switch strategies—such as transitioning from palbociclib to ribociclib or abemaciclib—represent pragmatic and more accessible options, especially where generic formulations exist. This emphasizes the need to adapt post-CDK4/6 treatment sequencing to the realities of local resource availability.

Patient Consent
Patient consent is not required.

Conflict of Interest
None declared.

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