Cutting-edge advances in endocrine therapy for breast cancer (Review)

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Abstract. Endocrine therapy remains one of the primary treatment modalities for estrogen receptor (ER) positive breast cancer, serving a pivotal role in improving patient outcomes and extending survival. Nevertheless, the gradual emergence of endocrine resistance continues to limit its clinical efficacy. In recent years, advances in molecular biology and genomics have driven the development of innovative technologies and therapeutic strategies in this field. The present review highlights the latest progress in endocrine therapy for breast cancer, including the introduction of next-generation selective ER degraders (SERDs), ER antagonists/degraders and selective ER modulators (SERMs). In addition, combination strategies integrating endocrine therapy with small-molecule inhibitors of critical signaling pathways, such as PI3K/AKT/mTOR and CDK4/6, have demonstrated promising potential in overcoming resistance. Cutting-edge technologies, such as single-cell sequencing and organoid models, are providing novel insights into treatment monitoring and the implementation of personalized therapy. Looking ahead, precision medicine platforms powered by artificial intelligence and big data are expected to further refine therapeutic strategies and ultimately improve patient prognosis. Collectively, endocrine therapy for breast cancer is evolving toward a more diversified, precise and individualized approach, offering patients broader treatment options and enhanced survival benefits.

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Abbreviations: ER, estrogen receptor; SERDs, selective estrogen receptor degraders; SERMs, selective estrogen receptor modulators; HR^+, hormone receptor-positive; TNBC, triple-negative breast cancer; PR progesterone receptor; PFS, progression-free survival; AIs, aromatase inhibitors; scRNA-seq, single-cell RNA-sequencing; ctDNA, circulating tumor DNA; TME, tumor microenvironment; CAFs, cancer-associated fibroblasts; HTS, high-throughput screening; ML, machine-learning; RL, reinforcement learning

Key words: estrogen receptor-positive breast cancer, endocrine therapy, CDK4/6 inhibitors, PI3K/AKT/mTOR pathway inhibitors, immune checkpoint inhibitors, single-cell sequencing, organoid technology, artificial intelligence, high-throughput screening technology

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1. Introduction

Breast cancer is one of the most common malignant tumors among women worldwide and a leading cause of cancer-related mortality, posing a notable threat to women's health. According to the latest report from the International Agency for Research on Cancer, breast cancer accounts for 11.6% of newly diagnosed cancer cases globally, making it the second most prevalent cancer after lung cancer (12.4%) (1). Despite continuous advancements in the treatment of breast cancer, its incidence continues to rise, and mortality rates vary markedly across different regions (1). In high-income countries, where early diagnosis and advanced treatment options are widely available, the 5-year survival rate reaches 80-90%; however, in low-income countries, survival rates generally remain <50% (2).

Breast cancer can be classified into different subtypes based on molecular biological characteristics and immunohistochemical markers, including hormone receptor-positive (HR^+) breast cancer, $HER2^+$ breast cancer and triple-negative breast cancer (TNBC), as well as rarer subtypes such as basal-like breast cancer and normal-like breast cancer (3). Increasing evidence suggests that distinct molecular drivers, non-coding RNAs and tumor microenvironmental factors contribute to subtype heterogeneity and therapeutic response differences (4,5). Each subtype differs notably in terms of incidence, distribution, pathological features and response to

treatment (6). For instance, recent advances in immunotherapeutic strategies have shown varying efficacy across molecular subtypes, particularly in TNBC, underscoring the biological diversity of breast cancer (7). This classification forms the basis for personalized treatment strategies and aids in optimizing treatment plans and prognosis assessments.

HR^+ breast cancer is the most common subtype, accounting for 60-65% of cases (8). Based on the Ki-67 proliferation index and molecular characteristics, HR^+ breast cancer can be further subclassified as follows: i) Luminal A, characterized by low Ki-67 expression (<14%), generally exhibits a more favorable prognosis and a higher sensitivity to endocrine therapy; in this context, Ki-67 is a nuclear marker of tumor cell proliferation that reflects the fraction of actively cycling cells, and is therefore widely used as a pragmatic indicator of tumor proliferative activity for risk stratification and surrogate subtype assignment (9); and ii) luminal B, defined by high Ki-67 expression (>14%), and often associated with HER2 upregulation or increased proliferative activity, this subtype is linked to a worse prognosis (10). Overall, HR^+ breast cancer has a relatively favorable prognosis; however, some patients may develop resistance due to the complexity of the hormone receptor signaling pathways and downstream regulatory networks (4,11). Estrogen receptor (ER) and progesterone receptor (PR) are not only crucial regulatory factors in cell proliferation and differentiation in breast cancer, but also serve as a critical foundation for understanding treatment sensitivity and resistance mechanisms (11). Emerging molecular studies have further highlighted the role of microRNAs (miRNA/miR; such as miR-185-5p) and long non-coding RNAs (such as MALAT1) in modulating ER signaling and tumor progression, providing additional insights into endocrine responsiveness and resistance biology (5,11).

Due to the central role of ER signaling in HR^+ breast cancer and the evolving therapeutic landscape aimed at overcoming endocrine resistance, a schematic overview summarizing the major milestones and emerging strategies in endocrine therapy is presented in Fig. 1. This illustration provides a structured framework for understanding the transition from traditional endocrine agents to next-generation therapies, combination regimens and precision-supportive technologies discussed in the following sections.

2. Role of endocrine therapy in HR^+ breast cancer treatment

Mechanisms of action and classification of endocrine therapy in HR^+ breast cancer. Endocrine therapy serves a pivotal role in the management of HR^+ breast cancer, with its primary mechanism involving the modulation of the ER signaling pathway to inhibit ER-mediated tumor cell proliferation and survival. The development and progression of breast cancer are strongly associated with the activity of both ER and PR. Activation of these receptors regulates several downstream signaling pathways, such as the expression of cell cycle-related genes (such as cyclin D1) and the stabilization of anti-apoptotic proteins (such as Bcl-2). Consequently, endocrine therapies exert their antitumor effects by inhibiting ER synthesis, competitively blocking ER binding or promoting ER degradation (6).

The main classes of endocrine therapy drugs for breast cancer include selective ER modulators (SERMs), which competitively bind to ERs to block the effects of estrogen. In breast tissue, they act as ER antagonists, whereas in bone and uterine tissue, they function as partial agonists. Tamoxifen, a representative SERM drug, is a cornerstone treatment for both premenopausal and postmenopausal patients with breast cancer (3). Raloxifene, another SERM, is primarily used for breast cancer prevention (12). Although SERMs have shown considerable efficacy in the adjuvant and neoadjuvant treatment of breast cancer, long-term use is associated with an increased risk of endometrial cancer and osteoporosis (7,9,10,12-14).

Aromatase is a key enzyme responsible for converting androstenedione to estradiol, representing the primary source of estrogen synthesis in postmenopausal women. Aromatase inhibitors (AIs) inhibit aromatase activity, thereby markedly reducing circulating estrogen levels and suppressing the growth of breast cancer (12). AIs are classified into two categories: i) Non-steroidal AIs (such as letrozole and anastrozole), which reversibly inhibit aromatase; and ii) steroidal AIs (such as exemestane), which act irreversibly. AIs are widely used in postmenopausal HR^+ patients with breast cancer and have demonstrated superior efficacy compared with tamoxifen, making them the preferred first-line therapy (15).

Selective ER degraders (SERDs) bind to ERs and induce their degradation, leading to the complete blockade of ER signaling. Fulvestrant is the currently approved SERD and is primarily used in HR^+ patients with advanced breast cancer who exhibit endocrine resistance. Due to their unique mechanism of action, SERDs are considered breakthrough endocrine agents, and next-generation oral SERDs (such as elacestrant) are under clinical development (16). Several next-generation oral SERDs have now progressed into late-stage clinical development. Among these agents, elacestrant currently has the most robust clinical evidence. In the randomized phase III EMERALD trial, elacestrant demonstrated a notable improvement in progression-free survival (PFS) compared with the investigator's choice of standard endocrine monotherapy in patients with $ER^+/HER2^-$ metastatic breast cancer who had previously received endocrine therapy in combination with a CDK4/6 inhibitor. Notably, the magnitude of benefit was more pronounced in tumors harboring ESR1 mutations, supporting the biological rationale for ER degradation in this molecularly defined subgroup (12). Subsequent updated analyses presented at the San Antonio Breast Cancer Symposium further indicated that patients with longer prior exposure to CDK4/6 inhibitors derived greater clinical benefit, suggesting that preserved endocrine sensitivity may identify a population particularly suited to an oral SERD-based strategy (17). Taken together, these findings support the integration of oral SERDs into contemporary treatment algorithms for endocrine-resistant $ER^+/HER2^-$ metastatic breast cancer. In particular, they appear especially relevant in the post-CDK4/6 inhibitor setting, where resistance is associated with ESR1-driven reactivation of ER signaling and where continued endocrine-based therapy remains clinically appropriate (18).

Beyond randomized phase III data, emerging real-world evidence has begun to provide complementary insights into the effectiveness of next-generation oral SERDs in routine oncology practice. Although the clinical adoption of elacestrant is relatively recent and long-term data remain limited, retrospective analyses derived from large US clinical-genomic

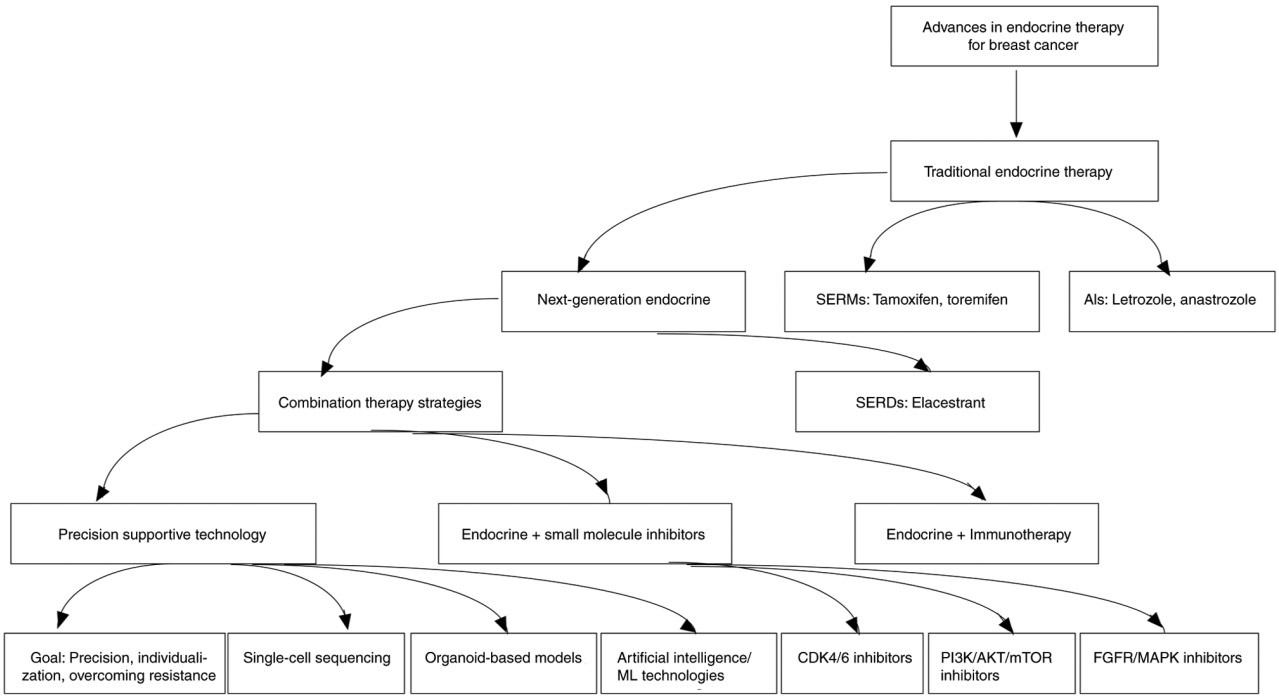

Figure 1. Schematic overview of advances in endocrine therapy for HR$^+$ breast cancer. The flowchart summarizes the major therapeutic strategies and technological advances in endocrine therapy for HR$^+$ breast cancer, including traditional endocrine agents, next-generation endocrine therapy regimens and precision supportive technologies, with the core goal of overcoming endocrine resistance and achieving precision and individualized treatment. Traditional endocrine therapy encompasses SERMs (tamoxifen and toremifen) and AIs (letrozole and anastrozole). Next-generation endocrine therapy features novel SERDs (elacestrant) and diversified combination strategies, namely endocrine therapy combined with immunotherapy and endocrine therapy plus small-molecule targeted inhibitors (PI3K/AKT/mTOR inhibitors, CDK4/6 inhibitors, FGFR/MAPK inhibitors). Precision supportive technologies for optimizing endocrine therapy include organoid-based models, artificial intelligence/ML technologies and single-cell sequencing, which provide critical technical support for the precision and individualization of HR$^+$ breast cancer treatment. HR$^+$, hormone receptor-positive; ER, estrogen receptor; SERMs, selective estrogen receptor modulators; AIs, aromatase inhibitors; SERDs, selective estrogen receptor degraders; ML, machine learning; FGFR, fibroblast growth factor receptor.

and administrative databases have suggested that treatment outcomes observed in real-world settings are broadly consistent with those reported in EMERALD, particularly in patients harboring ESR1 mutations (19). A real-world study published in Clinical Cancer Research evaluated elacestrant-treated patients with ER$^+$/HER2$^-$, ESR1-mutant metastatic breast cancer using integrated molecular and longitudinal clinical data, supporting its clinical activity outside the constraints of a randomized trial environment (19). Additional database-driven analyses presented at scientific meetings have reported real-world PFS estimates and treatment patterns that align with phase III findings (20).

In recent years, notable progress has been made in combining endocrine therapy with targeted therapies (such as CDK4/6 inhibitors and PI3K inhibitors). CDK4/6 inhibitors enhance the effectiveness of endocrine therapy by inhibiting CDKs involved in the cell cycle (21). PI3K inhibitors target mutations in the PI3K pathway, improving the overall response to endocrine therapy (22). These combination therapeutic strategies have markedly prolonged PFS and overall survival (OS) of patients, and represent a major focus of current research in the field of HR$^+$ breast cancer (Table I) (15,16,21,23,24).

The combination of AIs and CDK4/6 inhibitors has markedly prolonged PFS, establishing a new standard of care for HR$^+$ breast cancer treatment (Tables I and II) (15,16,21,23-28). Studies such as PALOMA-3 (25), MONALEESA-3 (21) and MONALEESA-7 (26) have demonstrated that CDK4/6 inhibitors combined with endocrine therapy can notably extend PFS and improve the objective response rate. However, the main adverse effects associated with CDK4/6 inhibitors include neutropenia, anemia, liver function abnormalities and fatigue. Therefore, close clinical monitoring of these treatment-related toxicities is essential.

Combination of endocrine therapy and immunotherapy. In recent years, immunotherapy has made notable progress in the treatment of TNBC (29), and the combination of endocrine therapy and immunotherapy in breast cancer has become an emerging research focus. Immune checkpoint inhibitors (ICIs), primarily targeting the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis, have established the clearest clinical benefit in TNBC, where higher tumor immunogenicity and immune infiltration make checkpoint blockade more actionable. In current practice, pembrolizumab combined with chemotherapy is a key ICI-based strategy in TNBC, supported by regulatory approvals and phase III evidence in both early-stage and advanced settings, with PD-L1 expression (such as CPS thresholds in metastatic disease) serving as an important selection biomarker (30-33). Early data from the I-SPY trial show that adding pembrolizumab to taxane-based neoadjuvant therapy results in an estimated pathologic complete response rate of 46 vs. 16% for HER2$^-$ patients, 60 vs. 20% for patients with TNBC and 34 vs. 13% for ER$^-$/PR$^+$/HER2$^-$ patients (34). In HR$^+$ breast cancer, the efficacy of immunotherapy is relatively low, partly due to the low level of immune infiltration

Table I. Major clinical studies on endocrine therapy for HR^+ breast cancer in the past 5 years.

First author, year	Clinical study	Study type	Sample size	Clinical stage	Experimental group	Control group	Study end points	Study results (experimental/ control group)	Related adverse events	(Refs.)
Johnston *et al*, 2023	monarchE	Phase III randomized controlled trial	5,637	Early-stage $HR^+/HER2^-$ high recurrence risk	Abemaciclib + endocrine	Endocrine	IDFS	4-year IDFS rate: 85.8 vs. 79.4%, HR 0.68,	Diarrhea, neutropenia	(15)
Mayer *et al*, 2021	PALLAS	Phase III randomized controlled trial	5,760	Early-stage $HR^+/HER2^-$	Palbociclib + endocrine	Endocrine	IDFS	No significant difference; HR 0.93	Neutropenia, fatigue	(16)
Neven *et al*, 2023	MONALEESA-3	Phase III randomized controlled trial	726	Recurrent or metastatic $HR^+/HER2^-$	Ribociclib + fulvestrant	Placebo + fulvestrant	OS	mOS: 67.6 vs. 51.8 months; HR 0.67	Neutropenia, abnormal liver function	(21)
Sledge *et al*, 2020	MONARCH 2	Phase III randomized controlled trial	669	Recurrent or metastatic $HR^+/HER2^-$	Abemaciclib + fulvestrant	Placebo + fulvestrant	OS	mOS: 46.7 vs. 37.3 months; HR 0.757	Diarrhea, neutropenia	(23)
Robertson *et al*, 2025	FALCON trial (final overall survival analysis)	Phase III randomized controlled trial	462	Recurrent or metastatic $HR^+/HER2^-$	Fulvestrant	Anastrozole	OS	mOS: 44.8 vs. 42.7 months; HR 0.97 mPFS: 16.6 vs. 13.8 months; HR 0.797	Joint pain, hot flashes	(24)

mOS, median overall survival; PFS, progression-free survival; m, median; HR, hazard ratio; IDFS, invasive disease-free survival.

Table II. Clinical study of HR+ endocrine therapy for breast cancer combined with CDK4/6 inhibitor in recent 5 years.

First author, year	Clinical study	Study type	Sample size	Clinical stage	Experimental group	(Refs.)
Neven *et al*, 2023	MONALEESA-3	Phase III randomized, double-blind, placebo-controlled study	726	Metastatic breast cancer	Ribociclib + fulvestrant	(21)
Cristofanilli *et al*, 2022	PALOMA-3	Phase III randomized, double-blind, placebo-controlled study	521	Metastatic breast cancer	Palbociclib + letrozole	(25)
Slamon *et al*, 2024	Ribociclib plus Endocrine Therapy	Phase III randomized, double-blind, placebo-controlled study	5101	HR+, HER2- early breast cancer	Ribociclib + aromatase or tamoxifen	(26)
Rugo *et al*, 2022	Post hoc analyses from PALOMA-2 and PALOMA-3 trials	Post hoc subgroup analysis (secondary analysis) of two phase 3 randomized controlled trials (PALOMA-2 and PALOMA-3)	PALOMA-2: cohort 1286 PALOMA-3 cohort: 549	Locally advanced or metastatic breast cancer	PALOMA-2: Palbociclib + letrozolePALOMA-3: Palbociclib + fulvestrant	(27)
Bardia *et al*, 2021	TRINITI-1	Multi center, open label phase I/II study	104	HR+/HER2- advanced breast cancer after previous treatment with CDK4/6 inhibitors	Rabosidine + exemestane + everolimus	(28)

HR+, hormone receptor-positive.

and a strong immunosuppressive microenvironment in these tumors (34). By contrast, HR+/HER2- breast cancer generally exhibits 'immune-cold' features [low tumor-infiltrating lymphocytes (TILs) and dominant immunosuppressive signaling], translating into modest and heterogeneous activity of ICIs as monotherapy or in unselected populations; nevertheless, ongoing trials are exploring rational combinations-such as endocrine therapy plus CDK4/6 inhibition with PD-1/PD-L1 blockade or other immunomodulators-to convert the tumor microenvironment (TME) and potentially extend benefit to biomarker-enriched HR+/HER2- subsets (35,36). Currently, several clinical trials are evaluating the combined efficacy of endocrine therapy and immunotherapy (Table III) (37-39). However, the discussion of predictive biomarkers for endocrine-immunotherapy combinations remains insufficient, particularly in HR+ breast cancer. Identification of reliable biomarkers is critical for guiding individualized treatment selection and improving therapeutic efficacy.

First, tumor immune microenvironment-related indicators may provide important predictive information. The level of TILs and the composition of immune cell subsets-including CD8+ cytotoxic T cells, regulatory T cells and tumor-associated macrophages-have been associated with response to immune checkpoint blockade in breast cancer (40,41). Although HR+ tumors generally exhibit lower TIL levels compared with TNBC, an immune-enriched subset of HR+ disease has been described, suggesting that quantitative and functional immune profiling may refine patient selection (40).

Second, immune checkpoint-related biomarkers, particularly PD-L1 expression, have been extensively investigated. In metastatic TNBC, PD-L1 positivity determined by validated companion diagnostic assays has demonstrated predictive value for atezolizumab benefit (42). However, in HR+ breast cancer, the predictive relevance of PD-L1 remains controversial. Differences in antibody clones (such as SP142 vs. 22C3), scoring systems (tumor cell vs. immune cell vs. combined positive score) and assay platforms introduce variability that limits cross-study comparability and clinical interpretation (43). Standardization of detection methodologies is therefore essential.

Third, genomic-related biomarkers, including tumor mutational burden (TMB) and microsatellite instability, may provide complementary predictive value. High TMB has been associated with improved response to ICIs across multiple tumor types (44). Although HR+ breast cancer typically exhibits lower TMB compared with TNBC, a subset of tumors with elevated mutational load or DNA repair deficiencies may display enhanced immunogenicity. Integration of genomic instability markers with endocrine resistance profiles may help identify patients who could benefit from combination strategies.

Table III. Clinical research on hormone receptor-positive breast cancer endocrine therapy combined with programmed cell death protein 1/programmed death-ligand 1 immunotherapy in previous years.

First author, year	Clinical study	Study type	Sample size	Clinical stage	Experimental group	(Refs.)
Jerusalem *et al*, 2023	CheckMate 7A8	Phase I/II	27	Advanced breast cancer	Nivolumab + endocrine therapy	(37)
Dirix *et al*, 2018	JAVELIN	Phase I	168	Locally advanced or metastatic breast cancer	Avirumab + endocrine therapy	(39)
Rugo *et al*, 2021	KEYNOTE-028	Phase I basket test	25	Advanced breast cancer	Pembrolizumab	(43)

Fourth, alterations in antigen presentation machinery and interferon signaling pathways may influence immune responsiveness. Deficiencies in major histocompatibility complex expression or disruptions in interferon-γ signaling can impair immune recognition, whereas tumors retaining intact antigen presentation and active interferon-related gene signatures may exhibit greater sensitivity to checkpoint blockade (45). These pathway-level biomarkers may provide mechanistic stratification beyond single-marker assessment.

Finally, circulating immune features and dynamic circulating tumor DNA (ctDNA) monitoring represent promising early predictive signals. Longitudinal ctDNA analysis has demonstrated utility in monitoring treatment response and emerging resistance in metastatic breast cancer (46). In the context of endocrine-immunotherapy combinations, changes in circulating immune cell subsets, cytokine profiles and ctDNA mutation dynamics (including ESR1 mutation burden) may serve as real-time indicators of therapeutic efficacy, although prospective validation remains necessary.

Additionally, immunotherapy may serve an important role in overcoming resistance to endocrine therapy. In breast cancer with ER mutations or downregulation, immunotherapy can serve as an alternative strategy and be combined with targeted therapies (47). Overall, although multiple candidate biomarkers have been proposed, robust validation in HR^+ breast cancer remains limited. Future research should prioritize biomarker-driven stratification designs, implement standardized detection methodologies and integrate multi-omic approaches to establish clinically actionable predictive models for endocrine-immunotherapy combinations.

Challenges of endocrine therapy: Resistance and efficacy limitations. Although endocrine therapy has markedly improved the survival of patients with HR^+ breast cancer, some patients experience resistance and limited efficacy. Resistance can be classified into primary resistance (present before treatment) and acquired resistance (developed over time after treatment), both of which are key challenges limiting the long-term effectiveness of endocrine therapy (11).

Patients with primary resistance show limited response to endocrine therapy, primarily due to mechanisms such as the loss of ER signaling pathways and molecular heterogeneity (48,49). Acquired resistance is a major challenge, particularly in patients undergoing long-term treatment or experiencing disease progression. Current research on resistance mechanisms focuses on the following aspects: i) Mutations in the ER gene (ESR1) are a key mechanism of acquired resistance (50); common mutation sites, such as Y537S and D538G, lead to ER activation that is independent of estrogen, thereby conferring resistance to AIs (51-53); ii) activation of alternative signaling pathways: Aberrant activation of pathways such as PI3K/AKT/mTOR, fibroblast growth factor receptor and MAPK can promote tumor growth independently of ER signaling, contributing to resistance (51,52,54); iii) changes in the TME: The presence of an immunosuppressive microenvironment and the secretion of pro-inflammatory cytokines may mediate resistance through non-ER-dependent pathways (52); and iv) compensatory estrogen synthesis: After AI treatment, tumors may increase local estrogen production through alternative pathways, thereby counteracting the therapeutic effects (55). For patients with rapidly progressing breast cancer, the efficacy of endocrine therapy is often limited, and numerous patients eventually require a switch to chemotherapy.

Age and menopausal status substantially influence endocrine responsiveness and resistance patterns in HR^+ breast cancer. In premenopausal women, persistent ovarian estrogen production necessitates ovarian function suppression (OFS) combined with tamoxifen or an AI. The SOFT and TEXT trials demonstrated that the addition of OFS markedly improves disease outcomes compared with tamoxifen alone, with exemestane plus OFS providing further benefit in selected higher-risk populations, including younger patients (particularly those aged <35 years), lymph node positivity (especially 4 or more positive lymph nodes), a high Ki-67 proliferation index (>20%), tumor grade 3, or the presence of lymphovascular invasion (56,57). However, incomplete ovarian suppression may represent a clinically relevant source of functional resistance, particularly in younger women with high ovarian reserve, as suboptimal estradiol suppression during AI plus OFS therapy has been associated with inferior outcomes (58). In the metastatic setting, the MONALEESA-7 trial established that adding ribociclib to endocrine therapy plus OFS markedly improves OS in premenopausal patients, reinforcing the importance of combined endocrine-targeted approaches in this subgroup (59).

By contrast, elderly patients represent a biologically and clinically heterogeneous population (60). Although HR^+ tumors are more prevalent in older women, treatment decisions are

frequently influenced by comorbidities, frailty, polypharmacy and tolerability considerations (61). Older individuals remain underrepresented in randomized trials. Observational analyses have suggested higher rates of dose modification and treatment discontinuation with CDK4/6 inhibitor-based regimens in elderly populations, underscoring the need for careful treatment individualization (62). Collectively, these age-specific differences highlight the importance of tailoring endocrine strategies across the lifespan, balancing efficacy with safety and patient-centered factors.

Rare HR$^+$ subtypes with a focus on invasive lobular carcinoma (ILC). HR$^+$ breast cancer is a heterogeneous entity that includes rare histological and molecular subtypes with distinct biological and clinical characteristics. Among these, ILC represents 10-15% of all breast cancers and constitutes the most common special histologic subtype of HR$^+$ disease (63,64). ILC is characterized by unique molecular features, most notably loss-of-function alterations in cadherin-1 (CDH1), encoding E-cadherin, which underlie the classical discohesive growth pattern of tumor cells (65,66).

Beyond CDH1 loss, ILC frequently harbors alterations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit a (PIK3CA), AKT1, T-box 3 and forkhead box A1, and may exhibit a luminal A-like transcriptional profile with relatively low proliferation indices, although substantial molecular heterogeneity exists (67). Clinically, ILC demonstrates distinctive metastatic patterns compared with invasive ductal carcinoma (IDC), with a higher propensity for metastasis to the peritoneum, gastrointestinal tract, ovaries and leptomeninges (64,68).

With respect to endocrine therapy, ILC is typically strongly ER$^+$ and historically considered highly endocrine-responsive. However, emerging data suggest that endocrine sensitivity, resistance trajectories and optimal therapeutic sequencing may differ from IDC. Retrospective analyses indicate potential differences in response to tamoxifen vs. AIs, with some studies suggesting improved outcomes with AI-based strategies in postmenopausal patients with ILC (69,70). Furthermore, genomic alterations enriched in ILC-such as PI3K pathway mutations-may have implications for targeted combination strategies involving CDK4/6 or PI3K inhibitors in endocrine-resistant settings. Nevertheless, despite these observations, ILC remains underrepresented in large randomized controlled trials, and prospective subtype-specific evidence remains limited. Consequently, optimal endocrine therapy selection and sequencing strategies for ILC are not yet fully defined.

Due to its distinct molecular landscape, metastatic behavior and potential therapeutic nuances, greater attention to ILC and other rare HR$^+$ subtypes is warranted. Future clinical trials incorporating histology-specific stratification, molecular profiling and prospective validation will be critical to refining precision endocrine therapy strategies for these understudied populations.

3. Advances in endocrine therapy for breast cancer

Single-cell RNA-sequencing (scRNA-seq). Single-cell sequencing technology provides powerful tools for revealing breast cancer heterogeneity and its endocrine therapy response mechanisms by analyzing the genome, transcriptome and epigenome features of individual cells at high resolution (71-73).

Revealing tumor heterogeneity through single-cell sequencing. Traditional population-based sequencing methods typically analyze tumor tissues as a whole, making it difficult to capture the differences between cell subpopulations within the tumor. Single-cell sequencing, by individually analyzing each cell in tumor samples, reveals the molecular differences and functional characteristics between tumor cell subpopulations. scRNA-seq can differentiate various subpopulations of cells in breast cancer, revealing some subgroups that are highly sensitive or resistant to endocrine therapy (72,74-76). Additionally, by analyzing the spatiotemporal distribution of gene mutations and expression patterns, single-cell sequencing can reconstruct the evolutionary trajectory of breast cancer from the initial clone to the late-stage resistant clone, providing clues for studying resistance mechanisms (77).

Analyzing resistance to endocrine therapy. Resistance to endocrine therapy is a major challenge that limits its efficacy. Single-cell sequencing provides the following key insights for studying resistance: i) Cell heterogeneity in ESR1 mutations: ESR1 mutations represent a well-established mechanism of secondary endocrine resistance in HR$^+$ breast cancer. Single-cell analyses have been proposed as a powerful tool to dissect clonal architecture; however, to date, no studies have directly applied single-cell sequencing to precisely quantify the intratumoral frequency of individual ESR1-mutant clones and to monitor their clonal expansion dynamics. Instead, analyses of ctDNA have demonstrated the coexistence of multiple ESR1-mutant clones exhibiting distinct evolutionary behaviors (78). Furthermore, ESR1 mutations are typically rare in primary tumors but occur at markedly higher frequencies in metastatic lesions (79). Consistent with these findings, RNA-seq-based analyses have also identified resistance-associated ESR1 mutations in early-stage primary breast cancers (80); and ii) interactions of signaling pathways: scRNA-seq and epigenomic analyses have revealed that specific endocrine-resistant breast cancer cell subpopulations exhibit aberrant activation of alternative signaling pathways, particularly the PI3K/AKT/mTOR axis, suggesting potential therapeutic targets to overcome resistance (72,81,82).

Analyzing the TME. The TME in HR$^+$ breast cancer exhibits substantial cellular heterogeneity, which influences the response to endocrine therapy (81). Single-cell sequencing provides valuable insights in two major aspects: i) Immune-cell lineage and functional analysis: scRNA-seq profiling of tumor-associated immune cells (such as T cells and macrophages) has revealed diverse activation and exhaustion states, indicating that an immune-suppressive microenvironment may attenuate endocrine responsiveness (75,81); and ii) stromal-tumor interactions: Single-cell and spatial analyses of cancer-associated fibroblasts (CAFs) have identified heterogeneous CAF subsets capable of modulating ER signaling through paracrine growth factor pathways, thereby contributing to endocrine resistance (72,83,84).

Clinical potential of single-cell sequencing. Single-cell sequencing has emerged as a powerful translational tool in breast cancer research, offering new perspectives for clinical application in endocrine therapy: i) Precision treatment guidance: By characterizing intratumoral heterogeneity and

identifying subpopulations with distinct endocrine sensitivity, single-cell profiling may help predict therapeutic response and support individualized treatment planning (72,75,81); ii) monitoring resistant clones: Integrating single-cell and ctDNA analyses enables real-time tracking of resistant ESR1-mutant or ligand-independent clones, thereby informing adaptive combination strategies (85,86); and iii) drug development: scRNA-seq and epigenomic analyses have uncovered novel molecular targets-such as atypical ER co-regulators and downstream signaling effectors-that are being explored for the next generation of endocrine therapies (87).

Despite its substantial translational promise, several technical and practical barriers currently limit the routine clinical implementation of single-cell sequencing. First, the overall cost of single-cell workflows-including tissue processing, library preparation, sequencing depth requirements and computational infrastructure-remains high, which constrains scalability and clinical adoption in routine oncology practice (88). Moreover, reimbursement pathways for clinical-grade single-cell assays are not yet well established in most healthcare systems. Second, single-cell sequencing requires high-quality biological material, typically fresh or optimally preserved tissue samples. Factors such as low tumor cellularity, ischemia time, necrosis and dissociation-induced transcriptional artifacts may notably compromise data reliability and downstream biological interpretation (89,90). These pre-analytical variables are particularly relevant in clinical breast cancer specimens, where tissue availability may be limited. Third, variability in experimental workflows-including cell dissociation protocols, chemistry platforms, sequencing depth and computational preprocessing-introduces substantial batch effects, thereby limiting reproducibility and cross-cohort comparability (91,92). Although computational integration methods have improved correction strategies, complete elimination of batch-driven bias remains challenging. Fourth, bioinformatic analysis pipelines for single-cell data are complex and computationally intensive, requiring advanced statistical modeling and multi-layered annotation frameworks. Currently, there is no universally accepted clinical interpretation standard for translating high-dimensional cellular states into actionable therapeutic decisions, particularly in the context of endocrine resistance (89,93).

To advance clinical-grade implementation, the development of high-quality reference atlases, harmonized quality-control (QC) standards and consensus reporting systems will be essential to ensure reproducibility, cross-platform comparability and clinically meaningful interpretation (90,94).

Research platforms for personalized treatment of breast cancer-organoid models. In recent years, organoid technology has gradually emerged in breast cancer research, providing a new platform for personalized treatment. Organoids are three-dimensional cell structures cultivated from patient tumor tissue that retain the molecular and genetic characteristics of the original tumor, including the complexity and heterogeneity of the TME (95,96). This technology overcomes the limitations of traditional two-dimensional cell cultures and animal models in simulating human tumor biological behavior (96,97), bringing revolutionary breakthroughs to the forefront of breast cancer endocrine therapy research.

First, organoid models provide more accurate tools for drug screening in endocrine therapy for breast cancer (98). ER^+ subtypes account for the majority of breast cancer patients, and selecting anti-estrogen drugs (such as tamoxifen) and AIs (such as letrozole) are the main strategies for endocrine therapy. However, due to individual differences, patients often show notable variations in drug responses. Organoid models can be directly cultivated from patient tumor tissue to create personalized models that simulate the drug response in the body of the patient (99). Studies have shown that testing endocrine drugs in patient with breast cancer-derived organoids can accurately predict clinical treatment outcomes for patients (76,100). This '*in vitro* testing-*in vivo* verification' approach helps quickly identify the most effective treatment plans, providing support for clinical decision-making (76). Additionally, organoids provide a platform for the development of combination therapy strategies (76). By studying the combined use of endocrine drugs and CDK4/6 inhibitors in organoids, the synergistic effects of drugs can be assessed (101). These research findings not only accelerate the development of new drugs but also improve treatment precision.

Second, endocrine therapy resistance has always been a major challenge in breast cancer treatment. Traditional research methods struggle to fully capture the dynamic process of resistance development, but organoid technology offers a new perspective (97). Patient-derived breast cancer organoids retain tumor heterogeneity and genetic mutation characteristics, simulating molecular changes during treatment over long-term cultures (96,98,102). Research shows that organoids can capture the dynamic evolution of ESR1 gene mutations during endocrine therapy, which is an important mechanism of tamoxifen and fulvestrant resistance (103). Furthermore, by integrating organoid models with scRNA-seq, researchers can comprehensively analyze resistance-related cell subpopulations and gene expression changes (104). Studies using organoids have found that under prolonged drug exposure, some breast cancer cells can escape immune suppression by upregulating the PI3K/AKT signaling pathway (97,102). This finding provides a basis for developing combination therapies to block the PI3K pathway (105). At the same time, organoid models also serve an important role in studying strategies to reverse endocrine therapy resistance (97). For example, combining anti-estrogen drugs with epigenetic modulators in organoids showed notable resistance reversal effects (104).

Lastly, another important application of organoid models is exploring the role of the tumor immune microenvironment in breast cancer treatment. The influence of the immune microenvironment on endocrine therapy for breast cancer is increasingly being recognized (96,106). By establishing co-culture systems of organoids and immune cells, the dynamic interactions between tumor cells and immune cells can be simulated (97,107). At the same time, organoids provide opportunities to analyze the roles of CAFs and immune cells in the TME (106,108). Researchers found that by introducing CAFs into organoids, they could induce resistance to endocrine therapy in tumor cells through the secretion of TGF-β (108). These findings provide important clues for targeted regulation of the immune microenvironment.

Although organoid technology holds great potential, its widespread application in personalized breast cancer

treatment still faces challenges. The success rate and growth efficiency of organoid cultures from different patient sources vary, which may be influenced by the quality of tumor samples and culture conditions (96). Importantly, notable inter-laboratory variability exists in organoid culture protocols. Differences in growth factor supplementation (such as EGF, R-spondin and Noggin), media composition and passaging strategies may influence clonal selection and phenotypic stability, thereby compromising reproducibility and cross-study comparability (109,110).

Moreover, most current organoid systems rely on extracellular matrix (ECM) components such as Matrigel, which possess undefined biochemical composition and substantial batch-to-batch variability. These inconsistencies can affect organoid architecture, differentiation status and drug response profiles, limiting standardization and clinical translation (111,112).

Although organoids are highly valuable for drug testing, scalability for high-throughput screening (HTS) remains constrained. Compared with conventional two-dimensional cell systems, organoid cultures require more complex handling procedures and longer expansion times, which restrict their integration into rapid and large-scale screening pipelines (113). In addition, the time required for successful organoid establishment and expansion-often several weeks-may limit their utility in real-time clinical decision-making, particularly in aggressive breast cancer cases where rapid therapeutic selection is required (99). Organoid platforms are also associated with substantial cost, technical complexity and infrastructure demands, including specialized culture systems, continuous growth factor supplementation and advanced imaging or molecular profiling capabilities, which may hinder routine clinical implementation (110). Furthermore, traditional epithelial-only organoid models often lack immune and stromal components, and therefore cannot fully recapitulate tumor-immune or tumor-stroma interactions. While co-culture systems incorporating immune cells or CAFs, as well as air-liquid interface platforms, can enhance biological fidelity, they substantially increase technical complexity and standardization challenge (114).

Therefore, further optimization of standardized culture methods is needed, as well as the development of defined ECM alternatives, scalable automation platforms and consensus QC standards before organoid models can be fully integrated into precision oncology workflows. In terms of application prospects, organoid models are expected to become a core technology for personalized treatment (107,109). By integrating organoids into clinical diagnostic and treatment processes, personalized organoid models can be rapidly established from patient-derived tumor tissue to screen the most suitable treatment plans and predict potential resistance during treatment (107). At the same time, combining organoids with CRISPR/Cas9 technology will enable in-depth exploration of gene editing potential in breast cancer treatment (96,97). As the technology continues to mature, organoid models will serve an increasingly important role in breast cancer basic research, drug development and clinical translation (96,107).

HTS technology: Drug development and target exploration. HTS technology serves a key role in the development of new drugs and target exploration for endocrine therapy in breast cancer. By rapidly and on a large scale assessing the impact of compounds on specific biological targets, HTS provides an efficient means of discovering potential therapeutic drugs and new treatment targets (96,106).

Application of HTS in new drug development for endocrine therapy in breast cancer. The emergence of endocrine therapy resistance and side effects in breast cancer has driven researchers to continuously seek new therapeutic drugs. HTS, implemented on automated robotic platforms and miniaturized microplate formats (such as 384- and 1,536-well plates), enables rapid testing of large compound libraries-ranging from thousands to tens of thousands of compounds per run-against cellular phenotypes. Using cell-based viability, proliferation and apoptosis assays or high-content imaging readouts, HTS accelerates the identification of chemical modulators of breast cancer cell proliferation and death and thereby expedites early-stage drug discovery (115). For instance, Sun *et al* (116) used HTS to identify novel coactivator binding inhibitors of ERα that at low micromolar concentrations suppress estrogen signaling and inhibit estrogen-stimulated reporter gene expression (117) These compounds, after further optimization and validation, are expected to develop into new endocrine therapy drugs.

Role of HTS in exploring new treatment targets for breast cancer. In addition to new drug development, HTS also serves an important role in discovering new treatment targets for breast cancer. By systematically screening molecules that regulate breast cancer cell proliferation, differentiation and apoptosis-using approaches such as high-throughput small-molecule screening and large-scale functional genomics (RNA interference/CRISPR) screens-researchers have identified candidate therapeutic targets that provide a rationale for the development of targeted treatment strategies (117-119). Recent HTS research, employing automated robotic platforms and high-content readouts, has been used to identify small-molecule modulators of the PI3K/AKT/mTOR signaling axis; several studies report HTS-derived hits that inhibit PI3K/AKT/mTOR activity and demonstrate antitumor efficacy in cellular and/or *in vivo* models (120,121). The PI3K/AKT/mTOR signaling axis serves a central role in breast cancer development and progression, and its aberrant activation has been strongly associated with resistance to endocrine therapies (122). Clinical and translational studies demonstrate that inhibition of this pathway by mTOR inhibitors (such as everolimus), PI3Kα inhibitors (such as alpelisib) or AKT inhibitors (such as capivasertib) can restore sensitivity or provide clinical benefit (123,124). In addition, HTS has been used to discover and optimize small-molecule modulators of PI3K/AKT/mTOR, offering new therapeutic candidates to overcome endocrine resistance (125).

Mechanistically, the PI3K/AKT/mTOR pathway functions as a central regulator of tumor cell proliferation, survival, metabolism and anti-apoptotic signaling. Upon activation by receptor tyrosine kinases or ER-associated signaling, PI3K generates PIP3, leading to AKT activation and downstream phosphorylation of multiple substrates that promote cell-cycle progression, protein synthesis and metabolic reprogramming

while inhibiting pro-apoptotic factors (126,127). Oncogenic alterations such as activating mutations in PIK3CA, loss of the tumor suppressor PTEN or aberrant AKT activation result in constitutive pathway activation in breast cancer (125,128). Persistent PI3K/AKT/mTOR signaling can promote ligand-independent ER activation and enhance estrogen-independent transcriptional programs, thereby driving resistance to endocrine therapies (127,129). This mechanistic framework provides the biological rationale for combining endocrine therapy with mTOR inhibitors, PI3Kα inhibitors or AKT inhibitors, aiming to suppress compensatory survival signaling and restore endocrine sensitivity (123).

Future development trends of HTS technology. With ongoing technological advances, HTS is evolving toward greater throughput and improved precision (130). The incorporation of microfluidic technologies-including droplet-based and arrayed microfluidic platforms-enables assays to be performed in drastically reduced volumes, increasing screening throughput and assay sensitivity (131). Concurrently, artificial intelligence and machine-learning (ML) methods have been integrated into HTS workflows to accelerate data processing, deconvolute complex readouts, prioritize true hits and predict compound-target relationships (132). Finally, the convergence of HTS with physiologically relevant patient-derived models (such as organoids and other 3D culture systems) points to a future in which HTS can be used for personalized drug screening tailored to individual tumor characteristics, thereby facilitating precision oncology (133).

Applications of artificial intelligence and ML in endocrine therapy for breast cancer. Previous studies have applied artificial intelligence and ML methods to breast cancer metabolomics and transcriptomics data to improve diagnostic and predictive capabilities (134,135). For example, Alakwaa *et al* (133) used a deep learning-based framework together with other ML algorithms to classify ER^+ vs. ER^- breast cancers from metabolomics data, achieving an area under the curve of 0.93. Similarly, in predicting response to neoadjuvant endocrine therapy, gene expression-based classifiers have been developed with high accuracy. These advances support three promising applications in endocrine therapy: i) Treatment response prediction; ii) analysis of resistance mechanisms; and iii) designing more personalized therapeutic strategies (136).

Prediction of treatment response. Endocrine therapy is the cornerstone for patients with HR^+ breast cancer; however, clinical responses vary substantially across individuals. Traditional predictive approaches, which mainly rely on single biomarkers such as ER or PR expression levels, often provide limited accuracy (137,138). Recent advances in ML have enabled the integration of multi-omics data-including genomics, transcriptomics and metabolomics to construct more robust predictive models (139-140). For example, Wu *et al* (140) conducted a large-scale analysis of patients with breast cancer and developed a Random Forest-based recurrence prediction model specifically for $HR^+/HER2^-$ early-stage breast cancer, which achieved a sensitivity of ~80% in predicting 5-year recurrence events. In parallel, deep learning algorithms have been applied to integrate genomic alterations, RNA expression profiles and proteomic features, enabling the prediction of patient sensitivity to different endocrine agents (137). Collectively, these models hold promise for improving the precision of treatment selection, while reducing unnecessary adverse effects and the economic burden associated with ineffective therapies.

Exploration of resistance mechanisms. Artificial intelligence and ML approaches offer powerful tools to dissect complex, high-dimensional molecular datasets to uncover resistance-associated mechanisms. Indeed, recent reviews have documented the application of artificial intelligence in tumor drug resistance to identify resistance biomarkers, infer signaling dependencies and stratify patient subsets based on predicted resistance risk (141,142). In breast cancer specifically, ML models have been deployed to integrate genomic, transcriptomic, proteomic and clinical data to predict resistance to endocrine agents and to prioritize candidate regulators or pathways underlying resistance (143). Taken together, integrating mechanistic insights (such as PI3K/AKT/mTOR activation) with ML-driven discovery pipelines could facilitate more precise resistance stratification and the rational design of combination strategies to overcome endocrine resistance.

Development of personalized treatment strategies. Beyond outcome prediction, artificial intelligence techniques also hold promise for designing personalized therapeutic strategies tailored to individual patients. Through reinforcement learning (RL), artificial intelligence agents can simulate the longitudinal effects of alternative treatment regimens, iteratively optimize policy and recommend adaptive therapeutic plans that adjust dynamically in response to disease evolution (144,145). For example, in non-breast cancer settings, simulated trials applying RL have been used to compare survival outcomes under different regimens; for instance, in relapsed extensive-stage small cell lung cancer, Bozcuk and Artaç (146) developed an RL-based simulated clinical trial comparing irinotecan plus ifosfamide with topotecan, illustrating the feasibility of this approach for evaluating alternative therapeutic strategies *in silico*. More recently, deep RL frameworks have been proposed to infer personalized adaptive therapy strategies by modeling tumor dynamics and treatment response trajectories (147).

In parallel, artificial intelligence can accelerate the identification of synergistic drug combinations that potentiate endocrine therapy. Although direct artificial intelligence-driven evaluations of combinations such as CDK4/6 inhibitors plus endocrine agents in resistant breast cancer remain scarce, clinical evidence already supports the efficacy of such combinations in $HR^+/HER2^-$ settings (148,149). With sufficiently large molecular and treatment response datasets, artificial intelligence models could, in principle, prioritize optimal combination regimens or novel targeted therapies for patient subgroups with endocrine resistance.

In summary, artificial intelligence and ML approaches not only enhance predictive accuracy but also open avenues toward adaptive, treatment-tailored strategies in endocrine therapy for breast cancer. As computational models mature and more multi-omic or longitudinal treatment datasets become available, these methodologies are expected to accelerate precision medicine and the discovery of novel therapeutic targets.

However, despite these promising advances, important methodological challenges remain regarding model

interpretability and external validation. Numerous artificial intelligence/ML models-particularly deep learning frameworks-function as 'black-box' systems, generating highly accurate predictions without transparent explanation of how specific variables contribute to decision-making. In the context of oncology, where treatment decisions directly affect patient survival and safety, limited interpretability may reduce clinician trust and hinder clinical adoption (150,151). To enhance transparency and clinical credibility, interpretable artificial intelligence strategies should be incorporated into predictive pipelines. These include feature attribution methods (such as SHapley Additive exPlanations values), variable importance reporting, biologically constrained modeling frameworks and pathway-informed architectures that align model outputs with known molecular mechanisms (152). Such approaches allow clinicians to understand which genomic, transcriptomic or clinical features drive predictions, thereby improving explainability and supporting hypothesis generation.

In addition, a number of existing artificial intelligence models in endocrine therapy research are trained on retrospective datasets derived from single institutions or publicly available cohorts (such as The Cancer Genome Atlas), which may introduce selection bias and limit generalizability. Without validation in independent external cohorts, model performance may be overestimated due to overfitting or dataset-specific artifacts (153). Therefore, future studies should prioritize multi-center external validation, prospective clinical evaluation and adherence to standardized reporting frameworks such as TRIPOD-AI or CONSORT-AI to reduce bias, enhance reproducibility and improve translational reliability (154,155). Strengthening interpretability, transparency and rigorous validation will be essential for translating artificial intelligence-driven endocrine therapy prediction tools from computational research settings into routine clinical oncology practice.

4. Conclusions

Endocrine therapy remains the cornerstone of treatment for HR^+ breast cancer, serving as both a standard adjuvant approach and a key therapeutic option for advanced disease. Its widespread implementation has markedly improved survival outcomes. Nevertheless, the emergence of endocrine resistance continues to pose a major clinical challenge, limiting long-term efficacy.

In recent years, combination strategies involving CDK4/6 inhibitors, PI3K/AKT/mTOR pathway inhibitors and ICIs have become a central focus of research, demonstrating promising potential to prolong PFS and overcome specific mechanisms of resistance. Concurrently, technological innovations-such as scRNA-seq, patient-derived organoids, HTS and artificial intelligence-have accelerated investigations into resistance biology and facilitated the design of personalized therapeutic strategies. Despite these advances, the intrinsic heterogeneity of breast cancer and the multifactorial nature of endocrine resistance continue to create substantial research gaps. Future directions are expected to emphasize the integration of multi-omics, computational modeling and precision oncology, with a focus on incorporating novel immunotherapies, biomarker-driven stratification and rational optimization of targeted drug combinations.

However, several limitations of the present review should be acknowledged. First, as a narrative synthesis of rapidly evolving literature, the review may not capture all emerging clinical trial data or newly reported therapeutic strategies. Second, many of the discussed approaches-particularly novel immunotherapy combinations and biomarker-driven strategies-remain under active investigation and their long-term clinical benefits require further validation in large-scale prospective studies. Additionally, variations in study design, patient populations and biomarker assessment methodologies across the cited studies may introduce heterogeneity that limits direct comparisons.

Ultimately, progress will depend on the synergistic convergence of technological innovation and clinical translation. By coupling drug discovery, mechanistic insight and immune modulation strategies, it will be possible to develop more precise, durable and patient-tailored treatment paradigms for breast cancer, thereby addressing the current limitations in endocrine therapy.

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Availability of data and materials

Not applicable.

Authors' contributions

YMD, SHW and HYQ designed the study. QL, YXQ and TTL were responsible for data collection and integration. YMD, LHS, QL, YXQ, TTL, SHW and HYQ performed data analysis and interpretation of the results, and drafted the manuscript. Data authentication is not applicable. All authors reviewed and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, an artificial intelligence tool (ChatGPT, developed by OpenAI; version GPT-4) was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

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