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Review

Drugging the luminal axis end to end: A review of next-generation endocrine and targeted therapies in HR + /HER2- metastatic breast cancer

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ABSTRACT

Hormone receptor-positive/HER2-negative (HR+/HER2-) breast cancer is driven by an interconnected signaling network centered on estrogen receptor (ER)-dependent transcription. ER signaling interacts bidirectionally with the PI3K-AKT-mTOR pathway and converges with it on the cyclin D-CDK4/6-RB-E2F machinery governing G1-S progression, a circuitry that cyclin E-CDK2 can reinforce or bypass during resistance. This network is now actionable at multiple levels, and recent years have produced an exceptional density of practice-changing innovations. Rather than cataloging individual agents, we interpret these advances as successive efforts to target one interdependent system, organized around three insights. First, ER pharmacology has diversified into mechanistically distinct classes -oral SERDs, PROTAC degraders, complete antagonists (CERANs), covalent antagonists (SERCAs) and modulators (SERMs), joined by KAT6 inhibition- yet the most consistent signal concentrates in the *ESR1*-mutant setting, a lesson in biomarker-gated development. Second, the principal constraint has been the tolerability ceiling of chronic multi-node blockade; mutant-selective PI3Kα inhibitors and CDK4- and CDK2-selective agents are defined less by new targets than by the selectivity that lifts that ceiling. Third, patient selection is shifting from clinicopathological categories to genomically defined subgroups assessed on tissue and/or circulating tumor DNA (*ctDNA*), with *ctDNA* additionally enabling dynamic monitoring and pre-emptive switching in selected scenarios. Synthesizing this landscape, we propose that the contemporary resistance taxonomy can serve as a therapeutic decision roadmap for durable, tolerable, biomarker-guided vertical blockade of the luminal axis.

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1. Introduction

Hormone receptor-positive/HER2-negative (HR+/HER2-) breast cancer (BC) represents the most common subtype of BC and one of the clearest examples of therapeutically exploitable lineage dependency [1–3].

Its biology is organized around a hierarchical, interconnected and therapeutically actionable signaling network centered on the estrogen receptor (ER). As a master transcriptional regulator, ER sustains cellular proliferation and survival through a context-dependent transcriptional program shaped by adaptive feedback and cross-talks with growth-factor signaling pathways [4,5].

Within this network, ER interacts bidirectionally with the phosphatidylinositol 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway, while both signaling systems converge on the cyclin D-cyclin-dependent kinase (CDK)4/6-retinoblastoma protein (RB)-E2F machinery that controls G1-to-S-phase cell-cycle progression [4].

PI3K-AKT-mTOR integrates metabolic, mitogenic, and growth-factor inputs reinforcing the ligand-independent ER activity, enabling cell-cycle progression [4].

For decades, this interlocked axis was only incompletely targeted by depriving cancer cells of estrogen: by lowering estrogen levels (with aromatase inhibitors, AI), competitively antagonizing ER (with tamoxifen), or inducing partial receptor degradation (with fulvestrant) [6–8].

The therapeutic landscape was then reshaped by the advent of CDK4/6 inhibitors (CDK4/6i: palbociclib, ribociclib and abemaciclib) whose combination with endocrine therapy (ET) substantially improved both progression-free survival (PFS) and, sometimes, overall survival (OS) over ET alone [9–15].

In parallel, the PI3K/AKT/mTOR pathway evolved from a biologically compelling but clinically elusive target into a therapeutically actionable one, as more selective agents (alpelisib, capivasertib and inavolisib) and biomarker-driven strategies were pursued [16–20]. More recently, the ER apex has re-emerged as a major therapeutic frontier, with next-generation ER-directed agents, including oral selective ER degraders (SERDs: i.e. elacestrant, imlunestrant and camizestrant), complete ER antagonists (CERANs: i.e. palazestrant), selective ER covalent antagonists (SERCAs), and proteolysis-targeting chimeras (PROTACs: i.e. vepdegestrant) designed to overcome the pharmacological and biological constraints of earlier ET [21–26].

These advances have shifted the central question in HR + /HER2- metastatic BC (mBC) from whether the luminal axis is druggable to how its nodes should be combined, sequenced, and re-targeted as the disease evolves under therapeutic pressure.

Although primary endocrine resistance is reported in up to 20% of cases, secondary resistance eventually emerges in most patients with HR + /HER2- mBC [27].

Endocrine resistance is recognized not as a single state, but as a convergent taxonomy of connected escape mechanisms including *ESR1* mutations and altered ER dependence, PIK3CA/AKT1/PTEN and mTOR pathway alterations, RB1 loss, cyclin E upregulation, CDK2 activation and growth-factor-mediated routes which can blur the boundary between endocrine-sensitive and endocrine-refractory disease [28,29]. Within this framework, these mechanisms can be read as prognostic biomarkers and as therapeutic decision tools [30,31].

Here, we conceptualize the luminal axis as a single, interdependent control system extending from ER transcriptional dependence to downstream survival programs. This view highlights three recurring principles. First, contemporary resistance biology can guide treatment selection because apparently distinct resistance routes often converge on a limited number of actionable exits from endocrine control. Second, the major constraint on durable multi-node blockade is not only biological redundancy, but also the tolerability ceiling imposed by chronic combinations. Third, patient selection is shifting from static clinicopathological categories toward genomic and dynamically monitored niches, with circulating tumor DNA (*ctDNA*) and tissue as the operational substrates.

Accordingly, we discuss representative next-generation endocrine and targeted therapies that aim to drug the luminal axis end to end.

Clinically advanced or clinically informative agents are summarized in Table 1, including approved therapies, positive or ongoing phase III strategies, and selected phase I/II or early-phase agents with regulatory status. Earlier pipeline compounds, preclinical programs and agents with limited clinical information are reported separately in Supplementary Table 1.

The search strategy and methodological approach for this narrative review are reported in the Supplementary Methodology and research strategy. Cytotoxic chemotherapy and antibody–drug conjugates (ADCs) are outside the scope of this review; indeed, much of the therapeutic strategy discussed here is directed precisely at extending endocrine-based disease control and delaying the transition to cytotoxic approaches.

2. The estrogen-receptor apex: one target, multiple pharmacological strategies

At the apex of the luminal axis, the ER is no longer approached as a single pharmacological target, but as a platform for mechanistically distinct therapeutic strategies. Conventional ET showed limitations: AI can be bypassed by emerging *ESR1* mutations that confer ligand-independent receptor activity; tamoxifen retains partial agonist properties; and fulvestrant is constrained by intramuscular administration, incomplete receptor suppression, suboptimal pharmacokinetic exposure and heterogenous activity [32,33].

ESR1 mutations arise under the pressure of estrogen deprivation, represent the most established genomic mechanism of acquired endocrine resistance, and are spatially and temporally heterogeneous; *ctDNA* has therefore become a highly attractive and clinically useful substrate for identifying emergent *ESR1* mutations and adapting therapy in selected settings, including before clinical-radiological progression. However, its performance depends on tumor shedding, disease burden, assay technology and alteration type, and plasma-negative results may require reflex tissue testing when clinical suspicion remains high [34–36].

The clinical evolution of oral SERDs testifies both the promise and the boundaries of ER targeting. Elacestrant established the principle that replacing fulvestrant with an oral SERD can improve PFS after prior exposure to ET [21]. Its approval, based on the EMERALD trial, was specifically limited to the *ESR1*-mutant population, reflecting the more favorable benefit–risk profile in this subgroup rather than in a broader unselected population [21].

Furthermore, the phase Ib/II ELEVATE trial reported clinical activity with elacestrant + everolimus after prior CDK4/6 inhibition also irrespectively of both *ESR1* and *PIK3CA* mutational status. However, although intriguing, these data derive from a non-randomized cohort of approximately 50 patients receiving the everolimus combination, and subgroup analyses according to the mutational status should be interpreted as descriptive rather than definitive predictive evidence [37].

Camizestrant, another oral SERD, has shown superior efficacy over fulvestrant in the SERENA-2 trial in patients with previously treated mBC, however, its most practice-changing evidence comes from the SERENA-6 trial [22,38].

Here, an early switch to camizestrant during first-line therapy with AI + CDK4/6i upon the emergence of *ESR1* mutation, detected by serial *ctDNA* monitoring before radiographic progression, significantly improved PFS, PFS2 and quality of life (QoL) over continuing the same regimen [38]. On this basis, camizestrant in combination with a CDK4/6i received FDA accelerated approval in September 2026 for *ESR1* mutations emerging during first-line AI + CDK4/6i, the first approval of a drug based on ctDNA monitoring of emerging mutations in the absence of radiographic progression; continued approval is contingent upon verification of clinical benefit [39].

Table 1
Clinically advanced or clinically informative endocrine and targeted agents directed against the luminal axis in HR + /HER2 − metastatic breast cancer.

Agent	Mechanism / distinctive feature	Key trial(s)	Stage /Phase	Evidence level / regulatory status
ER apex — oral SERD (selective ER degrader)				
Elacestrant	SERD-SERM hybrid	EMERALD, ELEVATE (advanced)ELEGANT (adjuvant)	EMERALD Phase 3ELEVATE Phase 1/2b;ELEGANT Phase 3	Regulatory-approved standard option in *ESR1*-mutated mBC after progression on ET
Camizestrant	Oral SERD; CNS-active	SERENA-1/2/-4/-6 (advanced) CAMBRIA-1/-2 (adjuvant)	SERENA-1 Phase 1SERENA-2 Phase 2SERENA-4/6, CAMBRIA 1/2 Phase 3	Regulatory-approved (FDA accelerated approval, September 2026) in combination with a CDK4/6i for *ESR1* mutation emerging during first-line AI + CDK4/6i and detected by ctDNA; OS immature
Giredestrant	Oral SERD	acelERA, persevERA, evERA, pionERA (advanced);lidERA (adjuvant)	acelERA, Phase 2persevERA. evERA, pionERA, lidERA Phase 3	Positive randomized phase III strategy awaiting/ undergoing regulatory implementation in combination with everolimus in mBC progressed on ET + CDK4/6i
Imlunestrant	Oral SERD	EMBER1, EMBER-3 (advanced); EMBER-4 (adj)	EMBER-1 Phase1EMBER3/4 Phase 3	Regulatory-approved (FDA approval, September 2025 and 2026) standard option in *ESR1*-mutated disease alone or in combination with abemaciclib in mBC progressed on ET
ER apex — PROTAC degrader				
Vepdegestrant (ARV-471)	PROTAC ER degrader; catalytic	ARV-471-mBC-101, VERITAC-2, VERITAC-3 (advanced)	ARV-471-mBC-101Phase 1VERITAC-2 Phase 3	Regulatory-approved (FDA approval May 2026) standard option in *ESR1*-mutated mBC after progression on ET
ER apex — complete ER antagonist (CERAN)				
Palazestrant (OP-1250)	CERAN + SERD	OPERA-01, OPERA-02 (advanced)	Phase 3	Phase III ongoing; no mature, randomized results
ER apex — covalent ER antagonist (SERCA)				
H3B-6545	Covalent ERα antagonist (Cys530)	NCT03250676, NCT04288089 (advanced)	Phase 1/2	Early-phase/preclinical hypothesis
ER apex — selective ER modulator (SERM)				
Lasofoxifene	SERM	ELAINE-1/-2/-3 (advanced)	ELAINE 1/2 Phase 2ELAINE 3 Phase 3	Randomized phase II signal (ELAINE-1, primary endpoint not met); phase III ongoing
Apex (epigenetic) — KAT6 inhibitor				
Prifetrastat (PF-07248144)	KAT6A/B inhibitor;↓ ER expression	NCT04606446KATSIS-1 (advanced)	NCT04606446 Phase 1KATSIS-1 Phase 3	Phase III ongoing; no mature, randomized results
MEN2312 (ISM5043)	KAT6 inhibitor	NCT06638307(advanced)	Phase 1b/2	Early-phase/preclinical hypothesis
OP-3136	KAT6A/B inhibitor	OP-3136–101(advanced)	Phase 1	Early-phase/preclinical hypothesis
PI3K/AKT/mTOR — PI3Kα inhibitor				
Alpelisib	PI3Kα inhibitor	SOLAR-1; BYLieve; EPIK-B5 (advanced)	Phase 2 and 3FDA-approved 2019 (*PIK3CA*-mut)	Regulatory-approved (FDA approval, April 2022) standard option for *PIK3CA*-mutated mBC progressed on ET
Inavolisib	PI3Kα inhibitor + mutant-p110α degrader	INAVO120(advanced)	Phase 3FDA-approved 2024 (*PIK3CA*-mut)	Regulatory-approved (FDA approval, October 2024) standard option for selected *PIK3CA*-mutated endocrine-resistant disease progressed while on or < 12 months of completing adjuvant ET
RLY-2608 (zovegalisib);	Mutant-selective PI3Kα inhibitor	ReDiscover-2(advanced)	Phase 3	Phase III ongoing; no mature, randomized results
STX-478 (tersolisib)		PIKALO-1, NCT07174336 (advanced)	PIKALO-1 Phase1/ 2NCT07174336 Phase 3	Phase III ongoing; no mature, randomized results
PI3K/AKT/mTOR — AKT / pan-PI3K-mTOR inhibitor				
Capivasertib	Pan-AKT inhibitor	CAPItello-291, CAPItello-292 (advanced)	CAPItello-291 Phase 3CAPItello-292 Phase 3 ongoing	Regulatory-approved (FDA approval, June 2026) standard option for *PIK3CA/AKT1/PTEN*-altered HR + /HER2 − mBC progressed on ET
Afuresertib		NCT04851613(advanced)	Phase 3	Phase III ongoing; no mature, randomized results
Gedatolisib	pan-PI3K/mTORC1/2	VIKTORIA-1; VIKTORIA-2 (advanced)	VIKTORIA-1 Phase 3FDA-approved 2026VIKTORIA-2 Phase 3ongoing	Regulatory-approved (FDA, July 2026) with fulvestrant ± palbociclib for *PIK3CA*-wild-type mBC progressed on ET; *PIK3CA*-mutant cohort positive (congress abstract only)
Cell-cycle — CDK4/6 inhibitor /degrader				
Ribociclib, Abemaciclib, Palbociclib	CDK4/6 inhibitors	MONALEESA-2/3/7; MONARCH 2/3; PALOMA 2/3 (advanced)	Phase 3	Regulatory-approved standard option as first-line treatment in combination with ET
Cell-cycle — CDK4-selective inhibitor				
Atirmociclib (PF-07220060)	Selective CDK4 inhibitor	FourLight-1/-2/-3(advanced)	FourLight-3 Phase 3FourLight 1–2 Phase 2	Randomized phase II signal (FourLight-1, sponsor-reported topline); phase III ongoing
Cell-cycle — CDK2-selective inhibitor / degrader				
Tegtociclib (PF-07104091)	Selective CDK2 inhibitor(CDK4/6i-resistant BC and CCNE1-amplified solid tumors other than BC)	NCT05262400, NCT04553133 (advanced)	Phase 1/2	Early-phase/preclinical hypothesis
Cell-cycle — CDK2/4/6 inhibitor				
Culmerciclib (TQB3616)	CDK2/4/6 inhibitor	NCT05375461(advanced)	Phase 3	Positive randomized phase III; regulatory approved in China (NMPA) only
Cell-cycle — CDK7 inhibitor				
Samuraciclib (CT7001)	CDK7 inhibitor	SUMIT-BC(advanced)	Phase 2	Randomized phase II signal (sponsor-reported topline)

Table 1 summarizes approved agents, positive or ongoing phase III strategies, and clinically informative phase I/II or selected early-phase agents with relevant activity data in HR + /HER2 − mBC

Evidence level/regulatory status definitions: "Regulatory-approved standard option" indicates regulatory-approved (FDA and/or EMA, unless otherwise specified) or clinically established options in HR + /HER2 − mBC; "Positive randomized phase III strategy awaiting/undergoing regulatory implementation" indicates agents or combinations supported by randomized phase III evidence but not yet fully implemented as standard in the indicated context; "Phase III ongoing" indicates strategies under registrational evaluation without mature practice-changing results. "Randomized phase II signal" indicates non-registrational but clinically informative activity data. "Early-phase/preclinical hypothesis" indicates phase I/II or preclinical data without randomized evidence.

Abbreviations: ABC, advanced breast cancer; adj, adjuvant; AKT, protein kinase B; BC, breast cancer; CDK, cyclin-dependent kinase; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CERAN, complete estrogen receptor antagonist; CNS, central nervous system; ctDNA, circulating tumor DNA; ER, estrogen receptor; ESR1, estrogen receptor 1; ET, endocrine therapy; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; KAT6, lysine acetyltransferase 6; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; mTORC1/2, mammalian target of rapamycin complex 1/2; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PROTAC, proteolysis-targeting chimera; PTEN, phosphatase and tensin homolog; SERCA, selective estrogen receptor covalent antagonist; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; SOC, standard of care.

However, the absence of mature OS data and the lack of validated surrogacy between the reported endpoints and OS leave uncertainty on this pre-emptive switch. Moreover, routine serial *ctDNA* monitoring may introduce substantial logistical complexity and financial burden, while its optimal timing, frequency, assay platform, and cost-effectiveness remain to be established.

Importantly, this evidence derived from the SERENA-6 only applies to its defined clinical and molecular scenario where a pre-emptive treatment switch is potentially justified, but it should not be extrapolated to routine serial ctDNA monitoring for all patients with HR + / HER2 − mBC, nor to anticipate treatment changes based on molecular progression involving biomarkers other than *ESR1* outside prospectively validated strategies.

Imlunestrant extended this pattern in the EMBER-3 trial where it demonstrated improved PFS when compared to ET in *ESR1*-mutated disease [40].

More interestingly, when combined with abemaciclib, imlunestrant produced even a broader PFS advantage over the investigational agent alone irrespective of *ESR1* status or PI3K-pathway alterations, although regulatory approval of both imlunestrant monotherapy and the combination (FDA, September 2026) is restricted to *ESR1*-mutated disease [23,41,42].

Lastly, giredestrant, although it did not significantly improve PFS versus ET in the acelERA trial, significantly improved PFS in combination with everolimus versus standard ET + everolimus in the phase III evERA trial, both in the *ESR1*-mutated and in the overall population and irrespective of *PIK3CA* mutations and PIK3CA/AKT1/PTEN-pathway alterations [43–45]. Together, these data suggest that the ER apex may be more potently targeted both when precisely selected by *ESR1* mutation and when embedded within rational combinations targeting interconnected resistance modules even in some biomarker-unselected groups.

Despite the clear benefit of oral SERDs in *ESR1*-mutant disease, selecting the right patients remains an urgent unmet clinical need, given the availability of alternative therapies. One example is the duration of prior CDK4/6i therapy in the first-line setting; indeed, while in the EMERALD trial, elacestrant benefit was magnified in patients whose disease has responded to a CDK4/6i for more than 12 months, in the evERA trial the oral combination was superior regardless from the time of exposure to CDK4/6i, suggesting the time on CDK4/6i as a clinical indicator of potential benefit from a SERD in monotherapy or in combination with other strategies [45,46].

This is particularly relevant because it remains important to consider whether and in whom their corresponding clinical improvement justifies the financial burden associated with these new costly therapies.

The same therapeutic niche is now being approached through several other agents.

PROTAC ER degraders, with vepdegestrant as the most advanced agent of the class, co-opt the ubiquitin–proteasome system for receptor destruction and, in the VERITAC-2 trial, vepdegestrant significantly improved PFS over fulvestrant in *ESR1*-mutated disease, leading to its FDA approval [24].

After promising preclinical evidence of activity in combination with CDK4/6i and PI3K inhibitors, vepdegestrant is under clinical investigation in combination with palbociclib as first-line therapy in the VERITAC-3 trial [47,48].

The class, however, is broader than its frontrunner: AC699 has shown early clinical activity, with ERD-3111/ERD-4001, HP568 and HRS-1358 behind it and AC682 discontinued (Supplementary Table 1) [49–54].

Other ER-directed modalities remain earlier in development but sharpen this mechanistic landscape. CERANs, with palazestrant as the most promising agent, are designed to combine antagonism and degradation by fully suppressing both activation-function domains of ER, with the ongoing phase III OPERA-01 and OPERA-02 trials evaluating it as monotherapy and in combination with ribociclib, respectively, and regardless of *ESR1* status [25,55,56].

SERCAs, such as H3B-6545, irreversibly engage ER at Cys530 and aim to enforce durable receptor suppression, with early-phase activity reported in endocrine-resistant HR + /HER2- disease especially in the presence of *ESR1* mutations [57].

Next-generation SERMs such as lasofoxifene seek to exploit high affinity for mutant ER while retaining a differentiated safety and pharmacologic profile.

In ELAINE-1, lasofoxifene showed numerical PFS improvement versus fulvestrant in patients with *ESR1*-mutated disease, but the primary PFS comparison was not statistically significant (HR 0.699; p = 0.138). Its continued development is therefore supported by a hypothesis-generating phase II signal, together with activity reported in combination with abemaciclib in ELAINE-2 and ongoing evaluation in the phase III ELAINE-3 trial [58–60].

Two patterns cut across this mechanistic diversity. The first is convergence: across oral SERDs, PROTAC degraders, and other ER-directed agents, the clearest signal for monotherapy repeatedly concentrates in *ESR1*-mutated tumors, where they can outperform fulvestrant or standard ET, whereas benefit in *ESR1*–wild-type populations is often attenuated.

This suggests that, outside the *ESR1*-mutant niche, their optimal development may lie in combination strategies that pair ER suppression with blockade of downstream proliferative pathways. This provides the strongest rationale for *ctDNA*-based *ESR1* testing as a gating biomarker and explains why the first approvals of elacestrant, imlunestrant, and vepdegestrant were all *ESR1*-restricted. The second is divergence: mechanistic differences among SERDs, PROTACs, CERANs, SERCAs, and SERMs are biologically real, but their clinical hierarchy remains unadjudicated. Completeness of antagonism, irreversibility, catalytic degradation, CNS penetration, once-daily oral dosing, safety, and compatibility with other agents may ultimately determine positioning as much as the core ER mechanism itself [49,50]. The apex, therefore, is no longer a single therapeutic target but a pharmacologic platform increasingly selected by *ctDNA* and tissue genotyping, strengthened by combinations, and judged by its capacity to delay escape into endocrine-independent biology (Table 1).

3. Epigenetic control of ER expression: KAT6 inhibition

An orthogonal and appealing way to target the ER apex is to reduce its transcriptional expression by epigenetic modifiers that act through the inhibition of lysine acetyltransferases 6 (KAT6A/B) [61].

KAT6A is located within the 8p11–p12 amplicon, a recurrent alteration enriched in luminal B disease and associated with adverse prognosis and endocrine resistance [61–63]. Functionally, KAT6A/B regulate chromatin accessibility and remodeling that sustain ERα expression, cell-cycle progression, E2F output and MYC-dependent proliferation as well as DNA damage response pathways [62]. KAT6 inhibition therefore targets the luminal axis upstream of receptor engagement, lowering ER expression and suppressing downstream proliferative programs in a manner at least partly independent of *ESR1* mutation or PI3K-pathway alterations.

This emerging strategy adds an epigenetic layer to the treatment of luminal BC where this biological rationale is compelling although prior efforts with entinostat, a histone deacetylase (HDAC) inhibitor, ultimately failed to demonstrate consistent clinical benefit, probably due to the lack of patient's selection or predictive biomarkers [64].

Clinical proof of concept comes from prifetrastat (PF-07248144), a first-in-class selective catalytic inhibitor of KAT6A/B (KAT6i). In a phase I study in heavily pretreated HR + /HER2- mBC, PF-07248144 showed antitumor activity both as monotherapy and in combination with fulvestrant [65].

Interestingly, durable activity was seen in both *ESR1*-mutant and wild-type tumors [65].

The toxicity profile appeared predominantly hematological except for dysgeusia, emerging as the characteristic and most frequent adverse event.

The most important signal, however, is expected to come from the ongoing phase III KATSIS trial which is evaluating prifetrastat + fulvestrant versus everolimus-based ET after progression on CDK4/6i [66]. Notably, the study excludes tumors with detectable *PIK3CA, AKT1* or *PTEN* alterations, thereby deliberately positioning KAT6 inhibition in the PI3K-pathway-wild-type post-CDK4/6i space.

Recently, another KAT6A/Bi, OP-3136 has demonstrated preliminary activity and a manageable safety profile, both as monotherapy and in combination with fulvestrant in BC [67].

Lastly, a third KAT6i, MEN2312, has entered first-in-human evaluation as monotherapy and in combination with elacestrant in mBC, further supporting the concept that KAT6 inhibition may be developed both as an independent endocrine-resistance strategy and as a partner for ER-directed therapies [68]. At present, the class should be viewed as promising rather than practice changing (Supplementary Table 1). If validated prospectively, this could make KAT6i particularly relevant in the growing population of patients with endocrine-resistant, post-CDK4/6i HR + /HER2 mBC who lack actionable alterations. ER-directed therapies are summarized in Fig. 1.

4. The convergence node

Beside the ER apex, the PI3K/AKT/mTOR pathway acts as a separate but interlocked effector node capable of sustaining a ligand-independent activation of the ER receptor leading to tumor growth even in the absence of estrogens.

Finally, the cyclin D1–CDK4/6 complex functions as a molecular synthesizer by integrating proliferative inputs from ER signaling, PI3K/AKT/mTOR pathway and other receptor tyrosine kinases (RTKs) (Fig. 2). In turn, AKT reinforces this node through convergent mechanisms: inactivation or cytoplasmic sequestration of the CDK inhibitors p21 and p27, FOXO-dependent regulation of CCND1 transcription, and mTORC1-mediated activity [4,69].

However, the shared output is RB hyperphosphorylation which leads to de-repression of E2F and ultimately to G1-S cell-cycle progression [4].

Once engaged, cyclin E-CDK2 further phosphorylates RB, creating a feed-forward loop that can sustain E2F transcriptional output leading to resistance to CDK4/6i [4,70].

Moreover, following CDK4/6 inhibition, the active, hypophosphorylated form of RB, can promote ER-responsive transcription regions which are normally not occupied by RB, unraveling a latent, broader transcriptional activity of RB [71].

This dual role establishes RB as a dynamic, versatile and context-dependent actor in cancer biology. RB-dependent activation of ER signaling provides a mechanistic basis for the synergy between CDK4/6i and ET, on the other hand in *ESR1*-mutant disease, this transcriptional program persists despite estrogen deprivation, preventing cell-cycle suppression. Pharmacological ER degradation abrogates this effect, offering a mechanistic explanation for the enhanced activity of SERDs in this setting.

In this architecture, endocrine dependence and cell-cycle commitment are not separate modules but mutually reinforcing layers of the same luminal control system. This explains why therapeutic resistance is rarely due to the failure of a single biological pathway since the

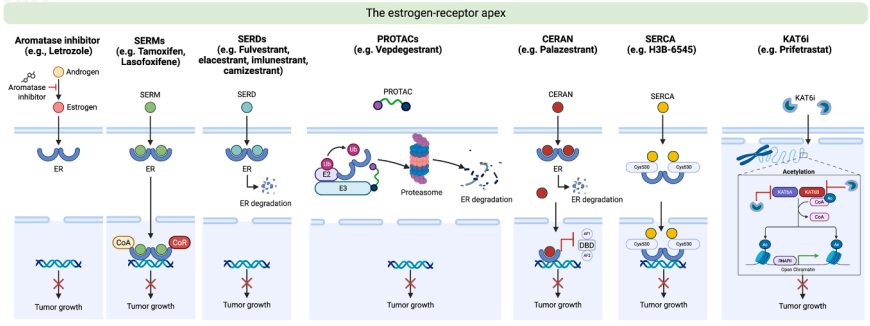

Fig. 1. Therapeutic strategies targeting the estrogen-receptor apex of the luminal axis. Fig. 1 summarizes the major pharmacological approaches directed at ER signaling in HR + /HER2- mBC. Aromatase inhibitors reduce estrogens synthesis and thereby limit ligand-dependent ER activation. Selective ER modulators (SERMs) bind ER and alter co-regulator recruitment, while selective ER degraders (SERDs) promote ER degradation. PROTAC ER degraders induce ubiquitin–proteasome-mediated receptor degradation through recruitment of an E3 ubiquitin ligase. Complete ER antagonists (CERANs) aim to block both ER activation-function domains while promoting receptor degradation, and selective ER covalent antagonists (SERCAs) irreversibly engage ER through covalent binding. KAT6 inhibitors represent an epigenetic strategy that suppresses ER expression by modulating chromatin acetylation. Together, these approaches illustrate the fragmentation of ER pharmacology into distinct therapeutic strategies converging on inhibition of ER-driven tumor growth. Abbreviations: AF1/2, activation function 1/2; CERAN, complete estrogen-receptor antagonist; CoA, co-activator; CoR, co-repressor; Cys530, cysteine 530; DBD, DNA-binding domain; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; ER, estrogen receptor; KAT6i, lysine acetyltransferase 6 inhibitor; PROTAC, proteolysis-targeting chimera; SERCA, selective estrogen-receptor covalent antagonist; SERD, selective estrogen-receptor degrader; SERM, selective estrogen-receptor modulator; Ub, ubiquitin. Created in BioRender. Caltavituro, A. (2026). Created in https://BioRender.com.

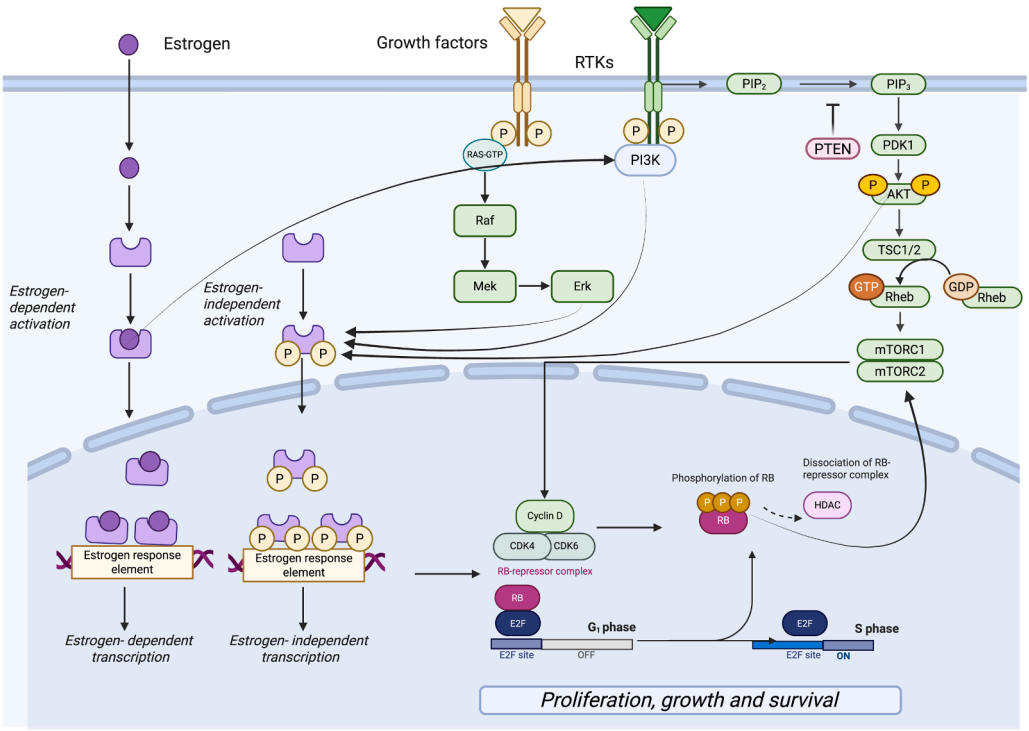

Fig. 2. Biological crosstalk between estrogen receptor, growth factor pathway and cell-cycle control in HR + /HER2- BC. Fig. 2 shows the crosstalk between the estrogen receptor pathway and other major growth factor signaling routes. Estrogen binding induces ligand-dependent estrogen receptor (ER) activation and transcription through estrogen-response elements. Receptor tyrosine kinase (RTK) signaling activates the RAS–RAF–MEK–ERK and PI3K–AKT–mTOR pathways, promoting ligand-independent ER phosphorylation and transcriptional activity. These interconnected pathways converge on cyclin D–CDK4/6, leading to retinoblastoma protein (RB) phosphorylation, dissociation of the RB–E2F repressor complex, activation of E2F-dependent transcription and progression from G1 to S phase. PTEN negatively regulates PI3K signaling by opposing the conversion of PIP2 to PIP3. Reciprocal crosstalk also connects the RB and mTOR pathways: phosphorylated RB can bind and restrain mTORC2 activity, whereas inhibition of RB phosphorylation disrupts this interaction, relieving mTORC2 suppression and triggering compensatory AKT activation. Collectively, these signaling and feedback networks promote tumor-cell proliferation, growth and survival and may contribute to adaptive resistance to CDK4/6 inhibition. Abbreviations: AKT, protein kinase B; CDK, cyclin-dependent kinase; ERK, extracellular signal-regulated kinase; HDAC, histone deacetylase; MEK, mitogen-activated protein kinase; mTORC, mechanistic//mammalian target of rapamycin complex; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog; RB, retinoblastoma protein; RTK, receptor tyrosine kinase; TSC1/2, tuberous sclerosis complex 1/2. Created in BioRender. Caltavituro, A. (2026). Created in https://BioRender.com.

inhibition of one node usually leads to a shift in signaling pressure to another one, allowing tumors to restore proliferative outputs through alternative routes. Therefore, the therapeutic opportunity is to read resistance as a rewiring, multi-layered event in which an *ESR1*-mutant or a PI3K/AKT/PTEN-altered tumor and a cyclin E/CDK2-driven disease may all escape endocrine control, but through different routes that should not necessarily be treated in the same way. Indeed, rather than applying uniform post-progression strategies treatment strategy should depend on matching these different routes to rational, tolerable combinations [30,31].

5. Drugging the node, part I: PI3K/AKT/mTOR

Pathway activation, through *PIK3CA* mutation (~40%), *PTEN* loss (12–15 %), *AKT1* mutation (1–4 %), is among the most common oncogenic events in BC and a driver of resistance [72,73].

The inhibition of PI3K/AKT/mTOR pathway is a story of tolerability issues. Indeed, for many years despite its centrality as a biological route, this did not translate into an effective actionable target since early pan-PI3K inhibitors were hindered by modest efficacy, broad pathway suppression and therefore limiting toxicity profile [74].

Progress mostly has come by widening the therapeutic window of these drugs through the selection of the right patients' population and the design of treatment schedules that protect the patient from undesirable toxicities.

The clearest proof comes from the INAVO120 trial where patients with endocrine-resistant, *PIK3CA*-mutated HR + /HER2- mBC relapsing during or shortly after adjuvant ET received the combination of inavolisib, palbociclib and fulvestrant which improved PFS compared with palbociclib and fulvestrant [20]. This regimen also delivered a significant OS benefit, establishing the first evidence that simultaneous blockade of ER, CDK4/6 and PI3Kα can be clinically worthwhile [75].

This is important because inavolisib is not merely a PI3Kα inhibitor as it also promotes the degradation of mutant catalytic subunit p110α, thereby adding a mutant-directed pharmacologic layer to the suppression of this pathway. However, INAVO120 also crystallizes the central limitation of this vertical blockade since the benefit comes at the cost of increased toxicity prompting the need to redefine the tolerability ceiling that next-generation agents must overcome [20,75].

The SOLAR-1 trial has established the superiority of the combination of alpelisib + fulvestrant, versus fulvestrant, in *PIK3CA*-mutated disease upon progression to ET, while the BYLieve and EPIK-B5 trials have both reinforced its activity in the contemporary post-CDK4/6i setting [16–18]. Nevertheless, the clinical positioning of alpelisib continues to be shaped by its metabolic toxicity, hyperglycemia, requiring careful patient selection and monitoring. The class lesson is clear: PI3Kα is a valid target, but wild-type PI3Kα inhibition narrows the therapeutic window.

AKT inhibition represents a parallel solution. Capivasertib + fulvestrant improved PFS in the CAPItello-291 trial becoming the new standard endocrine-based option for patients with *PIK3CA*-, *AKT1*- or *PTEN*-altered HR + /HER2- mBC progressed on ET

[19]. Its intermittent schedule is not a minor pharmacologic detail but part of a therapeutic concept where pathway suppression is delivered to preserve tolerability and reduce chronic metabolic stress. CAPItello-292 is now testing whether AKT inhibition can be moved into the first line setting in combination with fulvestrant and CDK4/6i, directly extending the INAVO120 principle from PI3Kα-mutant disease to the broader AKT-pathway-altered space [76].

Regardless of *PIK3CA* mutation, gedatolisib has reopened an older idea with a modern approach. This intravenous pan-PI3K/mTORC1/2 inhibitor showed, in the phase III VIKTORIA-1 trial, substantial post-CDK4/6i activity in both *PIK3CA*-wild-type and mutant HR + /HER2- mBC [77,78].

Indeed, both the triplet, with palbociclib and fulvestrant, and the doublet, without the CDK4/6i, have improved PFS over fulvestrant alone and fulvestrant + alpelisib [77,78]in the *PIK3CA*-wild-type and *PIK3CA*-mutant cohorts, respectively [75,76]; however, the *PIK3CA*--mutant cohort results (HR 0.50 for the triplet and 0.51 for the doublet versus alpelisib + fulvestrant) are currently available only as a congress abstract and await peer-reviewed publication. Based on these results gedatolisib + fulvestrant ± palbociclib received FDA approval in July 2026 for patients with HR + /HER2- mBC without a *PIK3CA* mutation detected [79].

Importantly, although the intravenous administration may limit its widespread adoption, the intermittent schedule appears to mitigate some of the metabolic liabilities associated with pan-pathway inhibition, suggesting that schedule manipulation can partially substitute for molecular selectivity.

However, the arrival of mutant-selective PI3Kα inhibitors may reshape the field by inhibiting oncogenic PI3Kα while sparing wild-type PI3Kα, the principal mediator of treatment-emergent hyperglycemia.

Zovegalisib, formerly RLY-2608, has provided one of the most advanced early clinical signals to date [80]. In combination with fulvestrant, it has shown durable activity in *PIK3CA*-mutated HR + /HER2- mBC with limited high-grade hyperglycemia, however, randomized phase III validation is ongoing in the ReDiscover-2 trial against capivasertib + fulvestrant [80,81].

Furthermore, zovegalisib is also being investigated in combination with CDK4/6i or atirmociclib in advanced tumors with *PIK3CA* mutations (NCT05216432).

Other mutant-selective PI3Kα inhibitors, such as STX-478, ETX-636, OKI-219 and LOXO-783, are in clinical development pursuing the same principle: decoupling antitumor activity from the metabolic toxicity imposed by wild-type PI3Kα inhibition (Supplementary Table 1).

These new-generation agents matter not only because they add options to the PI3K therapeutic toolbox, but because they may make effective strategies chronically deliverable. INAVO120 showed that vertical blockade of ER, CDK4/6 and PI3Kα can improve survival; capivasertib showed that intermittent pathway inhibition can be tolerable and clinically useful; gedatolisib showed that even broad PI3K/mTOR inhibition can be reconsidered when schedule and patient selection are optimized. Mutant-selective PI3Kα inhibition offers a further step: the possibility of preserving the efficacy of PI3Kα blockade while lifting the metabolic ceiling that has historically limited its use in combinations. In this sense, these agents can be viewed not only as pathway inhibitors, but as enablers of durable multi-node therapy.

6. Drugging the node, part II: the cell-cycle

Although CDK4/6i + ET represents the standard of care for HR + /HER2- mBC some patients demonstrate *de novo* resistance, and in those who initially respond, acquired resistance and disease progression are unfortunately inevitable [82]. This aspect underlies the importance of the cell-cycle node architecture where most mechanisms of escape converge on the restoration of RB-E2F output, either by disabling the pathway's gatekeeper, through *RB1* loss or, more frequently, by bypassing upstream CDK4/6 dependence through cyclin E-CDK2 engagement, driven by CCNE1 amplification, overexpression or loss of negative regulators such as p21 or p27 or other routes including PI3K/AKT/PTEN pathway activation, ER reactivation, RTKs signaling, and CDK6 upregulation [5,82].

Whatever the different biological mechanisms, they all share the same functional endpoint: functional RB inactivation by either loss of expression or renewed phosphorylation, E2F de-repression and G1-S progression despite prior CDK4/6 blockade.

The first strategy is to separate CDK4 from CDK6 to exploit the therapeutic asymmetry that lies between the two kinases.

In fact, in luminal BC, oncogenic cell-cycle dependence appears to be predominantly CDK4-driven, conversely CDK6 contributes substantially to the class-defining hematologic dose-limiting toxicity of all approved dual CDK4/6i, and it can also participate in resistance through an adaptive upregulation mechanism [83].

A CDK4-selective inhibitor (CDK4i) could therefore exert tumor cell-cycle suppression while sparing CDK6-dependent hematopoietic toxicity, widening the therapeutic window for a deeper and more durable blockade. Atirmociclib, also known as PF-07220060, is among the most advanced CDK4i in HR + /HER2- mBC after preliminary preclinical data supporting its activity in models with acquired resistance to CDK4/6i both as monotherapy and in combination with other agents (including CDK4/6i) [84].

Clinically, positive topline randomized phase II results have been reported from FourLight-1, evaluating atirmociclib + fulvestrant versus fulvestrant or everolimus + exemestane in patients previously treated with CDK4/6i-based therapy [85]. According to the sponsor-reported topline analysis, the study met its primary endpoint, with improved investigator-assessed PFS (HR 0.60; 95% CI 0.440–0.825; $p = 0.0007$). However, full peer-reviewed efficacy and safety data are awaited, OS remains immature, and atirmociclib should still be considered investigational.

This is particularly important since it suggests that CDK4i retain activity even after failure of a prior dual CDK4/6 inhibition [85]. After these promising data, the results of the phase III FourLight-3 trial, which is investigating the role of atirmociclib + letrozole as first-line of therapy are awaited [86]. Other CDK4-selective agents, including BGB-43395, HRS-6209 and AVZO-023 are pursuing the same principle, although their clinical positioning remains less mature.

The second strategy is to target the principal cell-cycle bypass: CDK2–cyclin E. CDK2 becomes particularly relevant when tumors escape CDK4/6 inhibition by amplifying CCNE1, increasing cyclin E expression, losing endogenous CDK inhibitors, or restoring E2F transcriptional output [70].

Selective CDK2 inhibition is therefore not a generic cell-cycle strategy, but a rational attempt to close the route by which RB phosphorylation is maintained after CDK4/6 blockade.

Preclinical studies with INX-315 showed that CDK2 inhibitors (CDK2i) can induce cell-cycle arrest and senescence-like states in CCNE1-amplified cancers and in CDK4/6i-resistant BC models [87]. Moreover, BLU-222 has provided complementary evidence that selective CDK2 inhibition can enhance the activity of CDK4/6i supporting combination development with ribociclib and fulvestrant [88,89].

Other selective CDK2i such as tegtociclib (PF-07104091), INCB123667, AVZO-021, BG-68501, AZD8421, ECI830 and NKT3447 remain in clinical development across HR + /HER2- BC and cyclin E-driven tumors (Supplementary Table 1).

The field is also beginning to move beyond catalytic inhibition with the development of CDK2 degraders and CDK2-directed PROTACs, such as NKT3964, which aim to eliminate the CDK2 protein rather than transiently inhibit its kinase activity, potentially producing deeper pathway suppression and avoiding compensatory cyclin E accumulation [70,90].

These approaches are still early, but they extend the same logic: if CDK2–cyclin E is the dominant escape route after CDK4/6 inhibition, then durable control may require disabling CDK2 more completely than

reversible inhibition allows.

One implication of this node model is the possibility of inducing a dual cell-cycle blockade with both a CDK4i and a CDK2i. In principle, this pairing could achieve a deeper RB dephosphorylation than either strategy alone while elegantly avoiding the excessive bone marrow toxicity expected from a conventional dual CDK4/6i with or without a CDK2i. In this way, sparing CDK6 from catalytic inhibition may therefore make vertical cell-cycle blockade clinically feasible and safe. For now, this remains a hypothesis under early clinical testing in the phase I/II NCT05262400 trial studying the combination of atirmociclib and tegtociclib in CDK4/6i-pretreated patients rather than an established standard, but it captures the direction of the field: moving from broad CDK4/6 suppression to a more precise control of the RB–E2F exit node [91].

Another intriguing strategy is the simultaneous inhibition of CDK2, CDK4, and CDK6 using a single multitarget agent. In the phase III CULMINATE-1 trial the addition of culmerciclib, a novel CDK2/4/6 inhibitor (CDK2/4/6i), to fulvestrant significantly improved PFS compared with fulvestrant + placebo, supporting simultaneous CDK2/4/6 inhibition as a potentially novel effective therapeutic strategy, although regulatory status, peer-reviewed safety interpretation and positioning relative to established ET-based options and outside of China, remain to be defined [92,93]. Although culmerciclib is the first agent of this class to demonstrate efficacy in a phase III trial, it is not the only CDK2/4/6i to have entered clinical development. Ebvaciclib (PF-06873600) showed preliminary antitumor activity, both as monotherapy and in combination with ET, in a first-in-human phase I/IIa study [94]. However, its clinical development was subsequently discontinued for business reasons rather than safety concerns or regulatory request.

Lastly, another interesting target is represented by the CDK-activating kinase (CAK), CDK7 which promotes cell-cycle progression through the phosphorylation of specific CDKs [95].

Samuraciclib, which is one of the most investigated CDK7 inhibitors (CDK7i) in BC, after the promising results of the phase I study (NCT03363893), has shown, according to sponsor-reported topline results, improved activity in combination with fulvestrant over fulvestrant alone in the phase II SUMIT-BC trial in CDK4/6i-pretreated patients; however, it remains investigational and requires further validation [96,97].

The interdependence between ER signaling, PI3K/AKT/mTOR pathway and cell-cycle control is depicted in Fig. 2, while in Fig. 3 is represented the therapeutic architecture of the luminal-axis.

7. Three cross-cutting insights

7.1. Resistance is a decision map

Since the luminal axis has one exit reached through multiple molecular interconnected routes, then resistance should be read as a

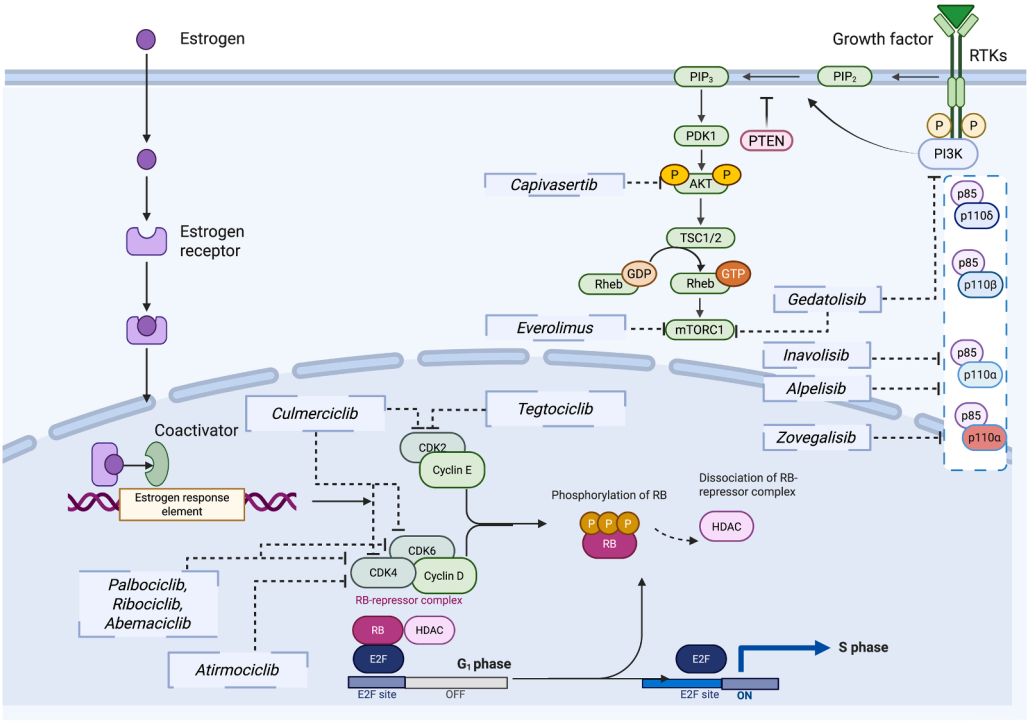

Fig. 3. Therapeutic architecture of the downstream luminal-axis effector node. Fig. 3 illustrates the functional integration of ER signaling, receptor tyrosine kinase input, PI3K/AKT/mTOR activation and cyclin D–CDK4/6–RB–E2F cell-cycle control in HR + /HER2- breast cancer. Together, these interactions provide the biological rationale for biomarker-directed vertical blockade and for next-generation strategies designed to overcome resistance while preserving tolerability. This network can be therapeutically intercepted at multiple levels. Alpelisib and inavolisib selectively inhibit PI3Kα (p110α) with the second also inducing the degradation of the enzyme; whereas gedatolisib provides broader pathway blockade by targeting all the four PI3K isoforms and mTOR complexes and zovegalisib is an allosteric, pan-mutant-selective PI3Kα inhibitor designed to suppress oncogenic *PIK3CA*-mutant signaling while sparing wild-type PI3Kα. Capivasertib inhibits AKT, while everolimus inhibits mTORC1. At the cell-cycle level, palbociclib, ribociclib and abemaciclib inhibit CDK4/6; atirmociclib selectively targets CDK4 while sparing CDK6; tegtociclib selectively inhibits CDK2; and culmerciclib simultaneously targets CDK2, CDK4 and CDK6. Inhibition of these nodes prevents cyclin D–CDK4/6- and cyclin E–CDK2-mediated RB phosphorylation, preserves the RB–E2F repressor complex and limits E2F-dependent transcription and G_1-to-S-phase progression. Solid arrows indicate pathway activation, black dotted lines ending in bars indicate pharmacological inhibition.. Abbreviations: AKT, protein kinase B; CDK, cyclin-dependent kinase; ERK, extracellular signal-regulated kinase; HDAC, histone deacetylase; MEK, mitogen-activated protein kinase; mTORC, mechanistic target of rapamycin complex; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog; RB, retinoblastoma protein; RTK, receptor tyrosine kinase; TSC1/2, tuberous sclerosis complex 1/2. Created in BioRender. Caltavituro, A. (2026). Created in https://BioRender.com.

therapeutic decision map (Table 2).

Resistance to ET and CDK4/6i is typically polyclonal, arising from intratumoral heterogeneity, with distinct cancer cell clones harboring different genomic alterations and activating multiple resistance pathways [98].

Furthermore, tumors retain collateral escape mechanisms that involve activation of RTKs such as FGFR, HER2 and EGFR [5,99].

Three principles are clinically useful. First, given a specific alteration, biological plausibility and clinical utility do not necessarily overlap, since utility depends on both frequency and actionability. This is the case of *RB1* loss which, although among the clearest biological explanations of CDK4/6i resistance, is relatively uncommon and still lacks a proper cell-cycle rescue strategy [82,100].

By contrast, more frequent routes such as *ESR1* mutation, PI3K/AKT/PTEN pathway activation, cyclin E-CDK2 engagement, and ER pathway reactivation lead to heterogeneous resistance phenotypes increasingly actionable with matched alteration-directed agents.

Second, the same biomarker may have different therapeutic meanings depending on context. High p16 expression, for example, may indicate functional RB pathway disruption and reduced sensitivity to CDK4/6i in one setting, while in CCNE1-driven tumors it may coexist with a dependence on cyclin E-CDK2 and therefore suggest vulnerability to CDK2-directed strategies [69].

Similarly, *ESR1* mutation predicts reduced benefit from AI-based ET but increased likelihood of benefit from ER degraders or antagonists [35]. Biomarkers should therefore be interpreted not as isolated labels, but as indicators of the route by which a tumor has escaped endocrine control.

Third, convergent resistance mechanisms may create cross-class liabilities. *PTEN* loss is a useful example: by activating downstream AKT signaling, it may reduce dependence on upstream PI3Kα and attenuate sensitivity to PI3Kα-selective inhibition, while at the same time favoring AKT-pathway blockade as a more robust therapeutic approach [101]. This illustrates the important point that, at disease progression, the choice of next treatment should not be only taken by asking whether a biomarker is present or not, but by asking where that biomarker sits in the axis and both which downstream output it restores. In practice, the value of resistance profiling lies in converting progression from a generic event into a routed problem.

Importantly, the clinical maturity of these resistance routes is heterogeneous. Indeed, *ESR1* mutations and *PIK3CA/AKT1/PTEN* alterations currently represent the most validated treatment-selection biomarkers, supported by prospective randomized evidence and approved targeted agents. By contrast, *RB1* loss, *CCNE1* amplification or cyclin E–CDK2 activation, CDK6-driven adaptation and KAT6-directed strategies remain largely investigational as treatment-selection tools and, although biologically compelling, they should be interpreted only as hypothesis-generating routes for clinical trials design rather than as established determinants of routine post-progression options. Thus, the proposed resistance routes are intended to organize biological reasoning and identify rational therapeutic hypotheses, not to substitute for evidence-based treatment algorithms.

7.2. The tolerability ceiling as a rate-limiting variable

The common lesson derived from the luminal-axis drug development is not that tolerability alone explains treatment failure, but that is one of the major constraints on translating biologically rational combinations into sustained clinical benefit.

As previously mentioned, resistance to endocrine-based strategies reflects biological heterogeneity, pathway redundancy, clonal evolution, adaptive feedback, and incomplete dependence on any single node of the axis [2,82,99]. Therefore, failure of combination strategies aiming to simultaneously block different pathways should be viewed as the product of both biological escape and clinical deliverability and treatment tolerability.

Moreover, although the specific toxicity profile of each single agent is highly predictable, adverse events become more relevant when co-inhibition of multiple nodes is pursued. The specific toxicities are largely class-dependent: PI3Kα and AKT-pathway inhibition are commonly limited by metabolic and mucocutaneous toxicity, including hyperglycemia, rash, diarrhea and stomatitis, with the relative contribution varying across agents and schedules. Dual CDK4/6 inhibition is constrained mainly by hematologic toxicity, particularly neutropenia, although abemaciclib is characterized by a greater gastrointestinal burden. mTOR inhibition adds stomatitis, fatigue, rash and metabolic disturbances, while broader PI3K/mTOR inhibition historically raised concerns about cumulative pathway-related toxicity.

In Table 3, we provide the representative rates of grade ≥ 3 toxicity, treatment discontinuation/dose modification and clinically defining adverse events alongside efficacy data for the major practice-changing combinations aiming to induce a multi-nodal blockade of the axis.

For these reasons, durable triplets were historically difficult to deliver, not because the rationale for vertical blockade was weak, but because the therapeutic window was too narrow to administer them.

To address this issue, the strategic response has been to shift from the older escalation model where maximally potent and broadly active inhibitors were combined, accepting additive cumulative toxicity, to scenarios where each agent was engineered to spare the tissue that drives its dose-limiting toxicity (i.e. mutant-selective PI3Kα inhibitors to

Table 2
Resistance routes at the luminal node mapped to candidate strategy.

Resistance route	Representative drivers	Implication	Candidate node-directed strategy
ER reactivation	*ESR1* mutation	AI ineffective; SERD affinity reduced	Next-generation oral SERD / PROTAC / CERAN / SERCA; KAT6 inhibition (investigational, genotype-agnostic) ± cell-cycle agent
PI3K/AKT/mTOR reactivation	*PIK3CA* mutation, PTEN loss, *AKT1* alteration	Reduced endocrine/CDK4/6i benefit (i.e. PTEN loss)	PI3Kα (mutant-selective), AKT or pan-PI3K/mTOR inhibitor + ET ± CDK4/6i
CDK2/cyclin E activation	*CCNE1* amplification, AMBRA1 loss, low p21 (*TP53* mut)	Reduced CDK4/6i benefit	Selective CDK2 inhibitor (± CDK4-selective inhibitor); CDK2/cyclin-E degrader (investigational)
Mitogenic rewiring	CDK6 amplification, FAT1/HIPPO	Reduced CDK4/6i benefit	CDK4-selective inhibitor (investigational)
RB/E2F uncoupling	*RB1* loss	Reduced rationale for further RB-dependent cell-cycle therapy (not a validated predictive biomarker)	Clinical trials or non–RB-dependent strategies (investigational)

Table 2 reports the resistance routes of HR + /HER2- mBC and their genomic determinants, suggesting candidate node-directed strategies. Except for *ESR1* and *PIK3CA/AKT1/PTEN* alterations, these routes are not validated treatment-selection biomarkers, and the listed strategies should be regarded as investigational.
Abbreviations: ADC, antibody–drug conjugate; AI, aromatase inhibitor; AKT, protein kinase B; AMBRA1, autophagy and beclin 1 regulator 1; CDK, cyclin-dependent kinase; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CERAN, complete estrogen receptor antagonist; E2F, E2 transcription factor; ER, estrogen receptor; ESR1, estrogen receptor 1; ET, endocrine therapy; FAT1, FAT atypical cadherin 1; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PROTAC, proteolysis-targeting chimera; PTEN, phosphatase and tensin homolog; RB, retinoblastoma protein; RB1, retinoblastoma 1; SERCA, selective estrogen receptor covalent antagonist; SERD, selective estrogen receptor degrader; TP53, tumor protein p53.

Table 3
Representative efficacy–toxicity trade-offs for PI3K/AKT/mTOR-pathway combinations in HR + /HER2 − advanced breast cancer.

Regimen/trial	Population/ biomarker	Comparator	PFS and OS data	Key grade ≥ 3 AEs	Discontinuation/dose modification	Regulatory status
Alpelisib + fulvestrant / SOLAR-1 [16]	Postmenopausal men/ women with HR + / HER2 − ABC; *PIK3CA*-mutated cohort after ET	Placebo + fulvestrant	mPFS 11.0 vs 5.7 mo; HR 0.65;mOS: 39.3 vs 31.4 mo; HR 0.86; 95% CI 0.64–1.15; p = 0.15, not statistically significant.	Grade 3/4 hyperglycemia 36.6%, rash 9.9%, grade 3 diarrhea 6.7%; metabolic toxicity is class-defining	Alpelisib discontinuation due to AEs 25.0%; common discontinuation causes included hyperglycemia, rash and diarrhea	FDA-approved standard option for *PIK3CA*-mutatedHR + /HER2 − advanced/metastatic BC followingprogression on or after an endocrine-based regimen.
Capivasertib + fulvestrant / CAPItello-291 [19]	HR + /HER2 − ABC after AI ± prior CDK4/6i; overall and *PIK3CA/AKT1/PTEN*-altered populations	Placebo + fulvestrant	Biomarker-altered mPFS 7.3 vs 3.1 mo; HR 0.50; OS immature/not definitive at primary analysis.	Grade ≥ 3 rash 12.1%, diarrhea 9.3%, hyperglycemia 2.3%; intermittent schedule reduces chronic metabolic burden	AEs leading to discontinuationof capivasertib/placebo 13.0% vs 2.3%	FDA-approved with fulvestrant for*PIK3CA/AKT1/PTEN*-altered HR + /HER2 −locally advanced/ metastatic BC after progressionon endocrine-based therapy in the metastatic settingor recurrence on/within 12 months after adjuvant therapy.
Everolimus + exemestane / BOLERO-2 [45]	Postmenopausal HR + /HER2 − advanced BC recurring/progressing after non-steroidal AI; biomarker-unselected	Placebo + exemestane	Investigator assessment mPFS: 7.8 vs 3.2 mo; HR 0.45; 95% CI 0.38–0.54; p < 0.0001.Central review mPFS: 11.0 vs 4.1 mo; HR 0.38;mOS 31.0 vs 26.6 mo; not statistically significant	Grade 3/4 AEs reported in 55.2% vs 29.4%; common grade 3/4 events included stomatitis, anemia, dyspnea, hyperglycemia, fatigue and pneumonitis	Everolimus dose interruption/ reduction in 66.8%; AEs leading to discontinuation of ≥ 1 study drug 26.3% vs 5.0%; discontinuation of both study drugs due to AEs 9% vs 3%	Regulatory-approved standard option; historical benchmarkfor endocrine + mTOR blockade and tolerability ceiling.
Giredestrant + everolimus / evERA [20]	ER + /HER2 − advanced BC after prior CDK4/6 inhibitor + ET; ITT and *ESR1*-mutated co-primary populations	SOC endocrine therapy + everolimus	ITT mPFS 8.77 vs 5.49 mo; HR 0.56; 95% CI 0.44–0.71; p < 0.0001. *ESR1*-mutated: 9.99 vs 5.45 mo; HR 0.38; 95% CI 0.27–0.54;OS immature; positive trend reported: ITT HR 0.69; 95% CI 0.47–1.00; *ESR1*-mutated HR 0.62; 95% CI 0.38–1.02	Grade 3/4 AEs occurred in 51.1% vs 37.1%. Most common AEs were stomatitis 47.3% vs 48.9%, diarrhea 26.9% vs 22.6%, and anemia 23.6% vs 21.0%. Key grade 3/4 AEs included anemia 6.0% vs 8.6%, hyperglycemia 3.3% vs 2.2%, hypokalemia 3.8% vs 2.7%, pneumonitis 2.7% vs 2.7%, stomatitis 2.7% vs 3.2%, neutrophil count decreased 2.2% vs 3.2%, and weight decreased 2.2% vs 3.2%. Serious AEs occurred in 29.1% vs 23.1%; fatal AEs 2.7% vs 2.7%. Bradycardia occurred in 3.8% vs 0.5%, all grade 1; no photopsia was reported.	Everolimus discontinuation due to AEs: 17.0% vs 11.8%; giredestrant or standard ET discontinuation due to AEs: 8.2% vs 6.5%. Dose interruptions due to AEs: 54.4% vs 43.0% overall; everolimus dose reductions due to AEs: 30.8% vs 26.3%.	Positive randomized phase III strategy awaiting/ undergoingregulatory implementation.
Inavolisib + palbociclib + fulvestrant / INAVO120 [20]	First-line advanced setting; *PIK3CA*-mutated endocrine-resistant disease recurring during/ ≤ 12 mo after adjuvant ET	Placebo + palbociclib + fulvestrant	mPFS 15.0 vs 7.3 mo; HR 0.43; updated mPFS 17.2 vs 7.3 mo; HR 0.42;OS: 34.0 vs 27.0 mo; HR 0.67	Grade 3–4 AEs mainly hematologic from palbociclib backbone: neutropenia 80.2% vs 78.4%; grade 3 hyperglycemia 5.6%, stomatitis/mucosal inflammation 5.6%, diarrhea 3.7%; no grade 3–5 rash reported	Inavolisib discontinuation due to AEs 6.8%; inavolisib dose interruption 69.1%, dose reduction 14.2%	FDA-approved triplet in the specific INAVO120first-line endocrine-resistant PIK3CA-mutated setting

(*continued on next page*)

Table 3 (*continued*)

Regimen/trial	Population/ biomarker	Comparator	PFS and OS data	Key grade ≥ 3 AEs	Discontinuation/dose modification	Regulatory status
Gedatolisib + fulvestrant ± palbociclib / VIKTORIA-1 [77]	Post-CDK4/6i HR + / HER2 − ABC; *PIK3CA*-wild-type cohort	Fulvestrant	Triplet mPFS 9.3 vs 2.0 mo; HR 0.24; doublet mPFS 7.4 vs 2.0 mo; HR 0.33;OS immature/not established	Triplet/doublet grade ≥ 3 TRAEs: neutropenia 62.3%/ 0.8%, stomatitis 19.2%/ 12.3%, rash 4.6%/5.4%, hyperglycemia 2.3%/2.3%, diarrhea 1.5%/0.8%	TRAE-related discontinuation 2.3% triplet, 3.1% doublet, 0% fulvestrant	FDA-approved (July 2026) with fulvestrant ± palbociclib in *PIK3CA*-wild-type disease

Table 3 summarizes selected phase III endocrine-based combinations illustrating the tolerability ceiling of chronic pathway blockade. Reported toxicities focus on clinically defining grade ≥ 3 adverse events, treatment discontinuation and/or dose modification when available. Cross-trial comparisons should be interpreted cautiously because of differences in eligibility criteria, prior therapy, biomarker selection, adverse-event definitions, follow-up, reporting standards and CTCAE versions.

Abbreviations: ABC, advanced breast cancer; AE, adverse event; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ET, endocrine therapy; FDA, US Food and Drug Administration; G, grade; HR, hazard ratio; HR + /HER2 −, hormone receptor-positive/human epidermal growth factor receptor 2-negative; mBC, metastatic breast cancer; mo, months; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; TRAE, treatment-related adverse event.

mitigate metabolic imbalances, CDK4i aim to preserve myelopoiesis by sparing CDK6; intermittent AKT or PI3K/mTOR schedules attempt to maintain pathway pressure while allowing normal tissues to recover) [19,77,85].

However, emerging agents introduce distinct liabilities: KAT6i have shown hematologic adverse events together with dysgeusia as a characteristic toxicity, whereas next-generation CDK4- or CDK2-directed approaches aim to widen the therapeutic window but still require prospective safety validation in chronic combinations.

Interestingly, the recovered tolerability can then be reinvested into durable multi-node blockade at biologically effective doses, rather than maximum tolerated doses. In this sense, window-widening agents are not incremental class extensions: they are the enabling technology for the vertical blockade that the wiring of the luminal axis demands.

7.3. *ctDNA as one of the operational substrates*

A limited set of molecular markers, many of which are well suited to *ctDNA*-based assessment rather than tissue-based determination, may help the choice of which part of the axis should be primarily targeted [102].

ESR1 mutations identify tumors in which AI pressure has made ER signaling independent from the ligand warranting ER-directed strategies [35].

PIK3CA, *AKT1* and *PTEN* alterations, guide the use of PI3K/AKT-pathway agents and, by exclusion, help position alternative strategies such as KAT6 inhibition or pan-PI3K/mTOR approaches in wild-type disease [74].

Historically, *PIK3CA* testing has mainly relied on DNA extracted from tissue samples, however, *ctDNA* assessment of this pathway alterations has dramatically increased offering the chance to look at the temporal molecular evolution and the spatial heterogeneity of the tumor not routinely captured by tissue-based analysis [103,104].

At present, the clearest and strongest prospective evidence for serial *ctDNA*-guided intervention comes from the prementioned SERENA-6; this trial provides the first proof of principle that molecular progression can be clinically actionable in a defined biomarker-treatment context [38]. However, it should not be interpreted as validation of routine serial *ctDNA* monitoring for all patients with HR + /HER2 − mBC, nor as evidence that any emerging *ctDNA* alteration should automatically anticipate treatment switch. Indeed, for most biomarkers beyond *ESR1*, treatment adaptation based on molecular progression remains largely investigational [38].

Liquid biopsy should therefore be viewed as an emerging operational substrate, complementary to tissue-based analysis, of biomarker-driven luminal-axis therapy, with its current clinical role in identifying established actionable alterations at baseline, disease progression and, in selected settings, even before. Its value lies not only in detecting actionable alterations, but in assigning progression to a biological route.

The clinical challenge for the coming years will be to determine when *ctDNA* should trigger immediate treatment change, when it should inform the next line at radiographic progression, and which alterations are sufficiently actionable to justify pre-emptive intervention, and how assays, sampling intervals, thresholds for molecular progression, turnaround time and cost-effectiveness should be standardized.

On the other hand, tissue sample biomarker analysis should be implemented since it would be useful to detect RB1 alterations, *CCNE1* amplification or overexpression, p16 alterations and other markers of cyclin E-CDK2 engagement and refine the use of next-generation cell-cycle therapies, although their implementation in clinical practice remains less mature than those already available for *ESR1*- or PI3K/AKT/PTEN- altered disease [69,70,87,88,90,100]. It should also be mentioned that when a *ctDNA* result is negative, reflex tissue testing may be useful, especially in low-shedding tumors and in disease harboring copy-number and/or loss of function mutations.

Furthermore, although testing for *ESR1* mutations and alterations in

the PI3K/AKT/PTEN pathway is now standard for treatment selection, biomarker-agnostic combinations remain clinically relevant. In the evERA trial, giredestrant + everolimus improved PFS versus standard ET + everolimus, with exploratory subgroup analyses showing broadly consistent benefit across PI3K-pathway alteration subgroups and both *ESR1* mutant and overall population. Interestingly, the magnitude of benefit in the population of the evERA trial was numerically similar to that observed with pathway-directed therapies in CAPItello-291 and EPIK-B5 trials. Although cross-trial comparisons should be interpreted cautiously, these findings suggest that biomarker-independent combinations may represent valuable alternatives when a pathway alteration is absent, testing is not feasible, or biomarker-directed therapy is unsuitable due to high toxicity profile. They do not, however, support routinely omitting molecular testing, which remains essential for identifying the full range of available targeted treatment options.

7.4. Escalation versus sequencing: toxicity and preservation of later options

The success of triplet strategies witnessed in the INAVO120 trial has strengthened the rationale for upfront multiple vertical blockades in molecularly selected and clinical high risk biologically aggressive disease [75].

However, escalation is not the only way to exploit the same biology. The alternative strategy is to engage the relevant nodes sequentially, shifting additional blockade when resistance is established.

This approach distributes toxicity over time and preserves later options, which may be preferable for many patients with indolent disease, marginal tolerance for triplets or uncertain dominant resistance biology. Escalation and sequencing should therefore be considered complementary rather than opposed but the evidence supporting upfront triplet therapy remains context specific. At present, the clearest clinically validated example comes from the prementioned INAVO120 trial, which suggests a benefit for this strategy in patients meeting the trial eligibility criteria, whereas, for now, extension of this principle to other molecular or clinical contexts and other triplet combinations remains investigational and should be tested prospectively.

Sequential or switch strategies are more attractive when the disease remains endocrine-sensitive, when toxicity preservation is a priority, or when resistance can be monitored and intercepted dynamically. The future algorithm will likely combine both logics: early escalation for tumors with high-risk and actionable biology, and adaptive sequencing for the broader population in whom maintaining QoL and preserving later endocrine-based options remain central goals.

A related question is when the luminal-axis approach should reasonably be abandoned in favor of non-endocrine therapies. The perpetual and continued pursuit of luminal-axis targeting is most appropriate when the disease retains evidence of endocrine sensitivity and endocrine dependency, the progression pace is indolent, organ function is preserved, and a validated or strongly plausible actionable resistance route is present. By contrast, in the presence of rapid clinical progression and deterioration, visceral crisis or impending organ impairment, especially when short duration of benefit from prior endocrine-based therapy has been observed and credible biomarker-matched strategies are lacking, transition to ADCs or chemotherapy should be preferred. Thus, the objective is not to indefinitely postpone cytotoxic or ADC-based therapy, but to deploy endocrine-based strategies while endocrine dependence remains clinically meaningful and to abandon them when the expected benefit from further luminal axis blockade is no longer plausible.

8. An integrated, biomarker-guided logic

These concepts converge into a treatment logic built around three questions: which node remains dominant, which resistance route has the tumor taken, and how much additional blockade is needed and the patient can tolerate?

First-line ET + CDK4/6i remains the reference backbone, with upfront escalation to an inavolisib-based triplet reserved for *PIK3CA*-mutated, endocrine-resistant early relapse patients where the biological alteration and clinical dismal prognosis justify the additional toxicity [9–15,20,75].

During treatment, serial *ctDNA* assessment may identify emergent *ESR1* mutations and enable pre-emptive endocrine switching before radiographic progression in this specific scenario [38].

At radiological progression, treatment selection should distinguish between biomarkers with established clinical actionability and resistance mechanisms that remain largely investigational using *ctDNA* and tissue genotyping. *ESR1*-mutated disease supports the use of clinically validated and approved next-generation ER-directed therapies, while *PIK3CA/AKT1/PTEN* alterations guide the use of PI3Kα-, mTOR or AKT-pathway inhibitors when available and clinically appropriate. Other resistance routes, including cyclin E–CDK2 activation, CDK6-driven adaptation, RB1 loss and epigenetic modifiers of ER transcription, are biologically informative but not yet robust and validated as routine treatment-selection biomarkers. Accordingly, they should currently be viewed primarily as clinical-trial or research-directed options rather than standard route-matched therapies.

The framework proposed in Fig. 4 is therefore intended as a conceptual map that clearly separates validated biomarker-driven choices from emerging therapeutic hypotheses, rather than as a prescriptive guideline.

9. Conclusions

The luminal axis in HR + /HER2- mBC is now therapeutically actionable across its continuum, from ER dependence to downstream cell-cycle escape. Viewing this biology as an interlocked control system helps integrate recent therapeutic advances. Resistance is therefore routed rather than random, with *ESR1* mutation, PI3K/AKT/PTEN activation, cyclin E–CDK2 bypass, CDK6 adaptation, *RB1* loss and epigenetic rewiring restoring a limited number of proliferative outputs. The central challenge is not only target validity, but also therapeutic sustainability in the context of biological heterogeneity, pathway redundancy and cumulative treatment burden. Durable multi-node blockade is biologically compelling but constrained by dose-limiting toxicity and cumulative treatment burden. Future progress will depend on defining when to escalate upfront versus sequence adaptively, adjudicating the expanding ER-directed classes, clarifying the niche for KAT6 inhibition, and testing whether next-generation triplets can deepen pathway suppression without recreating the toxicity ceiling of earlier combinations. A decade after the first CDK4/6i approval, the next major advances in HR + /HER2- mBC are likely to arise less from discovering entirely new vulnerabilities than from exploiting established ones with greater precision and strategic insight. The future of luminal-axis therapy will depend on biomarker-defined routing, dynamic *ctDNA*-guided adaptation, and tolerability-aware co-targeting of ER dependence, survival signaling and cell-cycle escape.

CRediT authorship contribution statement

Aldo Caltavituro: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Conceptualization. **Antonio Giordano:** Writing – review & editing, Visualization, Validation, Supervision. **Carmine De Angelis:** Writing – review & editing, Visualization, Validation, Supervision. **Roberto Buonaiuto:** Writing – review & editing, Visualization, Validation, Supervision. **Jacopo Canzian:** Writing – review & editing, Visualization, Validation, Supervision. **Martí Torres-Marcén:** Writing – review & editing, Visualization, Validation, Supervision. **Francesco Schettini:** Writing – review & editing, Visualization, Validation, Supervision. **Giampaolo Bianchini:** Writing – review & editing, Visualization, Validation,

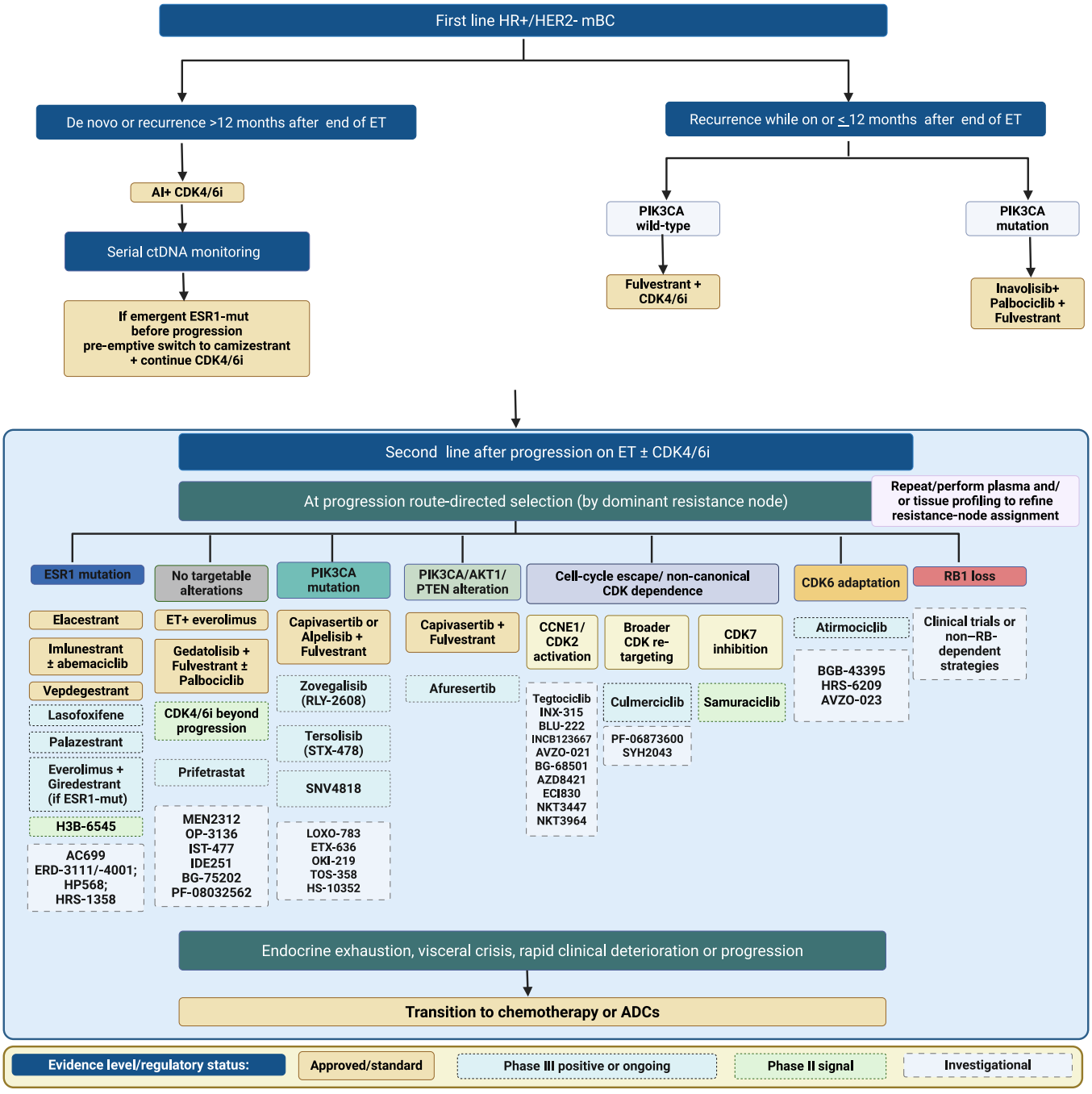

Fig. 4. Evidence-graded biomarker-guided roadmap for luminal-axis therapy in HR + /HER2 − metastatic breast cancer. Fig. 4 provides a conceptual, non-prescriptive framework for integrating endocrine-based and targeted strategies across first-line and post-progression settings in advanced HR + /HER2 − breast cancer. In the first-line setting, AI plus CDK4/6 inhibition remains the reference backbone for endocrine-sensitive disease, whereas fulvestrant plus CDK4/6 inhibition or inavolisib plus palbociclib and fulvestrant are positioned according to endocrine sensitivity and PIK3CA status in early recurrent disease. Serial ctDNA monitoring during first line may identify emergent ESR1 mutations before radiographic progression and support pre-emptive switching to camizestrant while continuing CDK4/6 inhibition in the specific setting evaluated by SERENA-6. After progression on endocrine therapy plus CDK4/6 inhibition, to repeat plasma and/or tissue profiling may refine assignment of dominant resistance nodes, including *ESR1* mutation, absence of targetable alterations, *PIK3CA* mutation, *PIK3CA/AKT1/PTEN* alteration, cell-cycle escape or non-canonical CDK dependence, CDK6 adaptation, and RB1 loss. Therapeutic options are visually coded according to evidence level and regulatory maturity: approved/standard options, phase III positive or ongoing strategies, phase II signals, and investigational approaches. The map also defines clinical boundaries for continued luminal-axis targeting; endocrine exhaustion, visceral crisis, rapid clinical deterioration, or fast progression should prompt transition to chemotherapy or ADCs rather than indefinite endocrine-based sequencing. The roadmap includes validated biomarkers (ESR1, PIK3CA/AKT1/PTEN) and exploratory resistance mechanisms (CCNE1/CDK2, CDK6, RB1, KAT6-related biology. Abbreviations: ADC, antibody–drug conjugate; AI, aromatase inhibitor; AKT1, AKT serine/threonine kinase 1; CDK, cyclin-dependent kinase; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; ER, estrogen receptor; ESR1, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; KAT6i, lysine acetyltransferase 6 inhibitor; mBC, metastatic breast cancer; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RB1, retinoblastoma 1.Created in BioRender. Caltavituro, A. (2026). Created in https://BioRender.com.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.117794.

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