Systematic Review

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Evolving Concepts and Contemporary Management of Early-Stage Breast Cancer: An Evidence-Based Approach to Grey Zones from a Comprehensive Breast Unit Part 2: Systemic Treatment

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ABSTRACT

Breast cancer represents the most frequently diagnosed malignancy among women globally, with significant progress in systemic therapy, surgical techniques, and radiotherapy contributing to improved clinical outcomes. However, many clinical scenarios encountered in daily practice are not fully addressed by randomized trials, leaving persistent grey zones in the management of early-stage breast cancer. To meet these challenges, the multidisciplinary panel at Research Institute of Senology, Acıbadem University outlined experience-based recommendations for clinical situations typically faced in daily practice. Herein we aim to reflect both current evidence and institutional practice and provide practical guidance in areas where uncertainty persists. As breast cancer treatment continues to evolve, updates will be required to integrate emerging data and refine individualized patient care.

Keywords: Breast cancer; early-stage; multidisciplinary; oncology; systemic

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Key Points

- Integrating genomic assays with traditional clinicopathologic factors allows clinicians to more accurately identify patients who can safely avoid chemotherapy and those who require treatment escalation.
- The addition of CDK4/6 inhibitors to endocrine therapy has emerged as an effective option for selected patients with high-risk disease, though careful consideration of toxicity, cost, and survival data is required.
- Continuing hormonal therapy beyond five years can reduce the risk of late recurrence in selected patients; newer prognostic tools can help determine which patients will benefit most.
- Trastuzumab-based therapy combined with chemotherapy is the cornerstone of treatment for human epidermal growth factor receptor 2 (HER2)-positive early breast cancer, with de-escalation or escalation strategies tailored to individual risk.
- Neoadjuvant treatment plays a crucial role in HER2(+) and triple-negative breast cancers, allowing early assessment of response and enabling a more tailored treatment approach that optimizes outcomes and guides postoperative management.

Introduction

Breast cancer (BC), consistently reported as the most frequent cancer in women with an estimated 2.3 million new cases leading to 670,000 deaths in 2022, has an uneven global burden that highlights the urgent need for standardized and unrestricted access to comprehensive management strategies (1). As a result of exceptional efforts by pre-clinical and clinical researchers worldwide, substantial advances in the understanding of biology and treatment have been achieved, leading to a 2.5% decrease in mortality, as reported in some high-income countries (2). However, because not all clinical scenarios correspond to clinical-trial settings, routine management of BC requires a personalized, evidence-guided approach tailored to each patient's needs.

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Herein, we provide practical recommendations for common clinical questions that arise during our weekly multidisciplinary tumor board meetings. The problems addressed here reflect our personalized approach, which aligns with emerging data on evolving clinical scenarios that we encounter in our daily practice at the Research Institute of Senology of Acıbadem University (RISA). We acknowledge that some of our statements may not be supported by strong evidence or may not be generalizable to all patients because of disparities in medical care, patient preferences, or limited availability of treatments. However, we believe that the recommendations included in this report will provide many physicians involved in BC care nationwide with guidance on a range of challenging and controversial issues. At RISA, we aimed to develop institution-specific standards to guide the evaluation and management of patients with early-stage disease. Our panel is a multidisciplinary team in an academic clinical setting specialized in BC, comprising general and plastic surgeons, medical oncologists, radiation oncologists, radiologists, clinical geneticists, a pathologist, and supportive medical personnel, including nurses, physiotherapists, nutrition specialists, and a psychologist. Initially, each clinical group identified clinical questions that were clinically relevant because of lack of robust data, pending data from clinical trials, or unique scenarios that could not be addressed by the available evidence and therefore required expert opinion. All these questions were discussed in detail in a separate meeting, and if a consensus on an issue was not reached, alternative opinions were put to a vote to determine the approach that best reflected the recommendations of the experts on the panel.

Since treatment of BC is rapidly evolving, the statements reported as RISA opinions may, in time, be challenged by emerging data from ongoing clinical trials. Therefore, this work will be updated every two years.

Clinical and Research Consequences

1. Systemic Treatment of Early-Stage Breast Cancer

1.1. Who Needs to be Referred for Predictive Genetic Testing?

1.1.1. Predictive Genetic Testing

In early-stage hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative [HR(+)/HER2(-)] BC, genomic assays serve as essential tools for guiding individualized adjuvant treatment decisions by distinguishing patients who are unlikely to benefit from chemotherapy and who can safely avoid its associated toxicity.

Candidates for these tests are patients with early-stage (stage I or II) HR(+)/HER2(-) BC who are node-negative (N0) or node-positive (N1), including premenopausal and postmenopausal patients (Table 1).

1.1.2. How Do We Manage Intermediate-Risk Patients?

1.1.2.a. Definition of the Patient With Intermediate Risk

Although a universally accepted definition of intermediate recurrence risk in early-stage HR(+)/HER2(-) invasive BC is lacking, specific anatomical and biological tumor characteristics may aid in risk stratification and guide treatment planning.

Tumors in this category are typically 2–5 cm in size and exhibit intermediate histologic differentiation (G2). Nodal involvement, if present, is usually limited to one to three lymph nodes. Hormone receptor expression is often low to intermediate, suggesting some degree of endocrine sensitivity, but not the robust responsiveness seen in low-risk tumors. Increasingly, genomic risk assessment tools provide additional refinement: an Oncotype DX recurrence score (RS) of 16–25, a MammaPrint profile showing high clinical but low genomic risk**,** or intermediate categorizations on Prosigna or EndoPredict assays are all consistent with this risk stratum. From a staging perspective, these tumors generally correspond

Table 1. Commercial genomic tests in early-stage HR(+)/HER2(–) breast cancer

	Gene panel	Prognostic role	Predictive role (chemo benefit)	Platform	Key trials
Oncotype DX	21 genes	Provides RS (0–100) estimating 10-year distant recurrence risk	Yes (for RS 11–25 in node-negative & RS ≤25 in 1–3 node-positive cases)	RT-PCR (FFPE tissue)	TAILORx (4), RxPONDER (5)
MammaPrint	70 genes	Classifies as genomic low vs. high risk	Yes (chemo benefit in high clinical/low genomic risk)	Microarray	MINDACT (6)
Prosigna (PAM50)	50 genes	ROR score + intrinsic subtype (e.g., luminal A/B)	Limited/indirect	NanoString nCounter	TransATAC (101), ABCSG-8 (102)
EndoPredict	12 genes + clinical data (EPclin score)	Estimates 10-year risk of distant metastasis combining molecular and clinical features	Limited (prognostic mainly)	RT-PCR (FFPE)	ABCSG-6/8 (102), GEICAM (103)
BC index	HOXB13:IL17BR ratio + MGI	Prognostic for late recurrence (beyond 5 years)	Yes (for extended endocrine therapy benefit)	RT-PCR	MA.17 (22), TransATAC (101)

ROR: Risk of recurrence; MGI: Molecular grade index; RS: Recurrence score; BC: Breast cancer; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2

to stage IIA or IIB according to American Joint Committee on Cancer criteria (3). The proliferation index also tends to be in a moderate range, with a Ki-67 between 10% and 25%**,** reflecting an intermediate biologic potential for recurrence. Further considerations for identifying intermediate-risk groups based on clinicopathologic findings are also discussed in Section 1.2. In conclusion, the data summarized so far highlight that the optimal use of adjuvant chemotherapy remains individualized.

1.1.2.b. Considerations Based on Clinicopathologic Factors and Predictive Genomic Tests

The key inclusion criteria for the choice of available tests are summarized in Table 2. In our practice, given financial considerations, choice is individualized, with preferential use of this approach for patients classified as borderline (gray-zone) risk.

1.1.3. Management of Intermediate-Risk Patient

The TAILORx trial (4), which focused mainly on the node-negative group, showed that premenopausal women aged ≤50 years with RS 16–25, particularly those with RS 21–25, benefited from chemotherapy, whereas postmenopausal women with RS 16–25 did not. Secondary analyses suggested that chemotherapy or ovarian suppression may also be considered for premenopausal patients with RS 16–20 if high-risk clinical features are present. For node-positive patients in the grey zone, the RxPONDER trial (5) concluded that postmenopausal women with RS ≤25 did not benefit from chemotherapy while premenopausal women with RS ≤25 had significant benefit in terms of invasive disease-free survival (iDFS) regardless of any high-risk criteria (5% improvement). In the MINDACT trial (6), patients with high clinical risk but low genomic risk were included. Although the chemotherapy benefit in women ≤50 years was modest (5%), it remained clinically meaningful and approached significance with longer follow-up. Nevertheless, the PlanB (7) trial demonstrated that patients with a low Oncotype DX RS (RS ≤11) could safely omit adjuvant chemotherapy regardless of nodal involvement. Among these patients, those treated with endocrine therapy (ET) alone achieved an excellent 5-year DFS rate, ranging from 91% to 94.4%.

It can be argued that across TAILORx, RxPONDER, and MINDACT, the chemotherapy benefit observed in premenopausal women was mainly due to chemotherapy-induced ovarian suppression. Notably, ET delivered to this patient group was suboptimal in these trials, with most patients receiving tamoxifen (TMX) as a single agent and ovarian function suppression (OFS) used in only 15–20% of cases. In current practice, OFS combined with an aromatase inhibitor (AI) is a reasonable alternative to chemotherapy for carefully selected premenopausal patients with favorable genomic risk.

The ADAPT trial (8) further personalized this approach by combining static genomic data with a dynamic early biological response, assessed by changes in Ki-67 after a short (3-week) course of preoperative ET. Chemotherapy was omitted for node-negative and 1–3-node-positive patients with RS ≤11 and for those with RS 12–25 who achieved a favorable Ki-67 response (≤10%) after 3 weeks of preoperative ET. On the other hand, persistently elevated Ki-67 was indicative of endocrine resistance and prompted initiation of chemotherapy. The 5-year iDFS rates in hormone-responsive tumors with RS <25 were reported as 93.2% in premenopausal patients and 92.8% in postmenopausal patients, supporting tailored de-escalation in selected estrogen receptors (ER)(+) cases. Prospective data from the high-risk stratum of the HR(+)/HER2(-) WSG-ADAPT trial (9) supported the view that low genomic risk could identify a subset with a favorable prognosis even among patients with more than four positive lymph nodes.

Based on these data, we recommend omitting chemotherapy in postmenopausal patients with RS ≤25. In premenopausal patients with low clinical risk and RS 16–20, OFS plus AI is favored as an alternative to chemotherapy, whereas we generally recommend chemotherapy for patients with high clinical risk and RS 16–20, as well as for those with an RS 21 or higher. For each patient, our multidisciplinary tumor board determines the most suitable management strategy through a comprehensive evaluation and discussion (Table 3).

1.2. How Do We Deliver Optimal Endocrine Therapy in Premenopausal Patients?

1.2.1.a. LHRH Analogues

SOFT and TEXT (10) prospectively evaluated luteinizing hormone-releasing hormone (LHRH) analogues combined with either exemestane or TMX in premenopausal women with BC. In the joint long-term analysis, exemestane plus OFS conferred the largest absolute distant disease-free survival benefit (approximately 10–15%) among very young patients and those with high-risk features (age

Table 2. Inclusion criteria for major genomic assay trials in early-stage HR(+)/HER2(–) breast cancer

Study name	Assay	Key inclusion criteria
TAILORx (4)	Oncotype DX	- Node negative - Tumor size >10 mm, or 6–10 mm with high-risk features (e.g., grade 2–3 or lymphovascular invasion) - Oncotype DX RS 0–25 randomized
RxPONDER (5)	Oncotype DX	- 1 to 3 positive axillary LN - Oncotype DX RS ≤25 - Both premenopausal and postmenopausal women included
MINDACT (6)	MammaPrint	- Women with early-stage breast cancer [HR(+) or HR(–); HER2(–) or HER2(+)] - Tumor size ≥1 cm - Node-neg or 1–3 positive LN - Clinical risk assessed using modified adjuvant! Online criteria - Eligible if MammaPrint result was low risk

RS: Recurrence score; LN: Lymph nodes; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2

<35, chemotherapy-treated, grade 3, Ki-67 ≥20%, T2, or 1–3 positive nodes). The benefit was also observed in women <40 and in those who remained premenopausal after chemotherapy. A STEPP-based composite risk model identified the greatest gain (~15%) among patients aged 35–39 with grade 3 tumors, Ki-67 ≥26%, and 1–3 nodes; a modest gain (4–6% at 8 years) among intermediate-risk profiles; and a minimal gain (~1%) among low-risk patients (no chemotherapy, age 40–44, T1N0, grade 1–2, ER/PR ≥50%, Ki-67 14–19%) (11). The outcomes of these prognostic clinical scenarios have recently been confirmed by a 15-year follow-up analysis (Table 4) (12).

The role of OFS was also evaluated in a patient-level meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group (EBCTCG), which demonstrated a significant and consistent benefit of combined endocrine treatment in patients who remained premenopausal after chemotherapy and in those who did not receive chemotherapy, across all age groups and irrespective of nodal status (Table 5) (13).

1.2.1.b. Aromatase Inhibitors

Although there have been numerous trials investigating the role of AIs in premenopausal patients, the benefit of AIs per se cannot be ascertained from the current evidence because AIs can only be used in combination with LHRH analogues in this setting.

The TEXT and SOFT trials, which provide the most robust data with the largest sample sizes, have shown that a 5-year combination of exemestane and triptorelin yields significant benefits in distant DFS and overall survival (OS) in higher-risk populations compared with TMX. This benefit was observed regardless of whether TMX was used as a single agent or in combination with OFS, as summarized above (Table 1).

The role of AI in premenopausal patients was also evaluated in a patient-level meta-analysis by the EBCTCG, which showed an absolute benefit of 3.2% in recurrence risk within the first four years after diagnosis; this benefit declined with further follow-up and did not translate into an OS benefit (14). The apparent absence of survival benefits, compared with the previous meta-analysis, could be attributed to the shorter follow-up in the current analysis, since substantial evidence demonstrates a significant benefit of AIs, especially in those with a higher risk of recurrence, as summarized above (15).

1.2.1.c. Risk-Based Clinical Scenarios in Endocrine Therapy

In parallel to the available evidence, we generally prefer to use LHRH analogues combined with AIs in high-risk patients requiring chemotherapy (node positive disease with a high-grade tumor or Ki-67 ≥20%; PR <20%, or those with a high risk of recurrence based on a genomic assay); or younger women aged ≤35 years. Nevertheless, we acknowledge that age is a continuous variable in clinical decision-making. In fact, subgroup analyses from the SOFT-TEXT trials, as well as from TAILOR-X, evaluating the role of chemotherapy compared with ET in those with intermediate-risk disease, have suggested that there is a benefit of chemotherapy in those younger than 40 years, whereas the small benefit observed in the 40–45-year age group may be attributable to the endocrine effects of chemotherapy (16). Therefore, we generally increase the age cutoff to 40 years in intermediate-risk patients for whom a combined endocrine approach with either TMX or AI is considered, regardless of prior chemotherapy. Although it is not possible to define a clear-cut patient profile, some clinical scenarios in which we can opt for combined ET include: intermediate-risk patients with an intermediate genomic risk, as determined by predictive genetic testing if available; or those aged 40–45 years who present with Luminal A or Luminal B disease, T2N0, grade 2–3

Table 3. Recommended treatment strategies for intermediate-risk patients

Patient profile	Recommended treatment
Postmenopausal, RS ≤25	Endocrine therapy alone
Premenopausal, RS ≤15 Premenopausal RS 16–20 & low clinical risk (node-neg)	Endocrine therapy (Tamoxifen only+/-OFS)
Premenopausal, RS 16–20 & high clinical risk Premenopausal, RS 21–25 & node-neg or 1–3 node-positive	Chemoendocrine therapy or OFS + AI as potential alternative (individualized decision-making needed)
Premenopausal, clinical high/genomic low risk [MINDACT (5)]	Chemotherapy debatable — strong endocrine therapy (OFS + AI) may be a suitable alternative

RS: Recurrence score; OFS: Ovarian function suppression; AI: Aromatase inhibitor

Table 4. Long-term follow-up analysis of TEXT and SOFT trials comparing combined endocrine therapy with single-agent TMX in high-risk subgroups

15-year OS (%)	E+OFS	TMX+OFS	TMX
Age <35y	79.4	75.6	
Age 36-39y	83.1	79.5	
Grade 3	SOFT: 82.9 TEXT: 80.6	SOFT: 74.8 TEXT: 76.2	SOFT: 74.6 TEXT: NA
Prior CTx	SOFT: 81.0	SOFT: 77.1	SOFT: 76.8

OS: Overall survival; E: Exemestane; OFS: Ovarian function suppression; TMX: Tamoxifen; CTx: Chemotherapy

tumors, or 1–3 involved lymph nodes, with a Ki-67 of 20–25%, as indicated by subgroup analyses of the TEXT and SOFT trials. An estimated 8-year absolute gain in distant recurrence-free survival (RFS) of 4% was observed, and this gain was more pronounced in the group that had not received prior chemotherapy. Notably, these data were during an earlier period when genomic tests were not widely available, and adjuvant therapy decisions were based solely on clinicopathologic features. Clinical judgment regarding the administration of combined ET must be individualized, incorporating shared decision-making with the patient through a comprehensive discussion of potential benefits, long-term toxicity, and the critical role of adherence.

1.2.1.d. Monitoring Menopausal Status During Endocrine Therapy

Based on evidence from the SOFT and the ASTTRA trials (17, 18), we discuss LHRH analogues as an add-on therapy for some patients with intermediate-risk disease. These patients are those who remain premenopausal following chemotherapy and display persistent ovulatory activity, based on physical examination and hormone measurements [high levels of estradiol and anti-müllerian hormone (AMH) and low levels of follicle-stimulating hormone (FSH)], indicating suboptimal endocrine suppression, or who show significant and persistent endometrial hyperplasia on TMX during follow-up examinations.

1.2.1.e. Duration of LHRH Analogues

Due to the lack of data on extended treatment durations, we generally recommend administering LHRH analogues for five years, consistent with the SOFT and TEXT trials. However, for patients experiencing a significant decline in quality of life due to severe menopausal symptoms, a two-year treatment period may be considered, as suggested by the ASTTRA trial (18).

1.2.1.f. Duration of Endocrine Therapy

Extended adjuvant ET is a reasonable option for endocrine-responsive BC at higher risk of late recurrence, but robust prospective data for premenopausal women remain limited. The ATLAS and aTTom trials, each of which enrolled only about 8% premenopausal participants, showed that extending TMX for an additional 5 years reduced recurrence and BC mortality, especially among node-positive patients. Nevertheless, the NSABP B-14 trial, which focused exclusively on node-negative patients, 26% of whom were premenopausal at diagnosis, failed to identify any benefit, suggesting that patients at lower risk may not require extended ET (19-21). However, there is evidence that menopausal status at the time of extension is pivotal. The MA-17 trial (22) found that letrozole administered for 5 years following 5 years of TMX improved DFS, with the greatest effect in women who were premenopausal at initial enrollment [hazard ratio (HR) 0.26 vs 0.67 for women who were postmenopausal at enrollment]. Although the benefit in node-negative patients could not be evaluated because of the small sample size, a clinically meaningful advantage was observed in node-positive patients (4-year DFS 93.8% vs 85.0%; HR 0.40), supporting extended AI therapy in higher-risk patients.

Based on evidence from these trials, we generally offer an additional 5 years of TMX or AIs after completion of an initial 5 years of ET, regardless of prior OFS use, for patients with stage II or III disease. However, in intermediate-risk patients with stage I-II disease, we consider a shorter total ET duration of 6–8 years, depending on changes in menopausal status and the toxicity profile. This approach is based on extrapolated evidence from multiple trials that have evaluated the role of the TMX-AI switch in the context of a shorter overall duration of ET, as summarized below.

1.2.1.g. Optimal Endocrine Therapy for Invasive Lobular Carcinoma

Invasive lobular carcinoma (ILC) has been associated with poorer long-term outcomes compared with invasive ductal carcinoma in large retrospective registry studies (23, 24). Preclinical and clinical data suggest distinct clinical and genomic profiles with different therapeutic implications (25). A recent subset analysis of the SOFT and TEXT databases showed a greater benefit in BC-free interval with exemestane plus OFS, consistent with findings from retrospective single-institution series (Table 6) (26, 27). Based on the limited available evidence, we generally recommend upfront combined ET for patients who present with intermediate- to high-risk ILC, and we discuss this option with those at lower risk of recurrence. Some patients may be considered for add-on LHRH analogues and may subsequently switch to an AI, depending on individual risk and toxicity profiles, as discussed above.

1.2.2. How Do We Deliver Optimal Endocrine Therapy in Postmenopausal Patients?

1.2.2.a. Definition of Menopause

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity and is confirmed after 12 consecutive months of amenorrhea in the absence of another pathological or physiological cause (28). Similarly, amenorrhea alone does not confirm menopause for up to 12 months following chemotherapy; therefore, a composite evaluation of ovarian functional status and biochemical criteria is required to assess menopausal status. Menopause typically occurs between 45 and 55 years of age, with a global mean of about 51 years. Universally accepted hormonal thresholds are FSH >40 IU/L and estradiol <20 pg/mL, whereas AMH levels, which decline during perimenopause, are usually undetectable (<0.1 ng/mL) at menopause (29).

1.2.2.b. Adjuvant Treatment Options for Postmenopausal Patients

Compared with TMX, AIs are more frequently used in the adjuvant treatment of postmenopausal early-stage BC patients. Several studies have evaluated the efficacy of AIs in early-stage postmenopausal BC: as upfront, sequential (switch), or extended adjuvant treatment (30, 31). Both upfront and switch strategies have demonstrated that AIs provide superior DFS compared with TMX in postmenopausal HR(+) patients. Large trials such as ATAC and BIG 1-98 (31, 32) confirmed the benefit of anastrozole and letrozole over TMX without a corresponding improvement in OS; by contrast, switch trials [IES (30), ITA (33), ABCSG-8 (34), ARNO (34)] demonstrated improved outcomes when patients transitioned to an AI after 2–3 years of TMX. A meta-analysis further established that both upfront and switch approaches reduce recurrence and BC mortality compared with continued TMX, although OS benefits remain modest (15).

Table 5. Combined endocrine treatment compared to single-agent therapy

20-year mortality (%)	OFS	Control
BC related	23.8%	34.7%
All cause	30.4%	42.0%

OFS: Ovarian function suppression; BC: Breast cancer

ET has been administered in various studies using different schedules and durations; however, the optimal duration remains unclear. Based on the studies mentioned, we recommend that postmenopausal patients with early-stage BC receive either 5 years of upfront adjuvant AI or 2–3 years of TMX followed by an AI to complete a total of 5 years of ET.

1.2.3. Extended Endocrine Treatment

Despite the efficacy of 5 years of adjuvant hormonal therapy in HR(+)/HER2(-) postmenopausal early-stage BC patients, prolonging ET appears to be a reasonable approach given the continued risk of recurrence. However, the optimal total duration remains undefined. Several studies have sought to answer this question (Table 7). The DATA trial (35) investigated the efficacy of 2–3 years of TMX followed by either 3 or 6 years of anastrozole and observed a significant DFS benefit with extended ET in lymph node-positive patients [84.4% *vs.* 76.2%, HR: 0.64, 95% confidence interval (CI): 0.46–0.89, p = 0.0075] and in those with tumors ≥2 cm (82.7% *vs.* 69.2%, HR: 0.53, 95% CI: 0.53–0.82, p = 0.0031).

The AERAS and NSABP B42 studies (36, 37) compared 5-year versus 10-year durations of adjuvant AI treatment. In both studies, extended ET was associated with improved DFS compared with shorter ET. No significant difference in OS was observed in either trial. The ABCSG-16 (SALSA) trial (38) also did not find a significant difference between the two arms in terms of DFS, but the 10-year arm had a higher incidence of osteoporosis-related fractures. The MA.17R phase III study showed that longer ET reduced the annual incidence of contralateral BC (49% *vs.* 21%; HR: 0.42; 95% CI: 0.22–0.81).

As discussed above, the optimal duration of extended ET remains unclear. Therefore, the decision should be made on a patient-specific basis. We recommend using an AI for 5 years after 2–3 years of TMX, or for 5 years after an initial 5 years of TMX. Five to ten years of TMX may be considered in postmenopausal patients who have contraindications to, or are unable to tolerate, AIs.

Table 6. Twelve-year BC-free interval from SOFT and TEXT trials based on histologic subgroups

12-year BCFI (%)	Tx	n	n	Tx HR	Tx HR
SOFT (21)		IDC	ILC	IDC	ILC
Luminal A-like	E+OFS	190	31	0.60 (0.35–1.04)	0.16 (0.03–0.78)
	T	183	20		
Luminal B-like	E+OFS	380	24	0.74 (0.54–1.03)	0.58 (0.14–2.33)
	T	407	22		
SOFT+TEXT (15)					
Luminal A-like	E+OFS	341	65	0.93 (0.59–1.47)	0.48 (0.15–1.56)
	T+OFS	350	73		
Luminal B-like	E+OFS	952	79	0.64 (0.52– 0.79)	0.70 (0.31–1.58)
	T+OFS	979	67		

BCFI: Breast cancer free interval; Tx: Treatment; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; E: Exemestane; TMX: Tamoxifen; OFS: Ovarian function suppression; HR: Hazard ratio

Table 7. Clinical trials evaluating extended endocrine therapy in early-stage breast cancer

Trial	Population	Treatment	5-year DFS	5-year OS
AERAS (36)	After 5 years of AI	Anastrozole 5 more years *vs.* stop	91.9% *vs.* 84.4% (p = 0.0004)	Not reported
NSABP B42 (37)	Prior AI or sequential ET	Letrozole 5 years *vs.* placebo	75.9% *vs.* 72.6% (10y) (p = 0.01)	NS
ABCSG-16 (38)	After 5-years of AI or TMX	Anastrozole 2 *vs.* 5 years	73.9% *vs.* 73.6% (p = 0.9)	87.5% *vs.* 87.3% (NS)
MA.17R (22)	Completed 10 years (5TMX + 5 AI)	Letrozole 5 years *vs.* placebo	95% *vs.* 91% (p = 0.01)	93% *vs.* 94% (p = 0.83)
DATA (35)	Completed 2-3 years of TMX	Anastrozole 3 *vs.* 6 years	69.2% *vs.* 66% (10y) (p = 0.073)	79.4% *vs.* 83.1% (p = 0.60)

DFS: Disease free survival; OS: Overall survival; AI: aromatase inhibitor; ET; Endocrine treatment; TMX: Tamoxifen; NS: Not significant

1.2.3.a. Biomarkers Predictive of Benefit from Extended Endocrine Therapy

Several studies evaluated predictive biomarkers to identify patient subgroups most likely to benefit from extended ET. These efforts led to the identification of the clinical treatment score post-5 years (CTS5) and the breast cancer index (BCI) as useful markers with the potential for routine clinical use.

CTS5 is an online tool designed to estimate the risk of late recurrence in postmenopausal patients who have completed 5 years of adjuvant ET. Using data from the ATAC and BIG 1-98 trials, CTS5 calculates late recurrence risk based on tumor size, tumor grade, the number of involved lymph nodes, and the patient's age at diagnosis (32, 39). In a retrospective analysis, the 10-year distant recurrence risk was reported as 2.9% in the CTS5 low-risk group, 7.2% in the intermediate-risk group, and 12.9% in the high-risk group (40). It was noted that extended ET may be beneficial for patients in the high-risk group.

Another potential predictor of benefit from extended ET is BCI. BCI combines two gene expression signatures that evaluate the response to ET. Secondary analyses of the MA.17, Trans-aTTom and IDEAL trials (41) showed that extended ET significantly improved DFS compared with the control group in HR(+) T1-T3 tumors, whether lymph node-negative or -positive with a high BCI (H/I) ratio.

Our recommendation is that extended ET be implemented after a comprehensive discussion with each patient, based on the available evidence. Patients most likely to benefit from extended ET:

1.High clinical risk factors;

a) Positive lymph nodes (especially >3)

b) Larger tumor size (≥T2)

c) High histologic grade (grade 2-3)

d) Lymphovascular invasion

e) Younger postmenopausal age (<60 years)

2.High genomic risk (if available): BCI predicts benefit from extended ET.

1.3. Whats is the Role of CDK4/6 Inhibitors in Adjuvant Setting?

Adjuvant CDKi, which have demonstrated marked efficacy in metastatic BC, have been extensively evaluated in earlier stages to prevent recurrence (42-44).

Four major randomized trials—PALLAS and PENELOPE-B (palbociclib), monarchE (abemaciclib), and NATALEE (ribociclib)—investigated these agents in the adjuvant setting (45-49). While the PALLAS and PENELOPE-B trials failed to show a statistically significant improvement in iDFS, both monarchE and NATALEE reported clinically meaningful improvements in iDFS in selected high-risk populations (47, 48). These results led to regulatory approvals and the incorporation of abemaciclib and ribociclib into major guidelines (e.g., National Comprehensive Cancer Network, European Society for Medical Oncology) for adjuvant use in HR(+)/HER2(–) early-stage BC patients at increased risk. However, several challenges persist: OS data for ribociclib remain immature; treatment discontinuation rates are substantial (up to 36%); toxicity profiles differ; and cost-effectiveness remains debated. Additionally, differences in trial design (e.g., inclusion criteria, risk definitions), treatment duration (2 *vs.* 3 years), endocrine backbone (AI *vs.* TMX), and menopausal status are critical factors that should be considered before widespread implementation.

1.3.1. Optimal Use of Adjuvant CDK Inhibitors

Among CDK4/6i investigated in the adjuvant setting, abemaciclib and ribociclib have shown the most robust efficacy in high-risk HR+/HER2– early BC. Table 8 summarizes the characteristics and results of the monarchE and NATALEE trials. The monarchE trial included patients with residual disease following neoadjuvant treatment (NAT), and subgroup analyses suggest that this cohort derived a substantial benefit from abemaciclib. However, the PENELOPE-B trial, which enrolled a similar NACT-exposed population, failed to demonstrate a benefit from palbociclib (HR: 0.93; p = 0.525) (46). This highlights the importance of differences in drug potency, pharmacokinetics, and treatment duration (Table 9). While both abemaciclib and ribociclib have demonstrated clinical utility, we individualize their use based on patient-specific clinical features. Given its shorter treatment duration and greater absolute iDFS benefit, abemaciclib appears to be the optimal choice for high-risk patients who have a high tumor burden or residual disease following NACT. Ribociclib, given its longer treatment window and broader eligibility criteria, may be preferred for a broader range of node-positive patients and considered in node-negative patients with high-risk biological features irrespective of chemotherapy use (47).

At our institution, we generally recommend adjuvant CDK4/6i, particularly for patients meeting the MonarchE or NATALEE criteria, based on results of the corresponding phase III trials showing improved iDFS in high-risk HR(+)/HER2(–) early-stage BC. We tend to use ribociclib in patients with high-risk, node-negative disease or

Table 8. Baseline characteristics of patients and updated efficacy outcomes of NATALEE and monarchE trials

	No of patients	Eligibility criteria	Treatment regimen	Prior chemotherapy	Treatment duration	iDFS	dRFS
NATALEE (47)	5.101	Stage II–III, incl. T2N0 + Ki-67 ≥20%, grade 3, or high genomic score (RS >26)	Ribociclib 400 mg/ day (3w on/1w off) + ET	65%	3 years	90.7% *vs.* 87.6% (3y) (Δ3.1%)	92.9% *vs.* 90.2%
monarchE (48)	5.637	≥4 positive nodes or 1–3 nodes + grade 3 or tumor size ≥5 cm	Abemaciclib 150 mg BID + ET	95%	2 years	83.6% *vs.* 76.0% (5y) (Δ7.6%)	88.4% *vs.* 82.5% (4yr)

RS: Recurrence score; ET: Encodrine treatment; BID: Twice a day; iDFS: Invasive disease-free survival; dRFS: Distant relapse-free survival

with microscopic nodal involvement. However, because of the lack of OS data, high cost, significant toxicity and limitations arising from informative censoring bias (as mentioned earlier), we discuss the available data with our patients to ensure an individualized approach and shared decision-making. We acknowledge that use of adjuvant CDK4/6i should be reserved for selected high-risk patients until final survival results from the phase III trials and translational data to guide identification of subgroups who may derive greater benefit are available.

Table 9. Gray zones in early breast cancer

Definition of intermediate-risk patients	-2–5 cm, intermediate histologic differentiation (G2) -One to three lymph nodes -Hormone receptor expression low to intermediate -Oncotype DX recurrence score of 16–25 -MammaPrint profile showing high clinical but low genomic risk -Ki-67 10–25%
Management of intermediate-risk patients	Refer Table 3
Rsk-based endocrine treatment (combined LHRH analouges with AIs)	-Node positive disease with a high-grade tumor or Ki-67 ≥20%, PR<20% -High risk of recurrence based on a genomic assay -Younger women aged ≤40 years. -Aged 40–45 years presenting with Luminal A or Luminal B, T2N0 grade 2-3 tumors or 1–3 involved lymph nodes with a Ki-67 20–25%
Duration of endocrine therapy (premenapousal)	-Stage II-III; 5 years of extended TMX or AIs following completion of an initial 5 years of endocrine therapy, regardless of prior OFS use. -Stage II-II disease Intermediate-risk patients; 6-8 years of ET depending on the changing menopausal status and toxicity profile
Duration of endocrine therapy (postmenapousal)	-5 years of upfront adjuvant AI or 2–3 years of TMX followed by an AI to complete 5 years of total ET - AI for 5 years following 2–3 years of TMX, or for 5 years following an initial 5 years of TMX (high-risk)
Extended endocrine therapy benefit	1. High clinical risk factors; a) Positive lymph nodes (especially >3) b) Larger tumor size (≥T2) c) High histologic grade (grade 2-3) d) Lymphovascular invasion e) Younger postmenopausal age (<60 years) 2. High genomic risk (if available): BCI predicts benefit from extended ET.
Adjuvant CDK4/6 inhibitor use	- High-risk patients with high tumor burden or residual disease following neoadjuvant treatment -High risk node-negative patients: should be individualized based on clinical and pathological features, genomic profiling (e.g., Oncotype DX, MammaPrint), and patient preferences Alternative in highly selected patients.
Replacing chemotherapy with ET+CDKi	- Postmenopausal women with strongly HR(+)/HER2(–), node-negative or limited node-positive disease, who have intermediate proliferation indices (Ki-67 <20%) and wish to avoid chemotherapy - Frail patients or ones with comorbidities, where chemotherapy-related toxicities pose unacceptable risks - Patients with low genomic but high clinical risk, where endocrine sensitivity is strong and risk of residual disease is modest
Adjuvant CDKi use in BRCA carriers	Sequential use of olaparib followed by CDK4/6i may be considered in select patients with a high risk of recurrence
Anthracycline use	- Less endocrine sensitive, -Luminal B, -Nod-positive stage II/III, -MP-H2 and Oncotype Dx RS ≥31 -For TNBC, tumors ≥1cm and in neoadjuvant treatment of stage II/III disease

Table 9. Continued

Omission of chemotherapy	-T1aN0 TNBC - T1N0 TNBC with histology of adenoid cystic carcinoma, secretory carcinoma, and low-grade adenosquamous carcinoma - Elderly (≥70 years) or frail patients with HER2(+) BC, especially those with small tumors or substantial comorbidities - HER2(+) tumors <3 mm
Adjuvant olaparib use	- Adjuvant treatment of *gBRCA1/2m* and high-risk TNBC - Adjuvant treatment of *BRCA* carriers with residual disease and a CPS+EG score ≥3 in HR(+) -Consideration of adjuvant olaparib in high-risk patients with germline *PALB2* mutations
Neoadjuvant endocrine therapy	Although not routinely recommended; -In the geriatric patients with locally advanced disease and significant comorbidities with ER ≥50%, PR ≥20%, Ki-67 <20%, grade 1–2, N0–N1
Adjuvant therapy in *BRCAm* TNBC patients without pCR	Concomitant use of olaparib with pembrolizumab
Management of ER low patients	Like TNBC in the preoperative setting but ET is recommended in adjuvant setting
De-escalation of adjuvant treatment in HER2(+) BC	Consider shorter durations of adjuvant trastuzumab in patients with a lower risk for recurrence, such as stage I and HR(+) disease
Treatment of elderly, frail patient with HER2(+)	Trastuzumab monotherapy may be considered

1.3.1.a. High-Risk Node-Negative Disease and Adjuvant CDK4/6i Use

Given the favorable results reported in the NATALEE trial, the use of adjuvant CDK4/6i in high-risk node-negative patients has generated increasing interest.

Unlike the monarchE trial, which almost exclusively enrolled node-positive patients, the NATALEE trial included approximately 24% node-negative patients. In a prespecified subgroup of T2N0 patients (n = 285), ribociclib plus ET led to a 4-year iDFS of 92.1% versus 87.0% with ET alone, corresponding to an absolute benefit of 5.1% (HR: 0.666; 95% CI: 0.397–1.118). Although this difference did not achieve statistical significance, it is suggestive of benefit and warrants further exploration (49). In contrast, abemaciclib has not been evaluated in node-negative patients, because the monarchE trial excluded this population by design, restricting enrollment to patients with ≥4 positive nodes or to those with 1–3 positive nodes who also had additional risk factors. Thus, there is no evidence supporting the use of abemaciclib in node-negative, high-risk disease.

When considering the clinical utility of ribociclib in this population, the modest absolute benefit must be weighed against toxicity. In the NATALEE trial, grade ≥3 neutropenia occurred in 44% of patients, and 20% discontinued treatment; this included patients in the node-negative subgroup, raising questions about the validity of the iDFS benefit, especially in a relatively low-risk patient group (49). Additionally, the treatment duration of 3 years may pose a burden for patients with an otherwise favorable prognosis.

Given these factors, a universal recommendation for CDK4/6 inhibition in all high-risk N0 patients is not currently justified. Instead, we recommend that patient selection be individualized based on clinical and pathological features, genomic profiling (e.g., Oncotype DX, MammaPrint), and patient preferences (16). Results of ongoing translational studies are awaited to identify molecular predictors of benefit in this population. According to the St. Gallen 2025 Consensus, the use of CDK4/6 inhibitors in stage II disease should follow a risk-adapted, individualized approach (50).

1.3.1.b. Can We Replace Chemotherapy With ET+CDKi?

The prospect of replacing chemotherapy with ET plus a CDK4/6i in selected HR(+)/HER2(–) early-stage BC patients has emerged as a conceptually appealing strategy, particularly in the era of biologically tailored treatment. This approach is particularly appealing for postmenopausal women with low clinical risk but high genomic risk who wish to avoid chemotherapy. Confirmatory data have been obtained from the NATALEE trial, which showed a benefit from adjuvant ribociclib in a small subgroup of node-negative patients who did not receive adjuvant chemotherapy, as discussed in the previous section. Based on encouraging data from these as well as phase I neoadjuvant proof-of-concept trials, including the neoMONARCH (abemaciclib), NeoPAL (palbociclib), and FELINE (ribociclib) showing a rapid suppression of cellular proliferation by CDK inhibitors, further clinical studies have been planned to evaluate the role of a response-guided approach that aims to identify subgroups of patients who may be spared chemotherapy (51-53). However, direct head-to-head comparisons between CDK4/6-based ET and chemotherapy in the early-stage setting remain limited. To date, no phase III trial has demonstrated non-inferiority of ET plus CDKi over chemotherapy in terms of iDFS or OS. Thus, CDKi is not a substitute for chemotherapy in patients at high clinical risk, or in those with residual disease after NAT. Nonetheless, certain patient subgroups merit individualized consideration in our daily practice;
- Postmenopausal women with strongly HR(+)/HER2(–), node-negative or limited node-positive disease, who have intermediate proliferation indices (Ki-67 <20%) and wish to avoid chemotherapy,
- Frail patients or ones with comorbidities, where chemotherapy-related toxicities pose unacceptable risks,

- Patients with low genomic but high clinical risk, where endocrine sensitivity is strong and risk of residual disease is modest. Data from ongoing studies and real-world cohorts are awaited before adopting this approach in routine clinical practice. In conclusion, while ET plus CDK4/6i cannot universally replace chemotherapy, they may serve as a valid alternative in highly selected patients. Until robust comparative efficacy data emerge, shared decision-making, incorporating clinical, genomic, and patient-preference factors, remains the cornerstone of treatment selection.

1.3.1.c. Considerations of Adjuvant CDKi Use in BRCA Carriers

Patients with HR(+)/HER2(-) early-stage BC carrying germline *BRCA1* or *BRCA2* mutations (*gBRCAm*) represent a biologically distinct subgroup. Real-world and retrospective studies have suggested that treatment outcomes with CDK4/6i may be worse in patients with pathogenic *gBRCAm* BC compared with those with *gBRCAwt* disease (54, 55). BRCA mutations are often associated with concurrent alterations in genes such as RB1 and TP53, which may contribute to resistance to both ET and CDK4/6i. In fact, confirmatory data have been reported in a recent meta-analysis of twenty-two studies, which showed significantly inferior outcomes with CDK4/6i, driven by shorter PFS in the *gBRCA2m* subgroup (56). Despite these concerns, current evidence suggests that CDK4/6i combined with ET is still more effective than ET alone for *gBRCAm* patients (53). While awaiting data from ongoing trials, sequential use of olaparib followed by CDK4/6i may be considered in selected patients at high risk of recurrence (57).

1.4. Are Adjuvant Anthracyclines Required for All Patients?

1.4.1.a. Available Evidence for Adjuvant Anthracycline Use

Although anthracyclines became standard in the 1980s–1990s, data from the mid-2000s showed that anti-HER2 and taxane-based backbones could achieve comparable efficacy with less toxicity. A patient-level EBCTCG meta-analysis across HR(+) and HR(-) disease determined that sequential use of anthracycline→taxane (AC-T) was broadly comparable to six cycles of docetaxel–cyclophosphamide (TC), with only a small overall advantage for anthracyclines, driven by concomitant anthracycline–taxane schedules that are rarely used today, regardless of hormone-receptor and nodal status (58). In the ABC trial (59), although non-inferiority of TC6 versus TaxAC was not met in the intention-to-treat population at approximately 7 years of follow-up, any clinical benefit from anthracyclines was confined to the ER-negative subset. Notably, a significant increase in leukemia risk and numerically higher cardiac deaths, together with a lack of OS benefit, do not support TC6 for most HR(+)/HER2(-) early BC. The West German Study PlanB trial (60) was a unique phase III study that evaluated the non-inferiority of TC6 versus EC-T, using either clinical or genomic risk criteria, in HER(-) early BC. Results showed that both regimens were equally effective in pN0 high-risk or pN1 with genomically intermediate-to-high-risk disease.

Data from the DBCG 07-READ trial (61), as well as other studies, are consistent with population-based case-control studies showing a higher 10-year cumulative incidence of HF with AC-T (4.1% vs 2.3%). In HER2(+) disease, BCIRG-006 trial (62) reported similar efficacy for anthracycline- and non-anthracycline trastuzumab backbones but more cardiotoxicity and leukemias with anthracyclines; while, de-escalation regimens such as 12-weekly paclitaxel–trastuzumab in the APT trial (63) and a longer non-anthracycline based chemotherapy with dual HER2 blockade in the TRAIN trial achieved excellent outcomes and high pathological complete response with lower toxicity (64).

Limited data exist specifically for patients with triple-negative BC (TNBC). Nevertheless, a recent meta-analysis of adjuvant chemotherapy in TNBC, including eight studies (n = 4292), showed non-inferiority of anthracycline-free regimens to anthracycline-based sequential regimens with respect to the risk of recurrence, but not to the risk of death (8).

1.4.1.b. Predictive Biomarkers of Anthracycline Benefit

Genomic stratification can identify subsets of HR(+)/HER2(-) early BC patients who preferentially benefit from anthracyclines. In the prospective real-world FLEX registry, MammaPrint ultra-high-risk (MP-H2) luminal B tumors had higher 3-year RFS with anthracycline-based therapy than with TC (97.7% *vs.* 86.4%); no advantage was seen for high-risk MP-H1 tumors (65). MP-H2 tumors were more frequently grade 3 and showed greater chemosensitivity, with a pathologic complete response (pCR) rate of 32% with AC-T versus 0% with TC (66). Complementary I-SPY data indicate that MP-H2 cancers share immune-related transcriptional features and clinical behavior with triple-negative disease, exhibit lower ER signaling (45% with ER 1–10% *vs.* 4% in MP-H1), and achieve higher pCR with pembrolizumab plus T-AC compared with MP-H1 (54% *vs.* 21%), consistent with anthracycline-sensitive, immunogenic biology (67). In TAILORx, among patients receiving chemotherapy, those with Oncotype DX RS≥31 experienced superior DRFI/DRFS/RFS with T-AC versus TC and showed a trend toward improved OS; benefit increased incrementally with higher RS scores when analyzed as a continuous variable, whereas no benefit was observed for patients with RS <31 (3). Approximately 58% concordance between RS≥31 and MP-H2 supports a shared aggressive phenotype in which anthracycline-containing regimens may be preferred over TC (4).

Another set of proposed predictive biomarkers to identify patients most likely to benefit from anthracyclines includes amplification or deletion (aberrations) of the *TOP2A* gene and chromosome 17 (CEP17) centromeric duplication. A pooled analysis of five trials reported improved outcomes with anthracycline-based therapy among patients harboring a *TOP2A* aberration or a CEP17 duplication (68).

1.4.1.c. Patients With HER2(+), TNBC and HR(+) Early BC Who Do Not Require Anthracycline-Based Adjuvant Chemotherapy

Contemporary evidence supports selective, rather than routine, use of anthracyclines, favoring non-anthracycline, taxane-based backbones in HR(+)/HER2(-) and many HER2(+) settings, while reserving anthracyclines for biologically or clinically high-risk subsets. In our practice, prefer anthracyclines for less endocrine-sensitive, luminal B, node-positive stage II/III, MP-H2, and Oncotype Dx RS ≥31 ER(+) BC. For TNBC, anthracyclines are essential components of adjuvant chemotherapy for tumors ≥1 cm and of neoadjuvant treatment of stage II/III disease, in combination with immunotherapy.

1.5. Which Patients Can Be Identified as Candidates for Omission of Chemotherapy?

Identifying patients in whom adjuvant chemotherapy can be safely omitted remains one of the most challenging aspects of early BC management, and is not within the scope of this paper. To optimize the risk-benefit balance for each patient, this decision requires careful integration of tumor biology, patient-specific factors, disease

characteristics, and available clinical evidence. Nevertheless, we specifically sought to examine the TNBC and HER2(+) subgroups, where the therapeutic boundaries are more clearly defined.

1.5.1. TNBC

1.5.1.a. T1a Disease

The management of very small TNBC, specifically T1a (≤0.5 cm) node-negative tumors, poses a clinical challenge, given the limited prospective data from randomized trials. Patients with T1a TNBC who did not receive adjuvant chemotherapy have consistently shown excellent outcomes in retrospective analyses, with 5-year dRFS rates ranging from 90% to 95% (69). Given the acute and long-term toxicities associated with systemic treatment, the absolute benefit of chemotherapy for this population is likely negligible. Our panel therefore concluded that patients with T1a, node-negative TNBC may safely omit adjuvant chemotherapy. However, for tumors measuring 4–5 mm, the potential for a minimal yet non-negligible benefit from adjuvant chemotherapy cannot be completely excluded. In these situations, individualized decision-making that integrates additional risk factors and includes a comprehensive discussion of the uncertain but possible advantages of systemic therapy is essential.

1.5.1.b. Low Risk TNBC Histology

The potential to omit chemotherapy also extends to certain rare histological variants of TNBC with favorable prognosis (70). Adenoid cystic carcinoma, secretory carcinoma, and low-grade adenosquamous carcinoma generally exhibit indolent behavior and excellent long-term outcomes despite their triple-negative immunophenotype. Our panel supports consideration of chemotherapy omission in patients with these special subtypes, particularly in T1N0 disease, following comprehensive multidisciplinary evaluation.

1.5.2. HER2(+) Disease

1.5.2.a. Frail Elderly Patients

The RESPECT trial (71) demonstrated that, in elderly patients (≥70 years) with HER2(+) BC, anti-HER2 therapy without chemotherapy may be considered in selected cases. This approach is particularly relevant for patients with significant comorbidities or functional limitations that preclude the safe administration of intensive chemotherapy regimens. Our panel supports the use of trastuzumab alone in elderly or frail patients with HER2(+) BC, especially those with small tumors or substantial comorbidities.

1.5.2.b. T1a Disease

Although HER2 amplification is generally associated with aggressive tumor biology, the absolute benefit of chemotherapy in very small tumors (≤5 mm) is limited. Our consensus emphasizes that chemotherapy plus trastuzumab may be omitted for selected patients with very small tumors, particularly those <3 mm. For tumors measuring 4–5 mm, however, chemotherapy plus trastuzumab should be considered, especially in HR(-) disease, which confers a higher risk of recurrence.

1.5.3. Optimal Use of Adjuvant Olaparib

The landmark OlympiA trial established olaparib as a new standard of care in the adjuvant setting for patients with *gBRCA1/2m* and high-risk early BC who had received neoadjuvant or adjuvant chemotherapy. This trial demonstrated significant improvements in both iDFS and OS (57).

1.5.3.a. TNBC

Among patients with TNBC and *gBRCA1/2m*, the evidence supporting adjuvant olaparib is strongest. Most patients with high-risk triple-negative disease, particularly those with node-positive disease or large primary tumors, undergo NAT. The management of TNBC patients with *gBRCA1/2m* who have residual disease following NAT requires careful consideration of all available options. The recently updated 6-year OlympiA analysis demonstrated a persistent benefit from adjuvant olaparib, with HRs of 0.72 for iDFS and 0.652 for OS (57). Based on these durable benefits, our panel recommends adjuvant olaparib for one year. Capecitabine administered for six months may be considered an alternative if olaparib is contraindicated or unavailable. For patients treated with neoadjuvant pembrolizumab, completion of the planned nine adjuvant cycles of pembrolizumab should remain a priority, with pembrolizumab administered in parallel with olaparib when feasible.

A subset of TNBC patients considered to have lower-risk disease proceeds directly to surgery. For BRCA carriers with either node-positive disease or a primary tumor ≥2 cm, as confirmed on the surgical specimen, our panel also supports adjuvant olaparib.

Overall, we strongly recommend adjuvant olaparib to all eligible patients with *gBRCA1/2m* and high-risk TNBC for one year following completion of definitive local and systemic therapy.

1.5.3.b. HR(+) Breast Cancer

The role of adjuvant olaparib in HR(+) disease is more limited (57). We support its use in patients with *gBRCA1/2m* who received adjuvant chemotherapy and had ≥4 positive lymph nodes.

For patients treated with NAT who did not achieve pCR, eligibility for adjuvant olaparib depends on the pretreatment clinical stage, post-treatment pathologic stage, estrogen receptor status, and tumor grade (CPS+EG score). For *BRCA* carriers with residual disease and a CPS+EG score ≥3, our consensus supports adjuvant olaparib for one year, although we acknowledge that the label excludes CPS-EG score due to concerns of undertreatment in selected cases with a lower score and higher risk of recurrence, who may be considered for adjuvant olaparib.

1.5.3.c. Role of Adjuvant Olaparib in *PALB2* PV Carriers

PALB2 mutations represent the second most common hereditary predisposition to BC after *BRCA1/2*. The *PALB2* protein interacts directly with *BRCA2* in homologous recombination repair, providing a strong biological rationale for PARP inhibitor sensitivity in *PALB2* mutation carriers (72).

The primary clinical evidence supporting the use of olaparib in *PALB2* mutation carriers derives from the TBCRC-048 trial, which reported a response rate of 82% in patients with metastatic BC harboring germline *PALB2* mutations (73). Additional support derives from the ongoing APOLLO trial, which is evaluating adjuvant olaparib in pancreatic cancer patients with *BRCA1/2* and *PALB2* mutations (74). Based on these data and the underlying biological rationale, our panel supports consideration of adjuvant olaparib for high-risk BC patients with germline *PALB2* mutations, as recommended in the St. Gallen 2025 Consensus (50). However, clinicians should carefully counsel patients regarding the off-label nature of this indication.

1.6. Neoadjuvant Treatment

1.6.1. Identification of the Patient Who Requires Neoadjuvant Treatment

Patient selection for NAT is linked to tumor biology, stage, and prognostic factors. For HER2(+) BC, NAT is strongly recommended in patients with stage II–III disease, with tumors exceeding 2 cm, or with node-positive status—particularly when accompanied by aggressive biological features. Evidence supports the combination of anthracycline/taxane-based chemotherapy with dual HER2 blockade using trastuzumab and pertuzumab (TP), which has significantly increased pCR rates in landmark studies (75-77). In TNBC, NAT should be considered for tumors ≥ T1c or those with nodal involvement, especially if tumors demonstrate high proliferation (Ki-67 ≥30%) or grade-3 histology. The integration of pembrolizumab into standard chemotherapy backbones in eligible patients is now considered standard of care (78). For HR(+)/HER2(-) disease, NAT is typically reserved for high-risk stage II–III cases. In Luminal A tumors with low proliferation, neoadjuvant ET may be considered in carefully selected older patients as a reasonable, less toxic alternative, whereas Luminal B tumors with high proliferation indices are more likely to benefit from chemotherapy (79, 80). We also consider the histopathological subtype, proliferation index, hormone receptor status, HER2 status, and nodal involvement when determining eligibility for NAT.

1.6.2. Predictive Genetic Tests to Determine Eligibility for Neoadjuvant Endocrine Therapy

Genomic assays such as Oncotype DX, MammaPrint, and EndoPredict are increasingly being evaluated for their ability to predict response to neoadjuvant ET in HR(+)/HER2(-) BC. Oncotype DX RS has been correlated with neoadjuvant ET outcomes in multiple studies, with lower RS associated with higher clinical response rates and higher rates of breast-conserving surgery (81). A meta-analysis confirmed significantly better neoadjuvant ET response rates in low-RS versus high-RS groups, and ongoing trials are investigating RS changes pre- and post-treatment as prognostic markers (82). MammaPrint, validated for adjuvant chemotherapy selection, is under evaluation for neoadjuvant ET guidance, with early data suggesting that molecular subtyping with MammaPrint/BluePrint may improve treatment prediction and the feasibility of neoadjuvant ET in low-risk cases (83). Although we rarely use this approach in our routine clinical practice — mostly in geriatric patients with locally advanced disease and significant comorbidities who would otherwise be unsuitable for chemotherapy — there is limited evidence to support its use in other settings. In such cases, integrating genomic profiling with established clinicopathological parameters (ER ≥50%, PR ≥20%, Ki-67 <20%, grade 1–2, N0–N1) may provide a more refined strategy to identify patients who are appropriate candidates for neoadjuvant ET (84).

1.6.3. Optimal Duration of Neoadjuvant Endocrine Therapy

The optimal duration for neoadjuvant ET, supported by multiple studies, is 4–6 months, allowing sufficient time for maximal tumor shrinkage (79). However, several studies have demonstrated that extending neoadjuvant ET with letrozole and exemestane for up to 24 months can further improve clinical response rates, increase BCS eligibility, and promote tumor downstaging (84, 85).

1.6.4. Role of Pembrolizumab for the Neoadjuvant Treatment of TNBC

The KEYNOTE-522 trial demonstrated that pembrolizumab combined with standard neoadjuvant chemotherapy in stage II and III TNBC significantly improved pCR rates (64.8% *vs.* 51.2%) and translated into significantly higher 3-year EFS (84.5% *vs.* 76.8%; HR: 0.63) and 5-year OS (95.1% *vs.* 94.4%; HR: 0.69), irrespective of PD-L1 expression status (78). These findings establish pembrolizumab as a backbone of NAT in high-risk early-stage TNBC, and it has been rapidly adopted in our routine clinical practice.

1.6.5. Choice of Adjuvant Therapy in *BRCAm* Breast Cancer Patients Without pCR After Pembrolizumab and Chemotherapy

Residual disease following NAT is a high-risk feature associated with recurrence, necessitating escalation of therapy. A subgroup analysis of the KEYNOTE-522 trial demonstrated that among patients with non-pCR the risk of recurrence ranged from 30% to 50%, depending on stage at presentation (86). Although adjuvant capecitabine has been established as a valid option for those with residual disease, translational analyses from the EA1131 and Geicam-Ciboma trials evaluating the role of capecitabine showed no benefit in basal subtypes, which are frequently associated with *BRCAm* tumors (87, 88). Based on the improved iDFS and OS benefits reported in the OlympiA trial (57) and the limitations of capecitabine in this subgroup, we generally recommend concomitant use of olaparib and pembrolizumab in patients with residual tumors following chemo-immunotherapy. Although the results from ongoing studies are pending, the St. Gallen Consensus, based on the available scientific evidence, also recommends capecitabine plus pembrolizumab or if the tumor is *BRCAm*, concurrent olaparib and pembrolizumab for patients with residual invasive tumor (50).

1.6.6. Optimal Use of Pembrolizumab in Patients With pCR

In patients achieving pCR after NAT, continuation of pembrolizumab to complete one year of therapy was associated with a sustained EFS benefit in the KEYNOTE-522 trial (86). At the second interim analysis, the 3-year EFS rate was 84.5% in the pembrolizumab group compared to 76.8% in the placebo group (HR: 0.63; 95% CI: 0.48–0.82; $p<0.001$) . This approach supports the concept that even in the absence of residual disease, maintaining immune checkpoint inhibition may consolidate long-term disease control. Although we acknowledge the KEYNOTE-522 data and consider continuation appropriate in our practice, treatment decisions for patients achieving pCR in the real-world setting may be guided by financial considerations.

1.6.7. Management of ER-Low Positive Breast Cancer

ER-low BC (2–5% of all BC), defined by estrogen receptor expression in 1%–10% of invasive tumor cells, represents a biologically heterogeneous subgroup with intermediate characteristics (some luminal and others basaloid) and an uncertain degree of endocrine responsiveness (89). Controversial data exist regarding management. Very recent data from the Mayo Clinic, presented at the 2024 ASCO Annual Meeting (90), demonstrated significantly worse OS in patients with ER-low tumors who received chemotherapy without adjuvant ET. However, emerging data suggest that ER-low BCs may align more

closely with TNBC in terms of their molecular profile and clinical behavior, rather than with conventional ER-positive disease (91). In our daily practice, we treat patients with ER-low BC similarly to those with TNBC in the preoperative setting, while incorporating adjuvant ET to maximize efficacy in line with available evidence.

1.7. Can Precision Approaches Refine Neoadjuvant and Adjuvant Treatment Strategies in HER2-Positive Early Breast Cancer?

1.7.1. Predictive Tests to Determine Eligibility for Neoadjuvant Treatment in HER2(+) Breast Cancer

HER2Dx is a 27-gene expression-based molecular assay designed to predict pCR and risk of recurrence in early-stage HER2(+) BC. The test evaluates four fundamental biological elements, including immune infiltration, HER2 signaling, tumor proliferation, and luminal differentiation. In the ESMO 2024 meta-analysis, patients classified as low risk by HER2Dx had a 6-year EFS of 97.2%, compared with 90.4% in the high-risk group (92). Validated by numerous prospective adjuvant and neoadjuvant trials, this diagnostic tool emerges as a promising approach for guiding individualized NAT strategies. Despite increasing support in high-resource healthcare facilities, long-term outcomes are awaited before it can be routinely used in practice.

1.7.2. Role of Dual Blockade for the Neoadjuvant Treatment of HER2(+) Early-Stage Breast Cancer

Multiple phase II trials have demonstrated that combining trastuzumab and pertuzumab with taxane-based chemotherapy provides clinical benefit through dual HER2 blockade. Earlier data from the NeoSphere and TRYPHEANA trials (75, 76) demonstrated significantly increased pCR rates, which translated into excellent long-term outcomes with taxane-backbone chemotherapy combined with HER2 blockade, including pertuzumab and trastuzumab. Confirmatory data from the phase III PEONY study, as well as meta-analyses, have established the role of dual HER2 blockade with pertuzumab as a standard approach for the neoadjuvant treatment of HER2(+) BC (93-95).

The use of a subcutaneous formulation combining TP (Phesgo®) may be considered based on results from the FeDeriCa study showing non-inferiority as compared to the intravenous formulation, offering the added benefits of reduced hospital stay and elimination of the need for an intravenous line (96).

1.7.3. Role of Non-Anthracycline-Based Regimens for the Neoadjuvant Treatment of HER2 (+) Breast Cancer

Anthracycline-free regimens reduce the risk of cardiotoxicity while maintaining comparable efficacy. The TRAIN-2 (64), a phase III trial, investigated the role of a combination of carboplatin and paclitaxel and dual HER2 blockade, compared with a standard anthracycline-based regimen. The non-anthracycline arm showed reduced cardiac dysfunction but did not differ significantly from the anthracycline-containing arm in pCR rates or EFS. Based on these and other data reviewed earlier in this manuscript, we generally prefer a non-anthracycline-based chemotherapy regimen, such as TCHP, for most patients with HER2 (+) disease who require neoadjuvant therapy, and for those who have cardiac risks or who wish to reduce long-term treatment complications.

1.7.4 Escalation of Treatment Following a Non-pCR After Neoadjuvant Treatment of HER2 (+) Breast Cancer

Residual disease following neoadjuvant HER2-targeted therapy is associated with an increased risk of recurrence. Escalation of adjuvant therapy in this setting has been validated by pivotal clinical trials.

1.7.5. Role of TDM-1

The KATHERINE trial (97) demonstrated that TDM-1 was superior to trastuzumab in the adjuvant setting, with a 50% reduction in the risk of invasive disease recurrence or death. At a median follow-up of 8.4 years, 7-year iDFS was 80.8% with TDM-1 compared with 67.1% with trastuzumab; this was accompanied by improvements in OS. Subgroup analyses showed a benefit in all subgroups, including those with residual microscopic disease. However, the 7-year iDFS rates of 69.5% and 39.6% in the ypN2 and ypN3 subgroups, respectively, highlight the need for escalation strategies in high-risk patients. We prefer TDM-1 for patients with residual HER2(+) disease following NAT.

1.7.6. Role of Neratinib

Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, demonstrated long-term efficacy in HR(+)/HER2(+) patients with early BC in the ExteNET trial (98). The final analysis of the trial showed that neratinib reduced the risk of invasive disease recurrence by 27% (HR: 0.73; 95% CI: 0.57–0.92) compared with placebo. The 8-year iDFS rates were 90.2% with neratinib and 87.7% with placebo. Twelve months of neratinib after trastuzumab-based adjuvant therapy resulted in a substantial long-term benefit, particularly in the HR(+) subgroup. Although ExteNET preceded the pertuzumab and TDM-1 era, there is a strong rationale to use neratinib as an add-on therapy in high-risk HR(+)/HER2(+) patients, especially those with residual N2 and N3 disease who may have a substantial recurrence risk, as high as 60%, as shown in a subset analysis of the KATHERINE trial (97).

1.7.7. De-Escalation Strategies in the Adjuvant Treatment of HER2(+) Early Breast Cancer

The WSG-ADAPT-HER2+/HR- trial (99) demonstrated that patients who responded well to paclitaxel and dual HER2 blockade achieved pCR rates exceeding 90% without the use of anthracyclines.

The APT trial (63), a phase II, single-arm study, investigated the role of weekly paclitaxel for 12 weeks with trastuzumab in patients with node-negative HER2(+) tumors measuring ≤3 cm. The ten-year follow-up of this combination revealed an encouraging iDFS and OS of 91.3%and 94.3%, respectively, demonstrating the effectiveness of this de-escalated regimen.

Regarding the duration of anti-HER2 blockade, numerous studies have evaluated the role of shorter trastuzumab durations, which have consistently shown outcomes similar to those of 1-year treatment. A patient-level meta-analysis of six randomized trials assessing shorter adjuvant trastuzumab durations reported similar OS, although non-inferiority could not be demonstrated (100).

In routine clinical practice, the APT regimen is the preferred adjuvant therapy for our patients with stage I HER2(+) BC. We also consider administering shorter durations of adjuvant trastuzumab in patients at

lower risk of recurrence, such as those with stage I, HR(+) disease, or those with cardiac comorbidities.

1.7.8. Treating the Elderly, Frail Patient With HER2(+) Breast Cancer

The RESPECT trial (71) investigated trastuzumab monotherapy compared with trastuzumab plus chemotherapy in patients aged ≥70 years. The 3-year DFS rates were 89.5% with trastuzumab alone and 93.8% with the combination; however, non-inferiority was not statistically confirmed. As discussed above, the results suggest that trastuzumab monotherapy provides adequate disease management with a more favorable safety profile, making it a suitable alternative for frail patients for whom chemotherapy may be harmful.

Conclusion

The recommendations presented here reflect a practice-informed, multidisciplinary approach to early BC care, supported by current evidence, yet aware of real-world variability in biology, resources, and patient preferences. We emphasize individualized risk stratification—integrating clinicopathologic features with genomic assays—alongside thoughtful use of OFS and AIs in selected premenopausal patients, selective rather than routine deployment of anthracyclines, and carefully targeted adoption of adjuvant CDK4/6 inhibitors in high-risk settings. We also outline situations where chemotherapy may reasonably be omitted (e.g., T1a TNBC and special low-risk histologies) and provide guidance for HER2-positive disease across neoadjuvant, escalation, and de-escalation pathways, including considerations for elderly or frail patients. These statements are intended to support shared decision-making at the point of care. We plan updates every two years to ensure this guidance remains a practical, patient-centered resource for clinicians navigating common—and often controversial—scenarios in everyday practice.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Ş.T., Ö.S., B.O.U., T.K., İ.Y., M.B., O.C., A.A., G.E.İ., C.U., Y.E.; Concept: G.E.İ., C.U., Y.E.; Design: C.U., Y.E.; Data Collection or Processing: E.Ş.T., Ö.S., B.O.U., T.K., İ.Y., M.B., O.C., A.A.; Analysis or Interpretation: E.Ş.T., Ö.S., B.O.U., T.K., İ.Y., M.B., O.C., A.A.; Literature Search: E.Ş.T., Ö.S., B.O.U., T.K., İ.Y., M.B., O.C., A.A.; Writing: E.Ş.T., Ö.S., B.O.U., T.K., İ.Y., M.B., O.C., A.A., G.E.İ., C.U., Y.E.

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