A narrative review: research progress of adjuvant intensive endocrine therapy for early breast cancer

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Background and Objective: Hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) breast cancer (BC) is the most prevalent subtype of all BCs. The primary treatment modality is endocrine therapy (ET). Traditional adjuvant ET for early-stage breast cancer (EBC) has undergone extensive exploration and is relatively well-established. However, patients at high risk of recurrence may still experience early relapse, necessitating consideration of intensified adjuvant ET to reduce recurrence risk. The objective of this narrative review is to examine various strategies for intensifying adjuvant ET in EBC, thoroughly analyze key clinical studies, and summarize the most effective treatment approaches supported by current evidence-based medicine. Furthermore, it addresses unresolved challenges that necessitate further refinement and investigation.

Methods: As of March 2024, a comprehensive literature search, compilation, and analysis were conducted across PubMed, Baidu Scholar, ClinicalTrials.gov, and relevant academic conferences.

Key Content and Findings: There are numerous methods to intensify adjuvant ET: (I) combining ovarian function suppression (OFS) to reduce estrogen levels in the body and induce a state of artificial menopause to enhance the efficacy of ET; (II) individual extension of the duration of ET based on patients' varying risks of recurrence, with high-risk patients covering two peak recurrence periods; (III) the addition of cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) can significantly extend invasive disease-free survival and reduce the risk of recurrence, serving as the main intensive treatment for high-risk patients; (IV) combination with bone-modifying drugs (BMD) can significantly reduce rates of bone metastasis and slightly enhance prognosis but is not commonly used in adjuvant settings; (V) combined with poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors, current studies only show a trend towards benefit in HR+ patients with germline *BRCA1/2* mutations; more data are still needed to support its clinical benefit. This narrative review examines various strategies for intensifying adjuvant ET in EBC, critically evaluates key clinical studies, and summarizes the most effective treatment approaches supported by current evidence-based medicine. Furthermore, it addresses unresolved challenges that necessitate further refinement and investigation.

Conclusions: In the context where traditional adjuvant ET is relatively well-established, the emergence of novel ET has notably addressed issues of endocrine resistance more effectively. Various intensified adjuvant ET has shown potential in further reducing recurrence risk among high-risk patients. However, additional research and time are essential to determine the optimal approaches for intensified adjuvant ET.

Keywords: Early breast cancer (early BC); adjuvant endocrine intensive therapy; hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−); research progress

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Introduction

According to the 2020 Global Cancer Statistics report, breast cancer (BC) has surpassed lung cancer to become the most prevalent cancer worldwide (1). The treatment of BC is based on molecular subtypes, including hormone receptor-positive (HR$^+$) (luminal type), human epidermal growth factor receptor 2-positive (HER2$^+$ type), and triple-negative breast cancer (TNBC). Over 90% of patients are diagnosed with early-stage BC (EBC) at the time of initial diagnosis, with approximately 70% classified as HR$^+$/HER2$^-$. While HR$^+$ EBC is not as poor in prognosis compared to other subtypes, but it is also prevalent, with a persistent risk of recurrence over the long term. Approximately half of patients experience recurrence after 5 years post-surgery, although adjuvant ET effectively delays this. However, due to significant variability in baseline clinical characteristics among these patients, standard ET may not suffice for those at high risk of recurrence, who often experience poorer outcomes. To further extend disease-free survival (DFS)/invasive DFS (iDFS), and reduce the risk of recurrence, intensified adjuvant ET has been introduced. In recent years, a myriad of strategies for intensified adjuvant ET has emerged, including extending the duration of adjuvant ET, combining it with ovarian function suppression (OFS), and incorporating CDK4/6 inhibitors. This review primarily explores the present situation and recent advancements in various intensified adjuvant ET strategies for EBC treatment. It assesses the optimal benefits of each strategy and identifies patient populations likely to derive the greatest benefit. *Figure 1* delineates a general adjuvant endocrine therapy (ET) approach for HR$^+$/HER2$^-$ EBC based on current available data. We present this article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-16/rc).

Methods

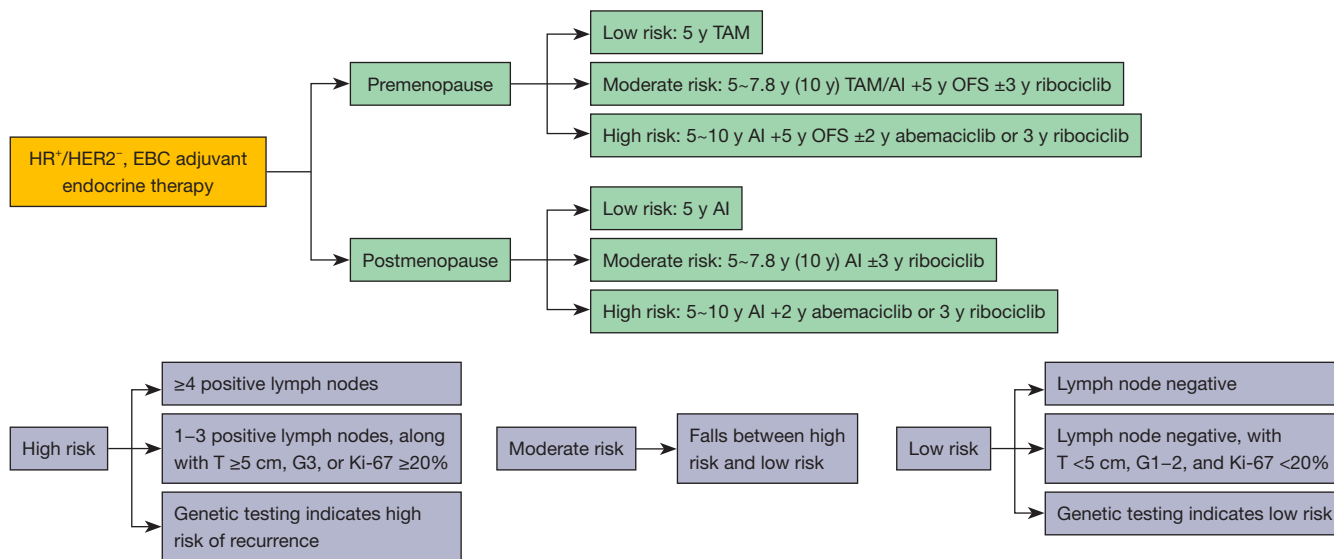This narrative review delineates the evolution of adjuvant

Figure 1 This figure delineates the recommended approach for adjuvant endocrine therapy in hormone receptor-positive, HER2$^-$ early-stage breast cancer, drawing upon evidence from evidence-based medicine and pertinent clinical studies. The principal determinants influencing recurrence risk predominantly encompass lymph node involvement, in conjunction with histological grade, tumor size, Ki-67 expression, genetic testing results, and the consideration of adjuvant (neo)chemotherapy. The BCI genetic test can assess the need for extending adjuvant endocrine therapy. (I) If accompanied by *BRCA1/2* mutation, consideration may be given to administering olaparib for 1 year. (II) For N0 patients considering ribociclib in combination therapy, the following criteria should be met: (i) grade 2, with Ki-67 ≥20% or genetic testing showing high risk or other high-risk factors; (ii) grade 3. (III) Ribociclib has not been approved by the FDA for use in EBC, based solely on the currently available data. HR$^+$, hormone receptor-positive; HER2$^-$, human epidermal growth factor receptor 2-negative; EBC, early-stage breast cancer; y, year; TAM, tamoxifen; AI, aromatase inhibitor; OFS, ovarian function suppression; T, tumor; G, grade; BCI, Breast Cancer Index; FDA, Food and Drug Administration.

intensified ET for EBC, gathering significant articles from different countries, and encompassing clinical studies and meta-analyses. Literature sources included PubMed, Baidu Scholar, ClinicalTrials.gov, and relevant academic conferences (*Table 1*). These articles were synthesized and analyzed, incorporating the authors' individual perspectives and insights. *Table 2* presents the search strategy. All figures and tables in this study are original and created by the authors unless otherwise stated.

Traditional adjuvant ET

Numerous studies have linked estrogen to an increased risk of BC (2,3). The precise mechanism remains unclear, but the prevailing theory suggests that estradiol stimulates cell proliferation via estrogen receptor α (ERα), initiating misreplication prior to mitosis and leads to mutation occurrence. Cumulative mutations over time culminate in neoplastic transformation. ET aims to reduce circulating estrogen levels or block its signaling pathways through various mechanisms, the brief mechanisms of several common methods to lower estrogen levels can be seen in *Figure 2*. Conventional therapeutic drugs primarily include selective estrogen receptor modulators (SERM) such as tamoxifen (TAM) and toremifene, mainly utilized in premenopausal patients. Aromatase inhibitors (AIs)—steroidal exemestane, and nonsteroidal letrozole and anastrozole (NSAI)—are indicated for postmenopausal patients or in combination with OFS in premenopausal patients.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis involving 21,457 patients across 20 studies (4), revealing that in ER+ patients, 5 years of TAM significantly reduced recurrence rates, with a maximum absolute benefit of 14.2% at 10 years, sustained thereafter. TAM also reduced 15-year mortality by about one-third. No additional benefit of TAM was observed in patients with low expression of ER (1–9%). Higher expression of ER appears to be associated with a better prognosis. Toremifene is structurally and mechanistically similar to TAM. To evaluate the efficacy differences and adverse reactions between TAM and toremifene, a meta-analysis was conducted that included four randomized controlled trials. These trials predominantly involved postmenopausal patients, with some peri-menopausal individuals included. The findings revealed no significant disparities in overall survival (OS) or DFS between TAM and toremifene. Similarly, there were no significant differences observed in adverse reactions between the two treatments (5). Another study compared the efficacy of TAM and toremifene specifically in premenopausal patients. Data with a median follow-up of 50.8 months suggested comparable OS rates between the two groups. However, toremifene demonstrated a significant advantage in recurrence-free survival. Adverse reactions were generally similar between the groups, although toremifene showed a marginally higher incidence of hot flashes, which reached statistical significance (P<0.001) (6,7). Patients with CYP2D6 enzyme mutations experienced a significant 23% increase in DFS after 5 years of toremifene treatment, primarily due to drug metabolism enzyme involvement, particularly prevalent in Chinese patients. However, there is currently limited clinical data available for toremifene in research studies. Therefore, if patients cannot tolerate TAM, have contraindications, or have mutations in the CYP2D6 enzyme, toremifene can be used as a substitute for TAM (8).

BIG1-98 is a randomized, phase III clinical trial that includes two- and four-arm experimental groups. In the two-arm comparison, the efficacy of 5 years of TAM *vs.* 5 years of letrozole is evaluated. The four-arm comparison examines the efficacy of 5 years of monotherapy with letrozole, 5 years of monotherapy with TAM, 2 years of TAM followed by 3 years of letrozole, and 2 years of letrozole followed by 3 years of TAM. The initial analysis in 2005, with a median follow-up of 25.8 years, did not involve crossover therapy. Data from the two monotherapy groups showed DFS rates of 84% for letrozole and 81.4% for TAM (P=0.003) (9). At a median follow-up of 71 months, the first analysis after completing crossover therapy confirmed significant benefits of letrozole over TAM in DFS and OS. However, there were no significant differences observed between the sequential therapy group and the letrozole monotherapy group (10). In the latest report at a median follow-up of 12.6 years, the letrozole monotherapy group continued to demonstrate relative DFS benefits over the TAM monotherapy group beyond the initial 10 years, although the magnitude of benefit decreased, particularly within the first 5 years of treatment. Conversely, the sequential therapy group did not show significant differences in DFS compared to the TAM monotherapy group after the initial 10 years. OS did not differ significantly across all four groups. Interestingly, AIs significantly reduced contralateral BC recurrence rates compared to TAM within the first 10 years. However, after 10 years, TAM exhibited a reversal effect. These changing trends observed after 10 years may be attributed to TAM's carry-over effect (11). In 2015, EBCTCG conducted a meta-

Table 1 Studies on adjuvant endocrine therapy in HR⁺ EBC

Endocrine therapy modalities	Intensive strategies	Menopausal status	Study	Recruit	Treatment options	Result
Conventional endocrine therapy	–	Postmenopausal	ATAC	9,366 patients	5 years of TAM *vs.* 5 years of ANA	Median follow-up of 68 months, DFS events: 575 *vs.* 651 (HR =0.87, 95% CI: 0.78–0.97, P=0.01)
			BIG1-98	8,010 HR⁺ patients	5 years of TAM *vs.* 5 years of LET *vs.* 5 years of TAM→LET *vs.* 5 years of LET→TAM	Median follow-up of 12.6 years, DFS: 9% RR reduction (HR =0.91, 95% CI: 0.81–1.01, P=0.08)
						Cumulative disease recurrence rates: 35.3% *vs.* 35.5% *vs.* 38.2% *vs.* 36.2% (treatment by time interaction, P=0.12)
Adjuvant intensive endocrine therapy	Combined ovarian function suppression	Premenopausal	ASTRRA	1,282 ER⁺ patients	5 years of TAM *vs.* 5 years of TAM + 2 years of OFS	8 years of DFS: 85.4% *vs.* 80.2% (HR =0.67, 95% CI: 0.51–0.87, P=0.003)
			SOFT and TEXT	4,690 HR⁺ patients	5 years of TAM + OFS *vs.* 5 years of EXE + OFS	12 years of DFS: 80.5% *vs.* 75.9% (HR =0.79, 95% CI: 0.70–0.90, P<0.001)
			ABCSG-12	1,803 HR⁺ patients	3 years of TAM + OFS *vs.* 3 years of ANA + OFS	47.8 months of DFS: 92.8% *vs.* 92% (HR =1.1, 95% CI: 0.78–1.53, P=0.59)
			HOBOE	1,065 HR⁺ patients	5 years of TAM + OFS *vs.* 5 years of LET + OFS	64 months DFS: 93.2% *vs.* 85.4% (HR =0.72, 95% CI: 0.48–1.07, P=0.06)
	Extended adjuvant endocrine therapy	Pre/postmenopausal	ATLAS	6,846 ER⁺ patients	5 years of TAM *vs.* 10 years of TAM	15-year follow-up cumulative recurrence: 21% *vs.* 25% (RR =0.84, 95% CI: 0.76–0.94; P=0.002)
			aTTOM	6,953 ER⁺ patients	5 years of TAM *vs.* 10 years of TAM	9 years of follow-up, recurrence rate was reduced (28% *vs.* 32%; P=0.003)
		Postmenopausal	MA17R	1,918 HR⁺ patients	3–5 years of TAM + 5 years of AI *vs.* 3–5 years of TAM + 10 years of AI	5 years of DFS: 95% *vs.* 91% (HR =0.66, 95% CI: 0.48–0.91, P=0.01)
			MA17	5,178 HR⁺ patients	5 years of TAM *vs.* 5 years of TAM + 5 years of LET	4 years of DFS: 92.8% *vs.* 86.8% (HR =0.57, 95% CI: 0.43–0.75, P<0.001)
			DATA	1,860 HR⁺ patients	2–3 years of TAM + 3 years of ANA *vs.* 2–3 years of TAM + 6 years of ANA	5 years of DFS: 83.1% *vs.* 79.4% (HR =0.79, 95% CI: 0.62–1.02, P=0.07)
			GIM4	2,056 patients who completed 2–3 years of TAM	2–3 years of TAM + 2–3 years of LET *vs.* 2–3 years of TAM + 5 years of LET	12 years of DFS: 67% *vs.* 62% (HR =0.78, 95% CI: 0.65–0.93, P=0.006)
			IDEAL	1,824 patients who completed 5 years of ET	5 years of ET + 2.5 years of LET *vs.* 5 years of ET + 5 years of LET	3 years of DFS: 82% *vs.* 83.4% (HR =0.92, 95% CI: 0.74–1.16, P=0.49)
			ABCSG-16	3,208 patients who completed 5 years of ET	5 years of ET + 2 years of ANA *vs.* 5 years of ET + 5 years of ANA	8 years of DFS: 73.9% *vs.* 73.6% (HR =0.99, 95% CI: 0.85–1.15, P=0.90)
			NSABP-B33	1,598 patients who completed 5 years of TAM	5 years of TAM + 5 years of EXE *vs.* 5 years of TAM	4 years of DFS: 91% *vs.* 89% (HR =0.68, P=0.07)
			NSABP-B42	3,966 patients who completed 5 years of TAM	5 years of TAM or AI *vs.* 5 years of TAM or AI + 5 years of LET	10 years of DFS: 75.9% *vs.* 72.6% (HR =0.85, 95% CI: 0.74–0.96, P=0.01)
			SOLE	4,884 HR⁺, LN+, operable patients	4–6 years of ET + 5 years of LET (continuous) *vs.* 4–6 years of ET + 5 years of LET (intermittent)	84 months of DFS: 81.4% *vs.* 81.5% (HR =1.03, 95% CI: 0.91–1.17, P=0.64)
	Combination CDK4/6 inhibitors	Pre/postmenopausal	MonarchE	5,637 HR⁺ clinical high-risk patients	2 years of abemaciclib + ET *vs.* ET	5 years of DFS: 83.6% *vs.* 79.4% (HR =0.68, 95% CI: 0.599–0.772, P<0.001)
			NATALEE	5,101 HR⁺ patients, stage II–III EBC	3 years of ribociclib + NSAI *vs.* NSAI	3 years of iDFS: 90.4% *vs.* 87.1% (HR =0.748, 95% CI: 0.618–0.906, P=0.001)
			PALLAS	5,796 HR⁺ patients, stage II–III EBC	2 years of palbociclib + ET *vs.* ET	4 years of iDFS: 84.2% *vs.* 84.5% (HR =0.96, 95% CI: 0.81–1.14, P=0.65)
			PENELOPE-B	1,708 HR⁺, CPS + EG score ≥3; CPS + EG =2, LN+	13 months of palbociclib + ET *vs.* ET	4 years of iDFS: 73% *vs.* 72.4% (HR =0.93, 95% CI: 0.74–1.17, P=0.53)

This table presents the latest follow-up results from recent clinical studies regarding adjuvant endocrine therapy in hormone receptor-positive, HER2-negative early-stage breast cancer. HR⁺, hormone receptor-positive; EBC, early-stage breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ER⁺, estrogen receptor-positive; TAM, tamoxifen; ET, endocrine therapy; LN+, lymph node-positive; CPS + EG, clinical pathological stage plus ER and grade; ANA, anastrozole; LET, letrozole; OFS, ovarian function suppression; EXE, exemestane; AI, aromatase inhibitor; NSAI, nonsteroidal aromatase inhibitor; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; RR, relative risk; iDFS, invasive DFS; HER2, human epidermal growth factor receptor 2.

Table 2 The search strategy summary

Items	Specification
Date of search	February 1, 2024 to April 15, 2024
Databases and other sources searched	PubMed, Baidu Scholar, ClinicalTrials.gov, and relevant conferences (such as the San Antonio Conference)
Search terms used	"Early breast cancer", "Endocrine therapy for breast cancer", "Early breast cancer and OFS", "Early breast cancer and CDK4/6 inhibitors", "Extended endocrine therapy", "Hormone receptor-positive, HER2-negative breast cancer", "Endocrine-enhanced therapy", "Bone-modifying agents", "Early breast cancer and bone-modifying agents", "Early breast cancer and olaparib"
Timeframe	2003–2024
Inclusion and exclusion criteria	Inclusion criteria: our selection primarily includes high-impact research articles, reviews, and clinical trials published in English. The focus is mainly on endocrine adjuvant therapy and related enhanced therapy for hormone receptor-positive, HER2-negative early breast cancer patients
	Exclusion criteria: papers with lower impact factors or perceived lower reliability were excluded. Additionally, studies that have been surpassed by more recent research with similar content were also excluded
Selection process	Most of the literature was selected by the author H.Y., supplemented by the second author G.L., and reviewed by all authors
Any additional considerations, if applicable	While reviewing the relevant literature, some cited references were taken into account. Additionally, certain relevant references were mentioned in conferences

CDK4/6, cyclin-dependent kinase 4/6; OFS, ovarian function suppression; HER2, human epidermal growth factor receptor 2.

analysis involving 31,920 postmenopausal patients, revealing significantly lower recurrence rates with AIs compared to TAM (P<0.00001) over a 10-year period. Sequential therapy did not provide significant additional benefit compared to AIs monotherapy, suggesting the need for individualized medication adjustments based on contraindications or intolerance. These findings align with those of the BIG1-98 and ATAC trials (12). Presently, in clinical practice for postmenopausal patients, AI-oriented extension programs are predominant, reflecting the established evidence from these studies. The specific detailed studies can be found in *Table 1*.

Novel endocrine therapies

Traditional ET remains the cornerstone for treating HR$^+$ EBC; however, an increasing number of patients encounter resistance, primarily due to *ESR1* gene mutations (13). Selective estrogen receptor downregulators (SERDs) like fulvestrant, Food and Drug Administration (FDA)-approved for advanced breast cancer (ABC), have reshaped treatment paradigms by effectively degrading ER. Compared to SERMs, SERDs offer enhanced efficacy of

ET in patients with *ESR1* mutations, thereby addressing endocrine resistance more comprehensively. Challenges such as intramuscular administration, low bioavailability, and poor blood-brain barrier permeability have prompted the development of next-generation SERDs. Elacestrant represents a promising SERD currently under investigation and is the sole FDA-approved oral treatment for ER$^+$/HER2$^-$ metastatic BC with *ESR1* mutations. Significant therapeutic benefits have been demonstrated in ABC, as evidenced by the EMERALD trial—a randomized, open-label phase III study. In this trial involving HR$^+$ ABC patients previously treated with CDK4/6 inhibitors, where 47.8% harbored *ESR1* mutations, elacestrant exhibited a median progression-free survival (PFS) benefit with an hazard ratio of 0.70 [95% confidence interval (CI): 0.55–0.88, P=0.002] over a median follow-up of 15.1 months. Although adverse reactions were more pronounced, they remained manageable within clinical thresholds (14). Numerous phase III trials are currently investigating the efficacy of SERDs in EBC, including Amcenestrant's AMEERA-6 (NCT05128773), Imlunestrant's EMBER-4 (NCT04647487), Giredestrant's lidERA (NCT04961996), Camizestrant's CAMBRIA-1 (NCT05774951), and
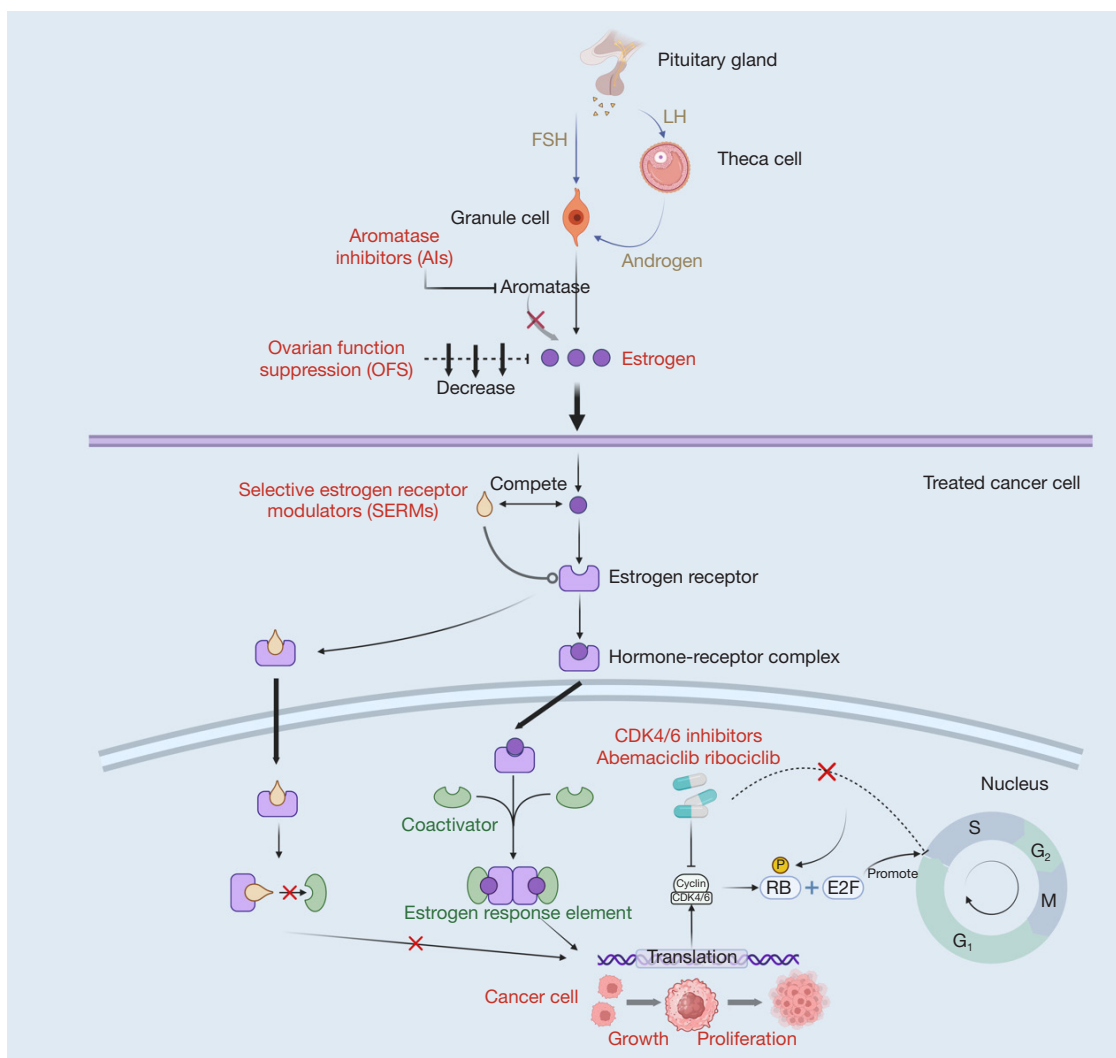
Figure 2 The figure above outlines several pivotal adjuvant endocrine therapy options and their concise mechanisms for patients with hormone receptor-positive, HER2-negative early-stage breast cancer. This includes the modulation of the hypothalamic-pituitary-gonadal axis to achieve partial estrogen suppression. Figure created with BioRender.com. HER2, human epidermal growth factor receptor 2; FSH, follicle-stimulating hormone; LH, luteinizing hormone; CDK4/6, cyclin-dependent kinase 4/6.

CAMBRIA-2 (NCT05952557). SERM/SERD hybrids exert dual effects by antagonizing and degrading ERα. Lasofoxifene has demonstrated superior anti-tumor activity compared to fulvestrant in mouse models of endocrine-resistant BC, particularly when combined with palbociclib, leading to a significant reduction in distant metastasis. However, its clinical benefit in humans remains unverified by phase III trials (15). Another SERM/SERD hybrid, bazedoxifene, not only antagonizes ER in mammary tissue but also exhibits osteogenic properties, effectively preventing osteoporosis (16). Innovative approaches like

Proteolysis Targeting Chimeras (PROTACs) are also being explored, it can reduce estrogen levels by degrading the ER. Even in patients with *ESR1* mutations and consequent endocrine resistance, PROTAC therapies—either as monotherapy or in combination with other targeted agents—have demonstrated robust anti-tumor effects in ABC settings (17). Selective estrogen receptor covalent antagonists (SERCAs), exemplified by compounds like 29c, represent a novel class of drugs designed to covalently bind and degrade ER, thereby disrupting ERα protein dynamics and function. These developments hold promise, albeit

in early clinical stages, offering potential advancements beyond traditional SERMs like TAM (18). Complete ER antagonists (CERANs) such as OP1250 are also undergoing clinical trials, targeting the ligand-binding pocket to achieve complete antagonism of ER transcriptional processes mediated by AF1 and AF2 (19). Numerous new types of ET have emerged, but most remain in the clinical research phase. Trials focusing on EBC are notably scarce; however, their demonstrated efficacy and potential to overcome endocrine resistance are highly anticipated (20,21).

Adjuvant intensive ET

Combined OFS

Tumors in younger BC patients often display a more aggressive nature, with age serving as an independent factor influencing the heightened risk of recurrence and mortality (22). In recent years, OFS has emerged as a useful approach to mitigating the risk of recurrence in premenopausal BC patients. Achieving postmenopausal status typically involves surgical ablation or pharmacological intervention in premenopausal women. Surgical ablation represents a permanent solution that achieves menopausal status swiftly. However, it is irreversible and carries potential long-term adverse effects due to extended estrogen deprivation. Medicine suppression primarily utilizes gonadotropin-releasing hormone (GnRH) analogues that competitively bind to GnRH receptors, thereby antagonizing normal GnRH activity and reducing estrogen secretion. A 2020 evaluation assessing OFS in premenopausal women with HR^+ EBC encompassed 15 studies involving 11,538 patients. The findings suggest that using medication for OFS significantly improves DFS and OS compared to not using OFS. Conversely, surgical ablation did not demonstrate significant differences in DFS and OS when compared to not using OFS (23). Hence, medication-based OFS may offer a more practical and effective approach.

The initial analysis of the SOFT study showed that the combination of OFS with TAM provided only a relative benefit compared to TAM alone, with higher-risk patients benefiting more noticeably (such as those who had previously received chemotherapy) (24). With a median follow-up of 12 years, recent data revealed a significant DFS benefit in the OFS group compared to TAM monotherapy across the overall population, the maximum absolute benefit reached 7.1%. The exemestane combination group reduced the risk of BC recurrence by approximately one-third at the

12-year mark. Significant DFS benefits were consistently observed for the exemestane combination group at all assessed time points. Overall, the exemestane combination group demonstrated the most favorable efficacy. However, at the 12-year OS endpoint, there was no significant difference observed between the OFS group and TAM monotherapy group. It is noteworthy that the exemestane combination group showed an OS benefit in follow-up beyond 5 years. It is intriguing that treatment effects display ongoing heterogeneity in subgroup analyses based on HER2 status (25).

The TEXT data, with a median follow-up of 13 years, shows that the exemestane group exhibited sustained DFS benefit compared to the TAM group. The absolute improvement in 12-year DFS was 4.6%, with DFS rates of 80.5% and 75.9%, respectively (P<0.001) (26). Both the TEXT and SOFT trials showcase the favorable efficacy of OFS, particularly accentuated in the AI combined with OFS group or in high-risk recurrent patients. Despite these promising results, there appears to be no significant difference in OS following 12 years of follow-up.

The use of OFS in the two seminal studies mentioned involved monthly injections over a period of 5 years. However, a study conducted a decade ago focused on premenopausal EBC patients with ER^+ tumors compared the efficacy of goserelin injections combined with TAM, administered either monthly (3.6 mg) or every 3 months (10.8 mg). The findings indicated that all patients achieved menopausal status within 24 weeks, with no significant differences observed in DFS or safety between the two dosing schedules. This suggests that both monthly and every 3 months regimens of OFS yield comparable clinical outcomes (27). Recently, a retrospective study published by American Society of Clinical Oncology (ASCO) analyzed the effectiveness of goserelin combined with AI, comparing monthly vs. every 3 months administration. This study, which included a substantial proportion of $HER2^-$ EBC patients, indirectly assessed estrogen levels over varying time intervals. Results showed that a greater proportion of patients receiving goserelin every 3 months maintained consistently lower estrogen levels (below 2.72 pg/mL) throughout the treatment period. This implies that the every 3 months schedule of OFS may more effectively suppress estrogen and sustain menopausal levels. Despite differences in baseline patient characteristics between these studies, the evidence suggests that the every 3 months strategy for OFS is equally, if not more, effective compared to the monthly approach. The optimal duration of OFS use

remains unclear, as previous clinical investigations examining OFS durations of 2, 3, and 5 years have reported varying degrees of benefit (25,26,28,29). In the latest National Comprehensive Cancer Network (NCCN) guidelines, it is recommended for premenopausal BC patients at high risk of recurrence to use standard ET combined with 5 years of OFS, or undergo surgical ablation, with consideration of adding CDK4/6 inhibitors to the ET (30).

Certainly, alongside OFS, prolonged estrogen deprivation leads to various adverse effects across several domains. The primary concerns include vascular constriction, gynecological and sexual dysfunction, musculoskeletal issues, and gastrointestinal disturbances (31). In the 2015 combined analysis of SOFT and TEXT trials, the impact on quality of life in OFS-treated groups was assessed. Hot flashes emerged as the most prevalent adverse effect, notably peaking at 6 months post-baseline, with significantly higher incidence in the TAM plus OFS group compared to AI plus OFS (P<0.0001). Moreover, significant changes were observed over the 5-year treatment period in gynecological and sexual symptoms, including vaginal dryness and impaired sexual arousal relative to baseline. While some symptoms showed improvement over time compared to the 6-month assessment, certain adverse effects failed to return to baseline levels. Overall, 14% of patients discontinued treatment due to adverse reactions (32). In previous investigation, we noted that premenopausal patients face the risk of ovarian insufficiency and even amenorrhea following adjuvant chemotherapy (33). Multiple clinical studies and meta-analyses have shown that chemotherapy-induced amenorrhea significantly benefits DFS and OS in BC, particularly in ER$^+$ BC patients. However, the specific mechanisms through which it affects BC prognosis remain unclear, partly due to the reduction in endogenous estrogen levels caused by amenorrhea, thereby decreasing stimulation of BC cells. In other words, while chemotherapy-induced amenorrhea is a side effect of chemotherapy, it is advantageous for the prognosis of BC patients (34,35). A randomized clinical trial examining the impact of OFS on long-term ovarian function and pregnancy outcomes during BC chemotherapy, with a median follow-up of 7.3 years, demonstrated the efficacy of OFS in enhancing the long-term recovery of ovarian function among BC patients. However, no significant difference in DFS was observed (36). The latest study from China included 330 premenopausal BC patients, who were randomized 1:1 to receive chemotherapy with or without OFS. One year after completing chemotherapy, the probability of experiencing ovarian insufficiency was 10.3% in the OFS group compared to 44.5% in the non-OFS group (P<0.001) (37). Currently, OFS is widely used in patients at high risk of recurrence, and most experts and guidelines recommend early administration of OFS during or after adjuvant chemotherapy to preserve ovarian function.

Extended adjuvant ET

Despite the coverage of the peak recurrence period of 2 to 3 years by the standard 5-year ET regimen, recurrence in HR$^+$ BC remains indefinite, with most recurrences occurring late. In conjunction with the findings from the EBCTCG study on the long-term recurrence risk of BC after 5 years of ET, meta-analysis has revealed that the long-term recurrence rate of BC is associated with various baseline characteristics. Among these, tumor size and lymph node status emerge as the two most closely correlated factors, with the correlation of the 20-year cumulative distant recurrence rate approximating an additive relationship, patients with T2N4-9 tumors have a high distant recurrence rate of up to 41% over 20 years (38). In 2022, experts utilized the RAND consensus method to initially screen 21 characteristics associated with high-risk features in HR$^+$/HER2$^-$ EBC. Following two rounds of expert selection, 12 features were identified as relevant high-risk factors for recurrence. Each high-risk feature underwent comprehensive literature review to assist clinical practitioners in optimizing personalized ET decisions for EBC patients (39). Prolonging adjuvant ET emerges as a critical strategy to mitigate recurrence and improve prognosis, particularly among patients with identified high-risk characteristics.

The ATLAS and aTTOM trials aimed to assess the efficacy of 5 vs. 10 years of TAM therapy in patients with EBC (40,41). The findings revealed that extending TAM treatment to 10 years could further reduce both recurrence and mortality rates in patients. ATLAS results indicated that while there was no significant difference in recurrence rates during the initial 5 years of continued treatment. However, significant disparities were observed during subsequent follow-up periods, with the curves gradually diverging from this time point onwards. Notably, at 15 years of follow-up from diagnosis, the cumulative incidence of recurrence was 25.1% in the extended-therapy group compared to 21.4% in the discontinuation-therapy group, yielding an absolute benefit increase of 3.7% (P=0.002). Similarly, a survival benefit was observed, with roughly a 20% reduction in mortality at the 15-year mark. The most recent aTTOM report supported the ATLAS findings; however, the

mortality benefit did not achieve statistical significance (21% *vs.* 24%). This discrepancy may be attributed to the presence of ER-negative patients within the study population. Both major TAM extension studies have thus far only reported 10-year follow-up data, necessitating further investigation to determine the optimal duration of therapy. The majority of extended therapy regimens discussed above are predominantly employed in premenopausal patients. Subsequent studies have indicated that extended AI therapy may confer greater benefits than TAM in postmenopausal patients.

The NSABP B-33 trial investigated the efficacy of continuing letrozole for 5 years in postmenopausal, HR⁺ patients who had previously received 5 years of TAM therapy. Despite premature unblinding influenced by findings from the MA.17 study, which led to 44% of the placebo group crossing over to letrozole, data at a median follow-up of 30 months still indicated no significant benefits (P=0.07) for the initially sequenced treatment group. Significant DFS benefits were particularly pronounced in subgroups with positive lymph nodes, those who underwent adjuvant chemotherapy, and tumors larger than 2 cm. This to some extent suggests that extending treatment in postmenopausal HR⁺ high-risk patients may be beneficial, a notion further supported by subsequent studies conducted by the research team. The B-42 trial investigated the extension of letrozole for 5 years following 5 years of ET. With a median follow-up of 10.3 years, the extended letrozole group demonstrated a 3.3% absolute benefit, with certain subgroups, such as those with node-positive disease, previous TAM use, bone mineral density ≤−2.0, and mastectomy, exhibiting an absolute benefit of 5 percentage points or more. Notably, in contrast to a median follow-up of 6.3 years, significant new differences in bone mineral density emerged in this multivariate analysis. Specifically, in patients with bone mineral density ≤−2.0, the extended-therapy arm appeared to confer a superior DFS benefit. This observation may be attributed to some patients with low bone mineral density already receiving bisphosphonates at enrollment. This may lead to imbalance between groups, thereby reducing the significance of DFS benefit in this subgroup (42). In the MA17R study, the duration of AI treatment was prolonged to 10 years. Following a median follow-up of 6.3 years, DFS was 95% in the letrozole group compared to 91% in the placebo group (P=0.01). Simultaneously, the letrozole group demonstrated significant advantages over the placebo group in reducing the incidence of contralateral BC. Additionally, in the

analysis of recurrence events, it was observed that the rate of local recurrence and bone metastasis was reduced to a greater extent in the extended treatment group (43).

Therefore, we think that extending ET to 10 years rather than 5 years may confer benefits to certain high-risk patients. To gain a better understanding of the optimal duration of treatment, extensive clinical studies and literature reviews have explored and summarized this topic (*Table 1*) (44,45).

The IDEAL trial compared the extension of letrozole therapy for 2.5 *vs.* 5 years following 5 years of initial ET. With a median follow-up of 6.6 years, no significant benefit was observed in the extended 5-year group. This suggests that the benefits of 10 years of ET may be realized earlier, with 7.5 years or less of ET providing comparable advantages (46). The ABCSG-16 trial, similar to the IDEAL study, compared the extension of anastrozole therapy for 2 *vs.* 5 years. Although the results aligned with those of IDEAL, showing no additional advantage with 5 years of anastrozole, a comparison of the extension durations (7.5 *vs.* 10 years in IDEAL *vs.* 7 *vs.* 10 years in ABCSG-16) suggests that the benefits of extended therapy may be more pronounced within the initial 2 years. Perhaps, considering the low recurrence risk profile of most enrolled patients, a 2-year extension may already be sufficient (47). The DATA study randomized patients who had previously received 2–3 years of TAM therapy in a 1:1 ratio to receive either 3 or 6 years of extended anastrozole treatment. The latest follow-up data are consistent with previous analyses, with 10-year adapted DFS rates of 69.2% and 66% respectively (hazard ratio =0.86, 95% CI: 0.72–1.01; P=0.07). There was a trend towards benefit, with the upper limit of the CI consistently hovering around the critical value of 1. Subgroup analysis indicated that patients at higher risk of recurrence derived greater benefit from the 6-year treatment regimen (48). The GIM4 study investigated the comparative efficacy between 2–3 years of TAM followed by either 2–3 years of letrozole or 5 years of letrozole. Following a median follow-up period of 11.7 years, the group receiving a 5-year extension (with a total treatment duration of 7–8 years) demonstrated a significant improvement in both DFS and OS compared to the group receiving a 2–3-year extension (with a total treatment duration of 5 years). This study stands out as one of the few where extended therapy contributed to improved OS outcomes (49). Both the DATA and GIM4 studies investigated the sequential use of AI following 2–3 years of adjuvant TAM, with differing durations of AI treatment. Interestingly, despite similar total

treatment durations (DATA: 5–6 *vs.* 8–9 years; GIM4: 5 *vs.* 7-8 years), the outcomes differed between the two studies. This variation could be attributed to differences in the primary endpoints (DATA: adapted DFS; GIM4: DFS) or the type of AI used in the extended treatment. Although the FATA-GIM3 study indicated no significant difference in efficacy among different AIs (50), the ALIQUOT study demonstrated that letrozole significantly reduced plasma hormone levels compared to anastrozole (51). Therefore, the reasons for these differences are not yet clear. Currently, the most recommended genetic testing method to predict whether BC patients can benefit from extended ET alone is the Breast Cancer Index (BCI). The efficacy of BCI has been validated in populations included in the aTTOM trial and IDEAL study (52,53).

Combined with CDK4/6 inhibitor targeted therapy

CDK4/6 inhibitors are cyclin-dependent kinase inhibitors that block the phosphorylation of Rb protein, thereby inhibiting the transition of cells from G1 phase to S phase, achieving the goal of suppressing tumor cell proliferation (54). In both first-line treatment and treatment after progression of ABC, CDK4/6 inhibitors have shown significant benefits. In several phase III clinical studies of ABC, the hazard ratio was mostly around 0.55, with PFS improving by approximately one year (55-59). However, in EBC, different CDK4/6 inhibitors have markedly different effects (*Table 1*). In the PENELOPE-B trial, which included high-risk patients with CPS + EG (clinical pathological stage plus ER and grade) ≥3 or CPS + EG =2 and positive lymph nodes who had received adjuvant chemotherapy. CPS + EG is a BC staging system integrating clinical cancer stage, final pathological stage, ER status, and nuclear grade. Its utility in neoadjuvant chemotherapy has been validated in prior studies. A higher score generally reflects heightened clinical and pathological risk factors, correlating with a poorer prognosis (60). Results from a median follow-up of 49 months indicate that the palbociclib treatment group did not show any benefit in iDFS compared to the placebo group. However, on the Kaplan-Meier curve for iDFS during palbociclib treatment, there was a brief separation between the two treatment groups, but after discontinuation of treatment, they quickly converged or even crossed over again (61). Based on an exploratory analysis combining previous findings, longer duration and intensity of palbociclib treatment were associated with improvements in iDFS (62). And palbociclib primarily

exerts its effects through anti-proliferative mechanisms, suggesting potential benefits in subgroups with high Ki-67 levels. However, the PENELOPE-B trial did not include high Ki-67 as an inclusion criterion; in the baseline analysis of the entire patient cohort, only 14% of patients had Ki-67 >25%. Unlike the high-risk inclusion criteria in the PENELOPE-B trial, PALLAS did not screen for high-risk patients at enrollment. Data from a median follow-up of 31 months still showed no significant improvement in iDFS with 2 years of palbociclib treatment. Approximately 42.2% of patients discontinued palbociclib prematurely, with most stopping due to adverse events, primarily neutropenia. Early discontinuation may impact drug levels and consequently treatment efficacy (62,63). The negative results from both trials suggest that palbociclib may not yet be suitable for EBC, although the specific reasons for these failures remain unclear and require further clinical investigation.

The first CDK4/6 inhibitor shown to significantly benefit EBC is abemaciclib, and the MonarchE trial overcome the limitation that CDK4/6 inhibitors only benefit patients with ABC. The trial included two cohorts: one based on clinical pathological characteristics and the other based on Ki-67, with the latter having a smaller sample size (64). In the latest median follow-up data of 54 months, the 5-year iDFS for the abemaciclib plus ET group *vs.* the ET alone group were 83.6% and 76%, respectively (hazard ratio =0.68, 95% CI: 0.599–0.772, P<0.001). There were similar significant benefits in most subgroups, with consistent benefits in cohort one and the intention-to-treat population (ITT). The benefit of abemaciclib has persisted since the end of the 2-year abemaciclib treatment, as evidenced by the continuous separation of the Kaplan-Meier curves for the two treatment groups, showing an increasing trend. This indicates that the carry-over effect of abemaciclib continues. Although the data for cohort two are still immature, we found that in the Ki-67 subgroups of cohort one, regardless of the Ki-67 value, we observed benefits in the abemaciclib combination treatment group (65). However, on the other hand, although the OS values in both treatment groups are still immature, there is still a trend of OS benefit in the ITT, and significant OS benefit is even observed in the high Ki-67 subgroup of cohort one. This may indicate that Ki-67 may be an independent factor in predicting patient prognosis. In previous studies, Ki-67 has been shown to affect prognosis and is a predictive factor for observing treatment response (66).

At the latest San Antonio Breast Cancer Symposium (SABCS), final iDFS data from NATALEE (67) were

presented. At a median follow-up of 33.3 months, which increased by 5.6 months from the second interim analysis, approximately 42.8% of patients completed 3 years of ribociclib in combination with NSAI therapy. The ribociclib combination therapy group demonstrated a 3-year iDFS of 90.7% compared to 87.6% in the NSAI group, showing an absolute benefit of 3.1% (P=0.001). Additionally, the ribociclib combination group reduced the risk of recurrence by 25.1% compared to the NSAI group. Subgroup analyses showed significant iDFS benefits with ribociclib combination therapy in stage II, III, and lymph node-positive patients. However, in lymph node-negative patients, there was only a trend towards benefit in the final analysis, with a hazard ratio (95% CI) of 0.723 (0.412–1.268). Regarding OS, there were 84 events (3.3%) in the ribociclib combination group and 3.4 events (3.4%) in the NSAI group, with an hazard ratio (95% CI) of 0.892 (0.661–1.203). OS data remains immature, because the proportion of events occurring in both treatment groups is less than 4%. The ribociclib dose in NATALEE was 400 mg, consistent with two-thirds of the dose used in ABC, suggesting improved tolerance and compliance. Compared to the second interim analysis, the additional 5.6 months of follow-up did not reveal new safety signals. Discontinuation due to adverse events increased to 19.5%, slightly higher than the increase observed in the previous interim analysis (<1%). Neutropenia was the most common adverse event leading to discontinuation.

Comparing the MonarchE and NATALEE studies, the baseline characteristics of the enrolled patients are significantly different. NATALEE included a broader population, notably incorporating N0 patients. However, data regarding iDFS benefits in this subgroup are still preliminary, and recent findings at the 2024 ASCO conference indicated no significant iDFS difference between the ribociclib combination and NSAI groups in the N0 subset. Additionally, both trials have data that are still maturing; MonarchE's Cohort 2 and ITT for OS, as well as overall data from NATALEE, require longer trial completion and follow-up to ensure more robust conclusions. Furthermore, the control groups differed between the studies. MonarchE utilized standard ET, whereas NATALEE used NSAI. Historically, transitioning from TAM to AI therapies has demonstrated superior efficacy in ET, potentially contributing to the observed higher iDFS in the MonarchE study. In summary, both abemaciclib and ribociclib are oral CDK4/6 inhibitors with established safety profiles in ABC research. However,

from the current evidence and data maturity perspective, abemaciclib benefits from 5 years of clinical use data, demonstrating more established efficacy and safety compared to ribociclib. Moreover, abemaciclib is currently the sole FDA-approved CDK4/6 inhibitor for high-risk EBC and is covered by insurance. Therefore, currently, when patients meet enrollment criteria for both MonarchE Cohort 1 and the NATALEE study, abemaciclib appears to be the preferred choice.

Other intensive adjuvant therapy

In adjuvant ET for EBC, bone loss to varying degrees is inevitable. Previous investigations have also explored whether addressing bone loss could impact overall patient prognosis. In a meta-analysis involving 18,766 patients treated with bisphosphonates, adjuvant therapy for 2 to 5 years demonstrated significant improvements in overall recurrence rates, distant recurrence rates, and BC mortality. These benefits were particularly pronounced in postmenopausal patients, notably in reducing the incidence of bone metastases with a relative risk (RR) of 0.83 (95% CI: 0.73–0.94, P=0.004), translating to a 1.1% absolute benefit over 10 years. This underscores why bisphosphonate therapy is more effective at reducing distant recurrence risks compared to other forms of recurrence. Conversely, no significant impact of bisphosphonates on outcomes was observed in premenopausal women. Given the strong association between age and menopausal status, current data do not specify the correlation between these factors and the observed benefits. Moreover, the meta-analysis found no notable differences in efficacy between different types of bisphosphonates (68). Further detailed investigations into bisphosphonate drugs are warranted. The SWOG S0307 trial compared the efficacy of different bisphosphonate drugs and found no significant differences in primary endpoints between them, both overall and in subgroup analyses (69). As for the optimal duration of adjuvant bisphosphonate therapy, it remains unclear. The SUCCESS trial compared the efficacy of adjuvant zoledronic acid therapy for 2 vs. 5 years in EBC patients following chemotherapy. Approximately 80% of the patients opted for combined ET with zoledronic acid following chemotherapy. The results showed no significant differences DFS and OS between the 5-year and 2-year treatment groups, irrespective of menopausal status. Conversely, the 5-year treatment group reported higher incidences of adverse events such as bone pain and joint pain (70). Therefore, the latest NCCN

guidelines tentatively recommend a duration of 2 to 3 years. The ZO-FAST trial investigated patients receiving adjuvant AI therapy in the HR⁺ EBC, randomly assigned to immediate or delayed (due to fractures or low bone density) zoledronic acid treatment. In the final analysis at 60 months of follow-up, patients receiving immediate zoledronic acid showed significant benefits in lumbar spine BMD compared to those with delayed treatment, with increases of +4.3% and −5.4%, respectively. Furthermore, analysis based on prior chemotherapy showed significant differences in BMD between the two treatment groups. Patients with prior chemotherapy in the immediate zoledronic acid group had a BMD increase of +3.65%, while the delayed treatment group showed a decrease of −5.784%. This suggests that both chemotherapy and AI therapy may adversely affect bone density in EBC patients (71). In postmenopausal patients, the evidence regarding the use of adjuvant bisphosphonates is relatively comprehensive. However, the HOBOE-2 trial compared the efficacy of single-agent TAM, single-agent letrozole, and letrozole combined with zoledronic acid in premenopausal patients. With a median follow-up of 64 months, significant differences were observed among the three groups. Subsequent pairwise comparisons revealed that, across all groups, the zoledronic acid group demonstrated the most pronounced DFS benefit. But there was no significant difference in OS among the three groups (72).

Another bone-modifying agent, denosumab, a fully human monoclonal antibody that can bind to the receptor activator of nuclear factor-kappa B ligand (RANKL) to block its binding with RANK, is a precise bone-targeted drug commonly used to improve bone loss and counteract bone metastasis. ABCSG-18 investigated the correlation between denosumab and DFS and OS in postmenopausal EBC patients. Multiple data reports consistently indicated that the denosumab group had benefits over the placebo group. Absolute benefits at 5 and 8 years were 1.9% and 3.1%, respectively. After a median follow-up of 73 months, the denosumab group continued to benefit in terms of DFS (95% CI: 69–98%, Cox P=0.02), with similar rates of adverse events and serious adverse events between the two groups (73). However, the D-CARE study's conclusions seem contradictory to ABCSG-18. Denosumab for 5 years appeared to not significantly improve the primary endpoint bone metastasis-free survival compared to placebo, with no significant benefits observed in any subgroup, specifically focusing on postmenopausal patients, similarly yielding no benefits. The specific reasons for the contradictory results of the two studies are unclear, but D-CARE employed a more intensive dosing regimen and higher drug doses (74). Currently, there are no head-to-head studies comparing the efficacy of zoledronic acid and denosumab in EBC. However, in a trial comparing denosumab with zoledronic acid, denosumab was shown to delay the time to first skeletal-related event but did not demonstrate significant benefits in terms of DFS or OS. Whether this study's conclusions can be extrapolated to EBC is uncertain. Apart from the above, the established advantages of denosumab include minimal renal toxicity and simpler administration. Therefore, based on previous research, the latest NCCN guidelines only recommend the use of zoledronic acid as adjuvant therapy to improve bone density and prognosis in postmenopausal women, with no clear evidence supporting the definite benefits of adjuvant denosumab use in this stage.

Olaparib is a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor that induces tumor cell death by blocking the repair of damaged DNA in cancer cells, particularly those with inherent *BRCA* gene mutations, which already have defective DNA repair mechanisms (60). The Olympia trial enrolled HER2⁻ EBC patients with germline *BRCA1* or *BRCA2* mutations and high-risk clinical-pathological features who received local treatment and (neo)adjuvant chemotherapy. The study evaluated the efficacy difference between 1 year of olaparib and placebo. At a median follow-up of 3.5 years, the olaparib treatment group demonstrated sustained benefit over placebo iDFS, with an absolute benefit of 7.3% at 4 years. Unlike the initial interim analysis where significant differences in 4-year OS first appeared, the olaparib group showed an absolute benefit of 3.4% in OS. Additionally, focusing on HR⁺/HER2⁻ patients, who constituted 17.8% of the total population, a smaller subset was enrolled. Given that most mutations in HR⁺ BC patients are of the *BRCA2* type, we observed a trend towards benefit in both the *BRCA2* and HR⁺/HER2⁻ subgroups, although less pronounced compared to the overall population (75,76). In HR⁺ BC, according to European Society for Medical Oncology (ESMO) guidelines, olaparib is recommended for patients who have completed (neo)adjuvant therapy and have four or more positive lymph nodes or non-pathological complete response with a CPS + EG score ≥3.

When patients meet the enrollment criteria for both MonarchE Cohort 1 and the Olympia study, although there is no specific clinical trial demonstrating the efficacy of abemaciclib in combination with olaparib for HR⁺ high-risk BC patients, current evidence from comprehensive

systematic reviews suggests that this combined treatment may be beneficial. Both national and international experts, along with the latest NCCN guidelines, consider the addition of olaparib to abemaciclib as a potentially beneficial alternative for patients eligible for abemaciclib who also have *BRCA1/2* mutations. However, the optimal sequence of administration remains unclear.

Conclusions

In summary, while HR⁺ BC generally has a better prognosis compared to other subtypes, patients with certain clinical high-risk factors still face a heightened risk of recurrence. Adjuvant ET intensification has shown potential to further reduce recurrence risk in high-risk patients and improve DFS or iDFS, significantly improving patient outcomes. In recent years, with the maturation of evidence-based medicine, the introduction of novel agents such as SERDs, CDK4/6 inhibitors, and PARP inhibitors has diversified treatment options. Despite these advancements offering hope, further research is needed to determine the optimal treatment duration, sequencing, and combination strategies to achieve superior therapeutic outcomes. Looking ahead, precision medicine based on molecular characteristics will continue to advance the individualization and precision of BC treatment, ultimately enhancing both survival and quality of life for patients.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-16/rc

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