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Review

De-Escalating Treatment Strategies for Patients with Human Epidermal Growth Factor Receptor-2 (HER2)-Positive Early-Stage Breast Cancer

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Simple Summary: Almost one in five patients with breast cancer have an aggressive subtype that expresses Human Epidermal Growth Factor-2 (HER2) receptor. The introduction of anti-HER2 therapy, like trastuzumab and pertuzumab, has dramatically improved treatment outcomes. However, such therapy is lengthy, costly, and can result in substantial cardiac toxicities. In this review, we discuss ways to de-escalate anti-HER2 therapy by shortening the treatment course to less than the 12-month standard, or minimizing companion chemotherapy. New molecular tools are emerging that should help physicians select which patients with HER2-positive breast cancer benefit most from aggressive and lengthy treatment regimens utilizing single or dual anti-HER2 therapy alone or in combination with chemotherapy.

Abstract: Almost one-fifth of breast cancer cases express Human Epidermal Growth Factor-2 (HER2), and such expression is associated with highly proliferative tumors and poor prognosis. The introduction of anti-HER2 therapies has dramatically changed the natural course of this aggressive subtype of breast cancer. However, anti-HER2 therapy can be associated with substantial toxicities, mostly cardiac, and high cost. Over the past few years, there has been growing interest in de-escalation of anti-HER2 therapies to minimize adverse events and healthcare costs, while maintaining the efficacy of treatment. Data from clinical observations and single-arm studies have eluted to the minimal impact of anti-HER2 therapy in low-risk patients, like those with node-negative and small tumors. Though single-arm, the APT trial, in which patients with node-negative, small tumors received single-agent paclitaxel for 12 cycles plus trastuzumab for 1 year, was a practice-changing study. Several other recently published studies, like the PERSEPHONE trial, have shown more convincing data that 6 months of trastuzumab is not inferior to 12 months, in terms of disease-free survival (DFS), suggesting that de-escalating strategies with shorter treatment may be appropriate for some low-risk patients. Other de-escalating strategies involved an adaptive, response-directed approach, and personalized therapy that depends on tumor genomic profiling.

Keywords: breast cancer; HER2; trastuzumab; pertuzumab; de-escalation; personalized medicine; targeted therapies; adjuvant therapies; neoadjuvant therapies

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1. Introduction

Breast cancer continues to be the most diagnosed cancer among women worldwide [1,2]. Almost one in five women with breast cancer has human epidermal growth factor receptor-2 (HER2)-positive disease, which means over 450,000 cases are diagnosed every year worldwide [3–5]. HER2-positive breast cancer is known for its aggressive clinicopathological features and poor prognosis [6,7]. However, this aggressive behavior can be offset by the utilization of anti-HER2 targeted therapy. In one of the earliest clinical trials which examined the clinical impact of anti-HER2 therapy, Slamon et al. had shown that the prognosis of patients with HER2-positive metastatic breast cancer, when treated

with trastuzumab, become similar to those with HER2-negative disease [8]. In early-stage breast cancer (EBC), several major clinical trials and meta-analyses had established the great benefit of trastuzumab and pertuzumab when combined with chemotherapy, both in the adjuvant and neoadjuvant settings [9–13]. However, there is disagreement on aggressiveness of therapy in a subgroup of HER2-positive patients with low-risk features. This group includes those with node-negative disease and small tumors, more so with tumors sized 10 mm or smaller (T1a-T1b). The management of such patients is highly variable across physicians and institutions [14–16]. In a recent study that investigated the variations in clinical management of patients with node-negative small tumors, investigators utilized an online questionnaire conducted across 70 breast medical oncologists in Spain. The questionnaire included 37 questions regarding management decisions of HER2-positive early breast cancer. Oncologists' responses were very heterogenous; 53% would recommend upfront surgery, thus avoiding neoadjuvant therapy for node-negative tumors measuring 1.0 cm or less. When asked about de-escalating the duration of anti-HER2 therapy for small tumors, 56% and 69% of responders were open to de-escalate the duration of adjuvant trastuzumab in pT1bN0 and pT1aN0 tumors, respectively [17]. Clinicopathological features, like young age, negative estrogen receptors (ERs), high grade, and high Ki-67 may influence the aggressiveness of suggested treatment for patients with node-negative small tumors [17]. In this review, we will discuss the rationale for de-escalation first, then address de-escalation strategies.

2. Rationale for De-Escalation

De-escalation refers to strategies that intend to reduce the duration, intensity, or complexity of the anti-HER2 treatment or the companion chemotherapy without compromising treatment outcomes [18]. Emerging data suggest that for certain low-risk patients, less intensive regimens, including both the anti-HER2 agents and the chemotherapy, may achieve comparable outcomes to standard aggressive protocols. Identifying these subsets through biomarkers and clinical characteristics is crucial for effective de-escalation.

2.1. Toxicity Reduction

Anti-HER2 therapies, particularly when combined with chemotherapy, can cause significant adverse effects, most importantly cardiotoxicity, but also including gastrointestinal and hematologic toxicities. De-escalation may thus improve the quality of life of such patients.

2.1.1. Cardiac Toxicity

Patients with breast cancer are at higher risk for cardiac adverse events secondary to chemotherapy, mostly anthracyclines and anti-HER2 therapy [19,20]. Radiation therapy, especially when it involves left-sided tumors, may add to this risk. In a recently published study, 829 patients with breast cancer (median age at diagnosis 54.2 years) who completed chemotherapy, including cardiotoxic agents, underwent echocardiographic screening every 2 years. Cardiac dysfunction was defined as left ventricular ejection fraction (LVEF) <50% after therapy initiation and included early- and late-onset cardiac dysfunction. Both anthracyclines and anti-HER2 (trastuzumab/pertuzumab) were given to 6.2% of the patients, while 16% received trastuzumab/pertuzumab alone, 39.7% received anthracyclines alone, and 38.1% received radiation alone. At a median follow-up of 8.6 (range, 1.8–39.8) years, and a total of 2,808 echocardiograms performed, the cumulative incidence of cardiac dysfunction increased from 1.8% at 2 years to 15.3% at 15 years from therapy initiation. In multivariable analysis, anthracyclines and trastuzumab/pertuzumab [hazard ratio (HR), 3.92, 95% CI, 1.74–8.85], anthracyclines [HR, 2.35 (95% CI, 1.25–4.4)], and non-Hispanic Black race [HR, 2.15 (95% CI, 1.37–3.38)] were important determinants of cardiac toxicity. Early-onset cardiac dysfunction was most prevalent among patients exposed to the combination of anthracyclines and trastuzumab/pertuzumab, while late-onset cardiac dysfunction was most prevalent among anthracycline- and radiation-exposed patients [21].

Such findings provide evidence to support the need for echocardiographic surveillance for several years after treatment with cardiotoxic agents and suggest a need to optimize cardiovascular risk factors to mitigate this potentially serious adverse event. Additionally, potential cardiac dysfunction can be a rationale to de-escalate anti-cancer therapy, when possible.

2.1.2. Hematological and Gastrointestinal Toxicities

Toxicities of anti-HER2 therapy, beyond the cardiac ones, are encountered significantly more when trastuzumab is combined with pertuzumab. Diarrhea, alopecia, and nausea are relatively common. However, leukopenia, neutropenia, and febrile neutropenia were seen in patients receiving concurrent chemotherapy, which is likely the cause of most of these toxicities.

2.2. Cost-Effectiveness

Anti-HER2 therapy is lengthy and expensive, and the financial burden on patients themselves and healthcare systems can be substantial [22–24]. Obviously, de-escalation can lead to significant cost savings. In a study aimed to systematically review economic evaluation (EE) of adjuvant trastuzumab compared with chemotherapy alone for HER2-positive EBC, authors included 22 eligible studies from high-income (HICs) and upper-middle income countries (UMICs). Incremental cost-effectiveness ratios (ICERs) were within the cost-effectiveness thresholds of HICs, but not UMICs [25]. Several other studies, from low-income countries (LICs) reached a conclusion that one year of adjuvant trastuzumab therapy for HER2-positive EBC, when compared to chemotherapy alone, may not represent value for money in such countries [26–29]. Obviously, things can be even worse when dual anti-HER2 therapy, both trastuzumab and pertuzumab, is used in the adjuvant or neoadjuvant therapy [30,31]. The introduction of generic drugs and biosimilars, if priced at a significantly discounted rate, especially for resource-restricted countries, should improve patients' access to such drugs [32,33].

3. Approaches to De-Escalation

Several strategies have been explored to de-escalate the therapy for patients with HER2-positive disease, including the anti-HER2 therapy itself, the companion chemotherapy, or both. This de-escalation can range from reducing the duration of therapy to minimizing the use of concurrent chemotherapy. While de-escalation strategies in high-income countries may be driven by factors related to toxicities, quality of life, and cost-effectiveness, cost and availability of anti-HER2 drugs, especially in low-income countries, may dictate de-escalation strategies. The lack of special funds to cover anti-HER2 therapy for refugees hosted in resource-restricted countries forced oncologists to delete anti-HER2 drugs, even for high-risk patients [23]. In a study conducted by our group, treatment outcomes of 113 Syrian refugees with breast cancer were reviewed. Though the majority of the patients received systemic chemotherapy, when indicated, only 11 (35.5%) of 31 patients with HER2-positive disease received any anti-HER2 therapy. Across all needed treatments, 37 (32.7%) patients had considerable deviations when judged against our institutional clinical practice guidelines (CPGs). Both DFS and OS of patients involved were significantly lower than patients treated at the same institution with no deviation [23].

3.1. Shortening the Duration of Trastuzumab

Since its introduction, and based on many clinical trials, the standard duration of trastuzumab therapy has been 12 months [9]. However, several trials have attempted to shorten this duration to 6 months or shorter (Table 1).

Table 1. Duration of anti-HER2 therapy, short vs. long.

Variables	Study [References]	Publication Dates	Key Findings
One Year vs. 2 Years	HERA trial [34]	2005 and 2013	Two years is not better than one year (HR 0.99; 95% CI, 0.85–1.14, $p = 0.86$). Two years was associated with more grade 3–4 adverse events and decrease in LVEF.
Nine Weeks vs. 12 Months	FINHER [35]	2008	Nine weeks of trastuzumab tended to have better dDFS than chemotherapy only (HR 0.65; 95% CI, 0.38–1.12; $p = 0.12$). LVEF remained unaltered.
	SOLD trial [36,37]	2018, 2024	Nine weeks is not non-inferior to 12 months for DFS. No substantial difference in dDFS and OS between the short and long group.
	ShortHER [38]	2023	Nine weeks is not non-inferior to 12 months (in higher-risk patients with N4+).
Six Months vs. 12 Months	PHARE Trial [39,40]	2013 and 2019	Six months is not non-inferior to 12 months. Cardiac events: 5.7% (12-month), 1.9% (6-month), $p < 0.0001$.
	PERSEPHONE Trial [41]	2019	Six months is not inferior to 12 months; 4-year DFS 89.4% (6-month), 89.8% (12-month), HR 1.07, 90% CI 0.93–1.24, non-inferiority $p = 0{\cdot}011$. Six-month treatment was associated with fewer severe adverse events.
Meta-analysis (Short vs. Long Duration)	Six studies (patients treated between 1999–2015) [42]	2019	DFS and OS were significantly improved with the 12-month trastuzumab regimen compared to shorter ones.

HER2: Human epidermal growth factor-2; HR: Hazard ratio: LVEF: Left ventricular ejection fraction; dDFS: Distant disease-free survival; DFS: Disease-free survival; OS: Overall survival; N4+: Four or more axillary lymph nodes involved.

3.1.1. Longer Is Not Necessarily Better

The landmark study, the HERA (HERceptin Adjuvant) trial, had a third arm which compared 2 years vs. 1 year of trastuzumab therapy after standard adjuvant chemotherapy, neoadjuvant chemotherapy, or both in 5102 patients with HER2-positive EBC [9]. After a median follow-up of 8 years, 2 years of adjuvant trastuzumab was not more effective than one year of treatment (HR 0·99; 95% CI, 0.85–1.14, $p = 0.86$). However, grade 3–4 adverse events and decrease in LVEF during treatment were reported more frequently in the 2-year treatment group (20.4% and 7.2%) than in the 1-year group (16.3% and 4.1%), respectively [34].

3.1.2. Ultrashort Trastuzumab, the 9-Week Attempt

The FINHER Study

The FINHER trial was among the very first studies that attempted to shorten the duration of anti-HER2 therapy. However, the chemotherapy regimen used is not among the known standard ones now or back then. In this study, 1010 patients with node-positive or high-risk node-negative breast cancer were randomly assigned to receive three cycles of docetaxel or vinorelbine, followed in both groups by three cycles of FEC (fluorouracil, epirubicin, and cyclophosphamide). Women with HER2-positive disease (n = 232) were assigned to receive or not receive trastuzumab for 9 weeks, along with docetaxel or vinorelbine. After a median follow-up of 62 months, patients treated with trastuzumab tended to have better distant disease-free survival (dDFS) than those treated with chemotherapy only (HR 0.65; 95% CI, 0.38–1.12; $p = 0.12$). The median LVEF of trastuzumab-treated patients remained unaltered during the 5-year follow-up; however, only one woman treated with

trastuzumab was diagnosed with heart failure [35]. Though this trial did not compare long vs. shortened trastuzumab therapy, it did pave the way for more studies to address this question. Additionally, patients included were high-risk (by inclusion criteria); the de-escalation strategies might not be their best option, if they can tolerate such therapy.

The SOLD Trial

The SOLD trial, an open-label randomized clinical trial, was closer to the standard of care in its choice of chemotherapy. A total of 2176 patients with HER2-positive EBC were randomized into two groups and the chemotherapy regimen was identical in the two groups: three cycles of 3-weekly docetaxel plus trastuzumab for 9 weeks, followed by three cycles of FEC. The first group (short trastuzumab) received no further trastuzumab, while the other group continued the drug for one full year from the start date. The study was updated recently, at a median follow-up of 8.1 years, and non-inferiority of the 9-week trastuzumab treatment could not be demonstrated for disease-free survival (DFS). However, the 5-year and 10-year OS rates were comparable between the 9-week (95.0% and 89.1%) and 1-year groups (95.9% and 88.2%); HR for all time points, 1.20; 90% CI, 0.94–1.54). Four patients (0.2%) died of a cardiac cause; three (75.0%) of these patients received trastuzumab for 9 weeks [36,37]. Failure to achieve its target may be a reflection of patients included in the study. To be realistic, high-risk HER2-positive patients may not be the best candidates for de-escalation trials. Many of such patients were enrolled in the SOLD trial, including 34% with ER-negative disease, 12% with stage III, and 11% with 4+ axillary lymph nodes.

The ShortHER Trial

This is the third study attempting the shorter 9-week trastuzumab therapy, and was updated and published recently. The ShortHER trial was a phase 3, non-inferiority, randomized trial comparing 9 weeks vs. 12 months of adjuvant trastuzumab with chemotherapy in patients with HER2-positive EBC. Patients were randomized to anthracycline-taxane combination chemotherapy plus 12 months or 9 weeks of trastuzumab. At a median follow-up of 9 years, the 10-year DFS for the whole group was similar: 77% vs. 78% in the long vs. short trastuzumab arm, respectively. Ten-year OS was also similar: 89% vs. 88% in the long vs. short arm, respectively. However, findings were not the same when higher-risk patients with $\geq$4 involved axillary lymph nodes (N4+) were considered. In this high-risk subgroup, the 10-year DFS rates in the long vs. short arm were 63% vs. 53%, and the 10-year OS rates in long vs. short arm were 84% vs. 64%. The updated analysis of the ShortHER trial showed that 12-month trastuzumab remains the standard treatment for patients with high-risk (N4+) disease. However, numerically, the differences for the patients at low (N0) or intermediate risk (N1-3) are negligible [38].

3.1.3. Six Months vs. 12 Months Trastuzumab

The PHARE Trial

Given the failure of the 9-week regimen, it was natural to try a longer course of trastuzumab. The PHARE trial was an open-label, randomized, phase 3 trial in many centers in France. Patients with HER2-positive EBC who had breast-axillary surgery and had been treated with at least four cycles of chemotherapy and up to 6 months of trastuzumab were randomized to continue trastuzumab for another 6 months (12 months total duration; control group) or to discontinue trastuzumab at 6 months (6 months total duration; experimental group). A total of 1691 patients were randomized to receive 12 months of trastuzumab and 1693 to receive 6 months of trastuzumab. After a median follow-up of 42.5 months, the 2-year DFS was 93.8% in the 12-month group and 91.1% in the 6-month group (HR 1.28; 95% CI, 1.05–1.56; $p = 0.29$). Cardiac events were reported significantly more in patients treated with the 12-month trastuzumab than those in the 6-month group; 5.7% vs. 1.9%, $p < 0.0001$ [39]. The study was updated few years later; at a median follow-up of 7·5 years, the authors concluded that shorter duration of anti-HER2 is not non-inferior to the standard 12-month regimen [40]. Similar to previously discussed

studies, the PHARE trial also enrolled higher-risk patients, including 15.1% with 4+ axillary lymph nodes and 38.5% with HR-negative disease.

PERSEPHONE Trial

This phase 3 trial compared 6 months vs. 12 months of adjuvant trastuzumab in HER2-positive early breast cancer. It demonstrated non-inferiority of the shorter regimen in terms of DFS, suggesting that 6 months could be a viable option for many patients. In this open-label, randomized, phase 3 non-inferiority trial, patients with HER2-positive EBC were recruited from 152 centers in the UK. Patients had to have a clear indication for chemotherapy and were randomized to receive either 6-month or 12-month trastuzumab every 3 weeks, intravenously or subcutaneously, given in combination with chemotherapy. At a median follow-up of 5·4 years, DFS events occurred in 13% of 2044 patients in the 6-month group and in 12% of 2045 patients in the 12-month group. Four-year DFS was 89·4% in the 6-month group and 89·8% in the 12-month group (HR 1.07; 90% CI, 0.93–1.24), non-inferiority $p = 0.011$. Additionally, the 6-month trastuzumab treatment was associated with fewer severe adverse events (19%) compared to 24% in the 12-month group, $p = 0{\cdot}0002$. Additionally, fewer patients in the 6-month group stopped the drug early because of cardiotoxicity, 3% compared to 8%, $p < 0{\cdot}0001$ [41].

3.1.4. The Meta-Analysis

Controversy continues regarding the optimal duration of trastuzumab, especially so after the encouraging results of the PERSEPHONE trial. This meta-analysis was performed to reassess the efficacy and safety of shorter durations of trastuzumab. A total of 11,496 patients who were enrolled in six studies were eligible. Disease-free survival was significantly improved with the 12-month trastuzumab regimen compared to shorter ones (HR = 1.13; 95% CI 1.03–1.25; $p = 0.01$). Similarly, OS was significantly better (HR = 1.16; 95% CI 1.01–1.32; $p = 0.03$). Survival benefits were more pronounced in patients with ER-negative and node-positive disease. However, patients treated with shorter duration experienced significantly fewer cardiac events (OR 0.52; 95% CI 0.43–0.62; $p < 0.00001$) [42].

Given the above data, and despite the well documented increased risk of cardiotoxicity, 12 months of adjuvant trastuzumab treatment offer a considerable survival advantage and should continue to be the standard and preferred treatment for HER2-positive EBC. However, shorter durations of trastuzumab therapy can be considered for patients with cardiac disease, those with small tumors, and with node-negative disease, especially in resource-restricted countries.

3.2. De-Escalating Concurrent Chemotherapy

Concurrent chemotherapy, with anti-HER2 therapy adds to toxicity, inconvenience, and cost of therapy. Several trials have evaluated reduced-intensity chemotherapy regimens with anti-HER2 in patients with low-risk HER2-positive EBC (Table 2).

Table 2. De-escalation of chemotherapy.

Strategy	Variables	Studies [References]	Publication Date(s)	Key Findings
De-escalating Concurrent Chemotherapy	Single-agent paclitaxel weekly for 12 weeks plus trastuzumab for 12 months	APT trial (Single-arm) [43–45]	2015, 2019, 2023	10-year iDFS: 91.3%. 10-year RFI: 96.3%. 10-year OS: 94.3%. 10-year BCSS: 98.8%.
	T-DM1 vs. paclitaxel (12 weeks) plus trastuzumab (12 months)	ATEMPT trial (Randomized) [46,47]	2021, 2024	Efficacy (T-DM1 arm): 5-year iDFS: 97.0%, 5-year RFI: 98.3%, 5-year OS: 97.8%, 5-year BCSS: 99.4%. Efficacy (TH arm): 5-year iDFS: 91.1%. Adverse events: No difference in CRT in both groups.
Monotherapy with anti-HER2 Agents (no chemotherapy)	Elderly patients (70–80 years); trastuzumab alone vs. trastuzumab plus chemotherapy	RESPECT (Open-label, randomized) [48]	2020	Trastuzumab monotherapy is not non-inferior to trastuzumab plus chemotherapy. Combination was associated with more AE and more deterioration in HRQoL.

iDFS: Invasive disease-free survival; RFI: Relapse-free interval; OS: Overall survival; BCSS: Breast cancer-specific survival; TH: Paclitaxel plus Trastuzumab; CRT: Clinically relevant toxicities; AE: Adverse events; HRQoL: Health-related quality of life.

3.2.1. The APT Trial

The APT (Adjuvant Paclitaxel and Trastuzumab) was designed to address de-escalating chemotherapy in patients with small, node-negative, HER2-positive EBC. In this phase 2 study, 410 patients with HER2-positive, node-negative, small breast cancer with tumors 3 cm or smaller were treated with weekly paclitaxel and trastuzumab for 12 weeks, followed by trastuzumab alone for 9 more months, to finish a total of 12 months of therapy. The primary analysis demonstrated a 3-year DFS of 98.7% [42]. In a follow-up analysis with a median follow-up of 6.5 years, the 7-year DFS was 93% with only four (1.0%) distant recurrences, 7-year recurrence-free interval (RFI) was 97.5%, and the 7-year OS was 95% [43]. On further follow-up, the 10-year invasive disease-free survival (iDFS) was 91.3% (95% CI, 88·3–94·4), 10-year RFI was 96.3% (95% CI, 94.3–98.3), and 10-year overall survival was 94.3% (95% CI, 91.8–96.8), and 10-year breast cancer-specific survival (BCSS) was 98.8% (95% CI, 97.6–100.0) (Table 3) [45].

Table 3. Survival outcomes of patients treated on the APT trial.

Outcome	At 3-Year (2015)	At 7-Year (2019)	At 10-Year (2023)
Invasive Disease-Free Survival (iDFS)	98.7 (95% CI, 97.6–99.8),	93% (95% CI, 90.4–96.2)	91.3% (95% CI, 88.3–94.4)
Recurrence-Free Interval (RFI)	99.2% (95% CI, 98.4–100.0)	97.5% (95% CI, 95.9–99.1)	96.3% (95% CI, 94.3–98.3)
Overall Survival (OS)	NR	95.0% (95% CI, 92.4–97.7)	94.3% (95% CI, 91·8–96·8)
Breast cancer-specific survival (BCSS)	NR	98.6% (95% CI, 97.0–100.0%)	98.8% (95% CI, 97.6–100.0)

iDFS: Invasive disease-free survival; RFI: Relapse-free interval; OS: Overall survival; BCSS: Breast cancer-specific survival; CI: Confidence interval; NR: Not reported.

3.2.2. The ATEMPT Trial

The study was designed to compare the incidence of clinically relevant toxicities (CRTs) in patients treated with ado-trastuzumab emtansine (T-DM1) vs. paclitaxel-trastuzumab (TH) and to evaluate iDFS in patients receiving T-DM1. Patients with stage I, HER2-positive EBC (n = 497) were randomly assigned 3:1 to T-DM1 (n = 383) or TH (n = 114). T-DM1 was given every 3 weeks for 17 cycles (total one year), while TH was given weekly for 12 weeks, followed by trastuzumab alone every 3 weeks for 39 weeks (total, one year). There was no difference in CRT in both groups; 46% of patients on T-DM1 and 47% of patients on TH. At its initial publication in 2021, T-DM1 was associated with excellent results; the 3-year iDFS was 97.8% [46]. The trial was updated in June 2024; after a median follow-up of 5.8 years, the 5-year iDFS was 97.0%, the RFI was 98.3%, the OS was 97.8%, and the BCSS was 99.4%. Though the study was not powered to study the difference between TH and T-DM1, the 5-year iDFS in the TH arm was 91.1% [47].

3.2.3. ADAPT Trial

Several clinical trials have tried to plan and direct a personalized therapy for HER2-postive breast cancer patients based on their initial response. The ADAPT trial is a prospective, phase 2 study investigating the potential of personalized treatment based on early response to neoadjuvant therapy. Initial results indicate that patients who achieve pCR after short-term preoperative therapy might be candidates for de-escalated post-operative treatment. Patients (n = 134) were randomized to 12 weeks of trastuzumab and pertuzumab with or without weekly paclitaxel. Early response was defined as a decline in Ki-67 from baseline by 30% or more, or low cellularity (<500 invasive tumor cells) at biopsy performed 3 weeks after starting therapy. The pCR rate in the taxanes and dual blockade was unexpectedly high at 90.5%, compared to 36.3% in the non-chemotherapy arm. Among the trastuzumab/pertuzumab arm, 24/92 (26.1%) were classified as non-responders, and only 8.3% achieved pCR compared with 44.7% in responders (38/92). The study concluded that early non-responders treated with dual anti-HER2 therapy, without chemotherapy, strongly predict failure to achieve pCR [49]. In a follow-up analysis, authors found that omission of further chemotherapy had no negative impact on iDFS in patients with pCR and concluded that weekly paclitaxel plus dual HER2 blockade for 12 weeks can be a de-escalated neoadjuvant regimen in patients with HR-negative, HER2-positive EBC [50].

3.3. Monotherapy with Anti-HER2 Agents

For patients with small, low-risk tumors or those with contraindications to chemotherapy, anti-HER2 monotherapy might be an option. Studies have shown that trastuzumab monotherapy can be effective in specific patient populations, though it is generally less effective than combination therapy.

RESPECT Trial

In one open-label, randomized controlled study, 275 patients aged 70–80 (mean age, 73.5) years with surgically treated HER2-positive patients with EBC received trastuzumab alone or trastuzumab plus chemotherapy. The study was designed to see if trastuzumab alone is not inferior to trastuzumab plus chemotherapy. After a mean follow-up of 4.1 years, the 3-year DFS was 89.5% with trastuzumab monotherapy vs. 93.8% with trastuzumab plus chemotherapy (HR 1.36; 95% CI, 0.72–2.58; $p = 0.51$). So, the study failed to show that trastuzumab monotherapy is not inferior; however, the observed loss of survival without chemotherapy [restricted mean survival time (RMST)] differed by only −0.39 months at 3 years. Adverse events were more common with the combination arm and that translated into more deterioration in health-related quality of life (HRQoL) at 2 months (31% for trastuzumab monotherapy vs. 48% for trastuzumab and chemotherapy; $p = 0.016$), and at 1 year (19% vs. 38%; $p = 0.009$). Though the non-inferiority for trastuzumab monotherapy was not met, given the added toxicity, poor quality of life, and the little observed loss of survival without the addition of chemotherapy (less than 1 month at 3 years), trastuzumab

monotherapy can be considered an alternative adjuvant therapy option for selected older patients like those enrolled in the RESPECT trial [48].

Targeted therapies such as tucatinib, trastuzumab deruxtecan, and neratinib have demonstrated impressive responses in advanced-stage breast cancer, including those with brain metastasis. Incorporating these agents, alone or in combination, in the post-neoadjuvant therapy may improve the prognosis of HER2-positive EBC [51]. The identification of biomarkers that help predict response to such agents may advance de-escalating strategies.

4. Biomarker-Guided Therapy

4.1. Image-Guided Therapy (PHERGain Trial)

As a continuation of the personalized approach, the PHERGain trial was conducted to optimize patient selection for anti-HER2 therapy utilizing positron emission tomography (PET) scans to identify patients who are likely to benefit from de-escalated neoadjuvant treatment. A total of 356 patients with HR-positive and HER2-positive breast cancer were randomized to two cycles of conventional TCHP regimen (docetaxel, carboplatin, trastuzumab, and pertuzumab) vs. a chemotherapy-free regimen with trastuzumab and pertuzumab in combination with endocrine treatment. Early metabolic response was evaluated by FDG-PET at baseline and after two cycles. Patients in the standard arm continued to receive TCHP for four more cycles. In the experimental arm, early responders continued to receive six more cycles of chemo-free treatment, while the non-responders were switched to receive six courses of TCHP. Following the eight cycles of the neoadjuvant chemotherapy-free group, a total of 38% of early responders achieved pCR and had a 3-year iDFS of 98.8%. However, when taken together, patients in the experimental arm had lower iDFS (95.4%) compared to the standard arm (98.3%). More outcome results, including OS, are still eagerly awaited [52,53].

Biomarkers that help predict response to anti-HER2 therapies can enable more personalized treatment approaches and thus de-escalation. The HER2DX risk score and tumor-infiltrating lymphocytes (TILs) are being studied to tailor therapy intensity based on individual risk profiles [54–57].

4.2. HER2DX Risk Score

Researchers from Spain and United States attempted to develop and validate a new risk scoring system (HER2DX) that can help oncologists decide on treatment aggressiveness of breast cancer patients with HER2-positive disease. The scoring system employs both clinical and genomic data to predict treatment response (pCR) and survival in early-stage HER2-positive breast cancer based on a 27-gene expression plus clinical features, tumor size, and nodal staging. The genomic data analysis utilizes four gene expression signatures tracking tumor cell proliferation, immune infiltration, luminal differentiation, and the expression of the HER2 amplicon. Various data sets, mostly based on the ShortHER database, were used to train, then verify and validate the predictive model. The HER2DX risk score was significantly associated with DFS in the ShortHER database ($p = 0.002$), and in an independent combined validation database; the 5-year DFS in the low-risk group was 97.4% compared to 84.7% in the high-risk group, $p = 0.005$. Overall survival was also better in the low-risk group (5-year OS: 95.8%) compared to 93.1% in the high-risk group, $p = 0.016$. Additionally, continuous HER2DX pCR likelihood score was significantly associated with pCR, $p < 0.0001$ [58].

In another independent study designed to test the ability of the HER2DX assay to predict the likelihood of pCR in patients with early-stage HER2-positive breast cancer who are receiving a de-escalated neoadjuvant therapy, pretreatment tumor biopsy samples from 80 of 97 patients enrolled in the single-arm, multicenter, prospective phase 2 DAPHNe clinical trial were used for HER2DX assay. Patients had newly diagnosed stage II-III HER2-positive disease and were treated with neoadjuvant paclitaxel weekly for 12 weeks plus trastuzumab and pertuzumab every 3 weeks for four cycles. The HER2DX pCR score

was significantly associated with pCR; the pCR rates were 92.6% in the HER2DX high, 63.6% in the medium, and 29.0% in the low pCR score groups (high vs. low odds ratio, 30.6; $p < 0.001$). The researchers concluded that the HER2DX pCR score assay may predict pCR following treatment with de-escalated neoadjuvant paclitaxel with trastuzumab and pertuzumab in patients with early-stage HER2-positive disease, and as such, the HER2DX pCR score might guide management decisions by identifying patients who are candidates for de-escalated approaches [59]. Several other studies reached similar conclusions [60–62].

5. Future Directions and Conclusions

As our understanding of HER2-positive breast cancer biology advances, future research will hopefully refine de-escalation strategies further. Integration of tumor genomic profiling may help identify patients who might benefit from less intensive therapy. Future research should focus on exploring the molecular heterogeneity of HER2-positive breast cancer to identify new prognostic and predictive biomarkers which could pave the way toward the development of truly personalized less burdensome treatment options. Collecting and analyzing data from routine clinical practice (real-world data) to validate de-escalation approaches, away from the very stringent clinical trial setup, should help move such approaches faster. Additionally, exploring novel combinations of targeted therapies may help avoid or reduce the need for traditional toxic chemotherapy. It is hoped that the application of artificial intelligence (AI) should identify clinical, pathological, and molecular markers that may help oncologists decide on aggressiveness of anti-cancer therapy. It is important to emphasize here that de-escalating strategies addressed here might not be an option for higher-risk HER2-positive patients like those with four or more positive lymph nodes.

In conclusion, treatment de-escalation of HER2-positive breast cancer patients holds promise for reducing both toxicity and costs, while maintaining efficacy and outcomes. We believe that the current available evidence justifies some of the de-escalation strategies addressed in this review, especially in resource-restricted countries.

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References

1. Bray, F.; Laversanne, M.; Sung, H.; Ferlay, J.; Siegel, R.L.; Soerjomataram, I.; Jemal, A. Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA A Cancer J. Clin.* **2024**, *74*, 229–263. [CrossRef] [PubMed]
2. Cancer Fact Sheet. The International Agency for Research on Cancer (IARC). Available online: https://gco.iarc.fr/today/en/fact-sheets-cancers (accessed on 2 July 2024).
3. Pan, L.; Li, J.; Xu, Q.; Gao, Z.; Yang, M.; Wu, X.; Li, X. HER2/PI3K/AKT Pathway in HER2-Positive Breast Cancer: A Review. *Medicine* **2024**, *103*, e38508. [CrossRef] [PubMed]
4. Moasser, M.M. The Oncogene HER2: Its Signaling and Transforming Functions and Its Role in Human Cancer Pathogenesis. *Oncogene* **2007**, *26*, 6469–6487. [CrossRef] [PubMed]
5. Fragomeni, S.M.; Sciallis, A.; Jeruss, J.S. Molecular Subtypes and Local-Regional Control of Breast Cancer. *Surg. Oncol. Clin. N. Am.* **2018**, *27*, 95–120. [CrossRef] [PubMed]
6. Loibl, S.; Gianni, L. HER2-Positive Breast Cancer. *Lancet* **2017**, *389*, 2415–2429. [CrossRef] [PubMed]
7. Ross, J.S.; Fletcher, J.A.; Linette, G.P.; Stec, J.; Clark, E.; Ayers, M.; Symmans, W.F.; Pusztai, L.; Bloom, K.J. The HER-2/*Neu* Gene and Protein in Breast Cancer 2003: Biomarker and Target of Therapy. *Oncologist* **2003**, *8*, 307–325. [CrossRef]
8. Slamon, D.J.; Leyland-Jones, B.; Shak, S.; Fuchs, H.; Paton, V.; Bajamonde, A.; Fleming, T.; Eiermann, W.; Wolter, J.; Pegram, M.; et al. Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. *N. Eng. J. Med.* **2001**, *344*, 783–792. [CrossRef]

9. Piccart-Gebhart, M.J.; Procter, M.; Leyland-Jones, B.; Goldhirsch, A.; Untch, M.; Smith, I.; Gianni, L.; Baselga, J.; Bell, R.; Jackisch, C.; et al. Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. *N. Eng. J. Med.* **2005**, *353*, 1659–1672. [CrossRef]
10. Gianni, L.; Dafni, U.; Gelber, R.D.; Azambuja, E.; Muehlbauer, S.; Goldhirsch, A.; Untch, M.; Smith, I.; Baselga, J.; Jackisch, C.; et al. Treatment with Trastuzumab for 1 Year after Adjuvant Chemotherapy in Patients with HER2-Positive Early Breast Cancer: A 4-Year Follow-up of a Randomised Controlled Trial. *Lancet Oncol.* **2011**, *12*, 236–244. [CrossRef]
11. Cameron, D.; Piccart-Gebhart, M.J.; Gelber, R.D.; Procter, M.; Goldhirsch, A.; De Azambuja, E.; Castro, G.; Untch, M.; Smith, I.; Gianni, L.; et al. 11 Years' Follow-up of Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Early Breast Cancer: Final Analysis of the HERceptin Adjuvant (HERA) Trial. *Lancet* **2017**, *389*, 1195–1205. [CrossRef]
12. Bradley, R.; Braybrooke, J.; Gray, R.; Hills, R.; Liu, Z.; Peto, R.; Davies, L.; Dodwell, D.; McGale, P.; Pan, H.; et al. Trastuzumab for Early-Stage, HER2-Positive Breast Cancer: A Meta-Analysis of 13 864 Women in Seven Randomised Trials. *Lancet Oncol.* **2021**, *22*, 1139–1150. [CrossRef]
13. Perez, E.A.; Romond, E.H.; Suman, V.J.; Jeong, J.-H.; Davidson, N.E.; Geyer, C.E.; Martino, S.; Mamounas, E.P.; Kaufman, P.A.; Wolmark, N. Four-Year Follow-Up of Trastuzumab Plus Adjuvant Chemotherapy for Operable Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Joint Analysis of Data from NCCTG N9831 and NSABP B-31. *J. Clin. Oncol.* **2011**, *29*, 3366–3373. [CrossRef] [PubMed]
14. Gonzalez-Angulo, A.M.; Litton, J.K.; Broglio, K.R.; Meric-Bernstam, F.; Rakkhit, R.; Cardoso, F.; Peintinger, F.; Hanrahan, E.O.; Sahin, A.; Guray, M.; et al. High Risk of Recurrence for Patients with Breast Cancer Who Have Human Epidermal Growth Factor Receptor 2–Positive, Node-Negative Tumors 1 Cm or Smaller. *J. Clin. Oncol.* **2009**, *27*, 5700–5706. [CrossRef] [PubMed]
15. Curigliano, G.; Viale, G.; Bagnardi, V.; Fumagalli, L.; Locatelli, M.; Rotmensz, N.; Ghisini, R.; Colleoni, M.; Munzone, E.; Veronesi, P.; et al. Clinical Relevance of *HER2* Overexpression/Amplification in Patients with Small Tumor Size and Node-Negative Breast Cancer. *J. Clin. Oncol.* **2009**, *27*, 5693–5699. [CrossRef] [PubMed]
16. Livi, L.; Meattini, I.; Saieva, C.; Franzese, C.; Di Cataldo, V.; Greto, D.; Franceschini, D.; Scotti, V.; Bonomo, P.; Nori, J.; et al. Prognostic Value of Positive Human Epidermal Growth Factor Receptor 2 Status and Negative Hormone Status in Patients with T1a/T1b, Lymph Node-negative Breast Cancer. *Cancer* **2012**, *118*, 3236–3243. [CrossRef]
17. Martínez-Sáez, O.; Cortés, J.; Ciruelos, E.; Marín-Aguilera, M.; González, G.; Paré, L.; Herrera, A.; Villagrasa-González, P.; Prat, A.; Martín, M. Management of Early-Stage HER2-Positive Breast Cancer and Attitudes towards HER2DX Test in Spain: Insights from a Nationwide Survey. *Clin. Transl. Oncol.* **2024**, *26*, 2060–2069. [CrossRef] [PubMed]
18. Paplomata, E.; Nahta, R.; O'Regan, R.M. Systemic Therapy for Early-Stage HER2-Positive Breast Cancers: Time for a Less-Is-More Approach? *Cancer* **2015**, *121*, 517–526. [CrossRef]
19. Appel, J.M.; Nielsen, D.; Zerahn, B.; Jensen, B.V.; Skagen, K. Anthracycline-Induced Chronic Cardiotoxicity and Heart Failure. *Acta Oncol.* **2007**, *46*, 576–580. [CrossRef]
20. Gonciar, D.; Mocan, L.; Zlibut, A.; Mocan, T.; Agoston-Coldea, L. Cardiotoxicity in HER2-Positive Breast Cancer Patients. *Heart Fail. Rev.* **2021**, *26*, 919–935. [CrossRef]
21. Bostany, G.; Chen, Y.; Francisco, L.; Dai, C.; Meng, Q.; Sparks, J.; Sessions, M.; Nabell, L.; Stringer-Reasor, E.; Khoury, K.; et al. Cardiac Dysfunction Among Breast Cancer Survivors: Role of Cardiotoxic Therapy and Cardiovascular Risk Factors. *J. Clin. Oncol.* **2024**, JCO-23. [CrossRef]
22. Khoirunnisa, S.M.; Suryanegara, F.D.A.; Setiawan, D.; Postma, M.J. Quality-Adjusted Life Years for HER2-Positive, Early-Stage Breast Cancer Using Trastuzumab-Containing Regimens in the Context of Cost-Effectiveness Studies: A Systematic Review. *Expert Rev. Pharmacoecon. Outcomes Res.* **2024**, *24*, 613–629. [CrossRef] [PubMed]
23. Abdel-Razeq, H.; Tamimi, F.; Abdel-Razeq, N.; El-Atrash, M.; Sharaf, B.; Mustafa, R.; Mansour, R.; Bater, R. Late Presentation and Suboptimal Treatment of Breast Cancer among Syrian Refugees: A Retrospective Study. *J. Int. Med. Res.* **2021**, *49*, 3000605211018448. [CrossRef] [PubMed]
24. Mansour, R.; Abdel-Razeq, H.; Al-Hussaini, M.; Shamieh, O.; Al-Ibraheem, A.; Al-Omari, A.; Mansour, A.H. Systemic Barriers to Optimal Cancer Care in Resource-Limited Countries: Jordanian Healthcare as an Example. *Cancers* **2024**, *16*, 1117. [CrossRef] [PubMed]
25. Genuino, A.J.; Gloria, M.A.J.; Chaikledkaew, U.; Reungwetwattana, T.; Thakkinstian, A. Economic Evaluation of Adjuvant Trastuzumab Therapy for HER2-Positive Early-Stage Breast Cancer: Systematic Review and Quality Assessment. *Expert Rev. Pharmacoecon. Outcomes Res.* **2021**, *21*, 1001–1010. [CrossRef] [PubMed]
26. Genuino, A.J.; Chaikledkaew, U.; Guerrero, A.M.; Reungwetwattana, T.; Thakkinstian, A. Cost-Utility Analysis of Adjuvant Trastuzumab Therapy for HER2-Positive Early-Stage Breast Cancer in the Philippines. *BMC Health Serv. Res.* **2019**, *19*, 874. [CrossRef]
27. Elsisi, G.H.; Nada, Y.; Rashad, N.; Carapinha, J.; Noor, A.O.; Almasri, D.M.; Zaidy, M.A.; Foad, A.; Khaled, H. Cost-Effectiveness of Six Months versus 1-Year Adjuvant Trastuzumab in HER2 Positive Early Breast Cancer in Egypt. *J. Med. Econ.* **2020**, *23*, 575–580. [CrossRef] [PubMed]
28. Erfani, P.; Bhangdia, K.; Stauber, C.; Mugunga, J.C.; Pace, L.E.; Fadelu, T. Economic Evaluations of Breast Cancer Care in Low- and Middle-Income Countries: A Scoping Review. *Oncologist* **2021**, *26*, e1406–e1417. [CrossRef]
29. Nguyen, A.Q.; Tran, O.T.M.; Nguyen, P.K.; Nguyen, H.T. Cost-Effectiveness of One-Year Adjuvant Trastuzumab Therapy in Treatment for Early-Stage Breast Cancer Patients with HER2+ in Vietnam. *PLoS ONE* **2024**, *19*, e0300474. [CrossRef]

30. Nuciforo, P.; Townend, J.; Piccart, M.J.; Fielding, S.; Gkolfi, P.; El-Abed, S.; de Azambuja, E.; Werutsky, G.; Bliss, J.; Moebus, V.; et al. Ten-Year Survival of Neoadjuvant Dual HER2 Blockade in Patients with HER2-Positive Breast Cancer. *Eur. J. Cancer* **2023**, *181*, 92–101. [CrossRef]
31. Piccart, M.; Procter, M.; Fumagalli, D.; de Azambuja, E.; Clark, E.; Ewer, M.S.; Restuccia, E.; Jerusalem, G.; Dent, S.; Reaby, L.; et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. *J. Clin. Oncol.* **2021**, *39*, 1448–1457. [CrossRef]
32. Mohan, M.V.T.K.; Prajapati, A.; Kothari, R.; Mandal, S.; Rao Srikanth, R.; Nagarkar, R.; Khane, S.; Santa, A.; Dadke, D. Efficacy and Safety of BP02 (Trastuzumab Biosimilar) in HER2-Positive Metastatic Breast Cancer: A Multicenter Phase III Study. *Clin. Drug Investig.* **2024**, *44*, 513–525. [CrossRef] [PubMed]
33. Gagliato, D.; Reinert, T.; Rocha, C.; Tavares, M.; Pimentel, S.; Fuzita, W.; Araújo, M.; Matias, D.; Aleixo, S.; França, B.; et al. Real-World Study of Adjuvant Biosimilar Trastuzumab-Dkst for HER2-Positive Breast Cancer Treatment in a Brazilian Population. *Oncol. Ther.* **2024**, *12*, 437–449. [CrossRef]
34. Goldhirsch, A.; Gelber, R.D.; Piccart-Gebhart, M.J.; De Azambuja, E.; Procter, M.; Suter, T.M.; Jackisch, C.; Cameron, D.; Weber, H.A.; Heinzmann, D.; et al. 2 Years versus 1 Year of Adjuvant Trastuzumab for HER2-Positive Breast Cancer (HERA): An Open-Label, Randomised Controlled Trial. *Lancet* **2013**, *382*, 1021–1028. [CrossRef] [PubMed]
35. Joensuu, H.; Bono, P.; Kataja, V.; Alanko, T.; Kokko, R.; Asola, R.; Utriainen, T.; Turpeenniemi-Hujanen, T.; Jyrkkiö, S.; Möykkynen, K.; et al. Fluorouracil, Epirubicin, and Cyclophosphamide with Either Docetaxel or Vinorelbine, With or Without Trastuzumab, As Adjuvant Treatments of Breast Cancer: Final Results of the FinHer Trial. *J. Clin. Oncol.* **2009**, *27*, 5685–5692. [CrossRef]
36. Joensuu, H.; Fraser, J.; Wildiers, H.; Huovinen, R.; Auvinen, P.; Utriainen, M.; Nyandoto, P.; Villman, K.K.; Halonen, P.; Granstam-Björneklett, H.; et al. Effect of Adjuvant Trastuzumab for a Duration of 9 Weeks vs 1 Year with Concomitant Chemotherapy for Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: The SOLD Randomized Clinical Trial. *JAMA Oncol.* **2018**, *4*, 1199–1206. [CrossRef]
37. Joensuu, H.; Fraser, J.; Wildiers, H.; Huovinen, R.; Auvinen, P.; Utriainen, M.; Villman, K.K.; Halonen, P.; Granstam-Björneklett, H.; Tanner, M.; et al. Long-Term Outcomes of Adjuvant Trastuzumab for 9 Weeks or 1 Year for ERBB2-Positive Breast Cancer: A Secondary Analysis of the SOLD Randomized Clinical Trial. *JAMA Netw. Open.* **2024**, *7*, e2429772. [CrossRef]
38. Conte, P.; Bisagni, G.; Piacentini, F.; Sarti, S.; Minichillo, S.; Anselmi, E.; Aieta, M.; Gebbia, V.; Schirone, A.; Musolino, A.; et al. Nine-Week Versus One-Year Trastuzumab for Early Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: 10-Year Update of the ShortHER Phase III Randomized Trial. *J. Clin. Oncol.* **2023**, *41*, 4976–4981. [CrossRef] [PubMed]
39. Pivot, X.; Romieu, G.; Debled, M.; Pierga, J.-Y.; Kerbrat, P.; Bachelot, T.; Lortholary, A.; Espié, M.; Fumoleau, P.; Serin, D.; et al. 6 Months versus 12 Months of Adjuvant Trastuzumab for Patients with HER2-Positive Early Breast Cancer (PHARE): A Randomised Phase 3 Trial. *Lancet Oncol.* **2013**, *14*, 741–748. [CrossRef]
40. Pivot, X.; Romieu, G.; Debled, M.; Pierga, J.-Y.; Kerbrat, P.; Bachelot, T.; Lortholary, A.; Espié, M.; Fumoleau, P.; Serin, D.; et al. 6 Months versus 12 Months of Adjuvant Trastuzumab in Early Breast Cancer (PHARE): Final Analysis of a Multicentre, Open-Label, Phase 3 Randomised Trial. *Lancet* **2019**, *393*, 2591–2598. [CrossRef]
41. Earl, H.M.; Hiller, L.; Vallier, A.-L.; Loi, S.; McAdam, K.; Hughes-Davies, L.; Harnett, A.N.; Ah-See, M.-L.; Simcock, R.; Rea, D.; et al. 6 versus 12 Months of Adjuvant Trastuzumab for HER2-Positive Early Breast Cancer (PERSEPHONE): 4-Year Disease-Free Survival Results of a Randomised Phase 3 Non-Inferiority Trial. *Lancet* **2019**, *393*, 2599–2612. [CrossRef]
42. Chen, L.; Zhou, W.; Hu, X.; Yi, M.; Ye, C.; Yao, G. Short-Duration versus 1-Year Adjuvant Trastuzumab in Early HER2 Positive Breast Cancer: A Meta-Analysis of Randomized Controlled Trials. *Cancer Treat. Rev.* **2019**, *75*, 12–19. [CrossRef] [PubMed]
43. Tolaney, S.M.; Barry, W.T.; Dang, C.T.; Yardley, D.A.; Moy, B.; Marcom, P.K.; Albain, K.S.; Rugo, H.S.; Ellis, M.; Shapira, I.; et al. Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer. *N. Eng. J. Med.* **2015**, *372*, 134–141. [CrossRef] [PubMed]
44. Tolaney, S.M.; Guo, H.; Pernas, S.; Barry, W.T.; Dillon, D.A.; Ritterhouse, L.; Schneider, B.P.; Shen, F.; Fuhrman, K.; Baltay, M.; et al. Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer. *J. Clin. Oncol.* **2019**, *37*, 1868–1875. [CrossRef] [PubMed]
45. Tolaney, S.M.; Tarantino, P.; Graham, N.; Tayob, N.; Parè, L.; Villacampa, G.; Dang, C.T.; Yardley, D.A.; Moy, B.; Marcom, P.K.; et al. Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer: Final 10-Year Analysis of the Open-Label, Single-Arm, Phase 2 APT Trial. *Lancet Oncol.* **2023**, *24*, 273–285. [CrossRef] [PubMed]
46. Tolaney, S.M.; Tayob, N.; Dang, C.; Yardley, D.A.; Isakoff, S.J.; Valero, V.; Faggen, M.; Mulvey, T.; Bose, R.; Hu, J.; et al. Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial. *J. Clin. Oncol.* **2021**, *39*, 2375–2385. [CrossRef]
47. Tarantino, P.; Tayob, N.; Villacampa, G.; Dang, C.; Yardley, D.A.; Isakoff, S.J.; Valero, V.; Faggen, M.; Mulvey, T.; Bose, R.; et al. Adjuvant Trastuzumab Emtansine Versus Paclitaxel Plus Trastuzumab for Stage I Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: 5-Year Results and Correlative Analyses From ATEMPT. *J. Clin. Oncol.* **2024**, JCO-23. [CrossRef]
48. Sawaki, M.; Taira, N.; Uemura, Y.; Saito, T.; Baba, S.; Kobayashi, K.; Kawashima, H.; Tsuneizumi, M.; Sagawa, N.; Bando, H.; et al. Randomized Controlled Trial of Trastuzumab with or Without Chemotherapy for HER2-Positive Early Breast Cancer in Older Patients. *J Clin Oncol* **2020**, *38*, 3743–3752. [CrossRef]

49. Nitz, U.A.; Gluz, O.; Christgen, M.; Grischke, E.-M.; Augustin, D.; Kuemmel, S.; Braun, M.; Potenberg, J.; Kohls, A.; Krauss, K.; et al. De-Escalation Strategies in HER2-Positive Early Breast Cancer (EBC): Final Analysis of the WSG-ADAPT HER2+/HR− Phase II Trial: Efficacy, Safety, and Predictive Markers for 12 Weeks of Neoadjuvant Dual Blockade with Trastuzumab and Pertuzumab ± Weekly Paclitaxel. *Ann. Oncol.* **2017**, *28*, 2768–2772. [PubMed]
50. Nitz, U.; Gluz, O.; Graeser, M.; Christgen, M.; Kuemmel, S.; Grischke, E.-M.; Braun, M.; Augustin, D.; Potenberg, J.; Krauss, K.; et al. De-Escalated Neoadjuvant Pertuzumab plus Trastuzumab Therapy with or without Weekly Paclitaxel in HER2-Positive, Hormone Receptor-Negative, Early Breast Cancer (WSG-ADAPT-HER2+/HR-): Survival Outcomes from a Multicentre, Open-Label, Randomised, Phase 2 Trial. *Lancet Oncol.* **2022**, *23*, 625–635.
51. Barot, S.V.; Roesch, E.; Abraham, J. Optimizing adjuvant and post-neoadjuvant therapy in HER2-positive early breast cancer. *Expert Rev. Anticancer Ther.* **2022**, *22*, 1289–1299. [CrossRef]
52. Pérez-García, J.M.; Gebhart, G.; Ruiz Borrego, M.; Stradella, A.; Bermejo, B.; Schmid, P.; Marmé, F.; Escrivá-de-Romani, S.; Calvo, L.; Ribelles, N.; et al. Chemotherapy de-escalation using an 18F-FDG-PET-based pathological response-adapted strategy in patients with HER2-positive early breast cancer (PHERGain): A multicentre, randomised, open-label, non-comparative, phase 2 trial. *Lancet Oncol.* **2021**, *22*, 858–871. [CrossRef] [PubMed]
53. Cortes, J.; Pérez-García, J.M.; Ruiz-Borrego, M.; Stradella, A.; Bermejo, B.; Escrivá-de-Romaní, S.; Calvo Martínez, L.; Ribelles, N.; Cortés Salgado, A.; Albacar, C.; et al. 3-Year Invasive Disease-Free Survival (iDFS) of the Strategy-Based, Randomized Phase II PHERGain Trial Evaluating Chemotherapy (CT) de-Escalation in Human Epidermal Growth Factor Receptor 2-Positive (HER2[+]) Early Breast Cancer (EBC). *JCO* **2023**, *41*, LBA506. [CrossRef]
54. Liefaard, M.C.; van der Voort, A.; van Seijen, M.; Thijssen, B.; Sanders, J.; Vonk, S.; Mittempergher, L.; Bhaskaran, R.; de Munck, L.; van Leeuwen-Stok, A.E.; et al. Tumor-infiltrating lymphocytes in HER2-positive breast cancer treated with neoadjuvant chemotherapy and dual HER2-blockade. *NPJ Breast Cancer* **2024**, *10*, 29. [CrossRef] [PubMed]
55. Fan, Y.; Li, X.; Zhong, P.; Guo, H.; Han, D.; Tian, W.; Fan, J. Radiological Features for Predicting the Status of CD8-Positive Lymphocytes in HER2 Positive Breast Cancer. *Balkan Med. J.* **2024**, *41*, 213–221. [CrossRef]
56. Bae, S.J.; Kim, J.H.; Lee, M.J.; Baek, S.H.; Kook, Y.; Ahn, S.G.; Cha, Y.J.; Jeong, J. Predictive Markers of Treatment Response to Neoadjuvant Systemic Therapy with Dual HER2-Blockade. *Cancers* **2024**, *16*, 842. [CrossRef] [PubMed]
57. Ciarka, A.; Piątek, M.; Pęksa, R.; Kunc, M.; Senkus, E. Tumor-Infiltrating Lymphocytes (TILs) in Breast Cancer: Prognostic and Predictive Significance across Molecular Subtypes. *Biomedicines* **2024**, *12*, 763. [CrossRef]
58. Prat, A.; Guarneri, V.; Pascual, T.; Brasó-Maristany, F.; Sanfeliu, E.; Paré, L.; Schettini, F.; Martínez, D.; Jares, P.; Griguolo, G.; et al. Development and Validation of the New HER2DX Assay for Predicting Pathological Response and Survival Outcome in Early-Stage HER2-Positive Breast Cancer. *EBioMedicine* **2022**, *75*, 103801. [CrossRef]
59. Waks, A.G.; Ogayo, E.R.; Paré, L.; Marín-Aguilera, M.; Brasó-Maristany, F.; Galván, P.; Castillo, O.; Martínez-Sáez, O.; Vivancos, A.; Villagrasa, P.; et al. Assessment of the HER2DX Assay in Patients with ERBB2-Positive Breast Cancer Treated With Neoadjuvant Paclitaxel, Trastuzumab, and Pertuzumab. *JAMA Oncol.* **2023**, *9*, 835–840. [CrossRef]
60. Guarneri, V.; Bras-Maristany, F.; Dieci, M.V.; Griguolo, G.; Par, L.; Mar Ín-Aguilera, M.; Miglietta, F.; Bottosso, M.; Giorgi, C.A.; Blasco, P.; et al. HER2DX Genomic Test in HER2-Positive/Hormone Receptor-Positive Breast Cancer Treated with Neoadjuvant Trastuzumab and Pertuzumab: A Correlative Analysis from the PerELISA Trial. *EBioMedicine* **2022**, *85*, 104320. [CrossRef]
61. Bueno-Muiño, C.; Echavarría, I.; López-Tarruella, S.; Roche-Molina, M.; Del Monte-Millán, M.; Massarrah, T.; Jerez, Y.; Ayala de la Peña, F.; García-Sáenz, J.Á.; Moreno, F.; et al. Assessment of a Genomic Assay in Patients with ERBB2-Positive Breast Cancer Following Neoadjuvant Trastuzumab-Based Chemotherapy with or Without Pertuzumab. *JAMA Oncol.* **2023**, *9*, 841–846. [CrossRef]
62. Villacampa, G.; Tung, N.M.; Pernas, S.; Paré, L.; Bueno-Muiño, C.; Echavarría, I.; López-Tarruella, S.; Roche-Molina, M.; Del Monte-Millán, M.; Marín-Aguilera, M.; et al. Association of HER2DX with Pathological Complete Response and Survival Outcomes in HER2-Positive Breast Cancer. *Ann. Oncol.* **2023**, *34*, 783–795. [CrossRef] [PubMed]

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SPECIAL ARTICLE

Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INCIDENCE AND EPIDEMIOLOGY

Global estimates indicated 2.3 million new cases of breast cancer in 2020, contributing to nearly 12% of all new cancer cases, with 685 000 deaths in the same year.[1] Breast cancer detection has increased due to improvements in screening techniques. The mortality rate has decreased in recent years in Western populations, especially in younger age groups,[2,3] but breast cancer is still the leading cause of cancer-related deaths for women worldwide. Most early breast cancer (EBC) cases can be cured by multimodality treatment, although cure rates vary by clinical stage and subtype.

SCREENING, DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Breast cancer screening

Details on screening are covered in the Supplementary Material Section 1, available at https://doi.org/10.1016/j.

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annonc.2023.11.016, and are also described in the European Society for Medical Oncology (ESMO) Clinical Practice Guideline (CPG) for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes.[4]

DIAGNOSIS AND IMAGING

Diagnosis and imaging are described in the Supplementary Material Section 2, available at https://doi.org/10.1016/j.annonc.2023.11.016. Figure 1 shows a proposed algorithm for the diagnostic work-up and staging of EBC.

Hereditary breast cancer

Details on hereditary breast cancer are covered in the Supplementary Material Section 3, available at https://doi.org/10.1016/j.annonc.2023.11.016.

Histomorphological assessment, biomarkers and molecular pathology

Histomorphological assessment, biomarkers and molecular pathology are described in the Supplementary Material Section 4 and Supplementary Tables S1-S4, available at https://doi.org/10.1016/j.annonc.2023.11.016.

Recommendations

- Regular (every 2 years) mammography screening is recommended in average-risk women 50-69 years of age [I, A]. Regular mammography may also be carried out in women 45-49 and 70-74 years of age, although there is less evidence of benefit [I, B].
- Screening in women with a strong family history or known germline *BRCA1/2* and other high-risk pathogenic variants (PVs) should follow the ESMO CPG for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes [III, A].
- Further diagnostic work-up is based on clinical examination and imaging, including bilateral mammography and ultrasound (US) of both breasts and regional lymph nodes (LNs) or two-dimensional digital mammography in the symptomatic setting [I, A].
- Digital breast tomosynthesis (with or without synthetic mammography) and contrast-enhanced mammography can be considered as alternatives, where available and appropriate [II, B].
- Magnetic resonance imaging (MRI) of the breasts is recommended in case of uncertainties following standard imaging and in special clinical situations [e.g. familial breast cancer associated with germline *BRCA1/2* mutation (*gBRCA1/2m*) and other high-risk PVs, lobular cancers, suspicion of multifocality and/or multicentricity, presence of breast implants] [I, A].
- Assessment of distant metastases (bone, liver and lung) is recommended only in patients with stage IIb and higher disease (especially with extended LN involvement), patients with a high risk of recurrence at first diagnosis and/or symptomatic patients [III, A].
- Pretreatment pathological assessment, including a complete histomorphological, immunohistochemical and molecular assessment, if applicable, is recommended at the time of diagnosis and should include primary tumour histology and axillary node histology/cytology (if node involvement is suspected clinically) [I, A].
- Assessment should include histological type, grade and immunohistochemistry (IHC) evaluation of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) biomarkers and a proliferation marker such as Ki-67 [I, A]. FISH testing should be carried out in cases of an equivocal HER2 IHC score (HER2 2+) [I, A; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-A].
- Tumours should be grouped into biological subtypes, defined by routine histology and IHC results, as luminal A like, luminal B like, HER2 positive and triple negative [I, A]. Supplementary Material Section 4, available at https://doi.org/10.1016/j.annonc.2023.11.016, provides details on subtype classification.
- In cases of hormone receptor (HR)-positive, HER2-negative EBC with uncertainty about indications for adjuvant chemotherapy (ChT) (after consideration of all clinical and pathological factors), gene expression assays and endocrine response assessment in the preoperative setting can be used [II, B].
- Tumour-infiltrating lymphocytes (TILs) may add prognostic and predictive information, particularly in triple-negative breast cancer (TNBC) and HER2-positive breast cancer, but there are no distinct TIL thresholds for treatment decisions [I, B].
- Programmed death-ligand 1 (PD-L1) expression levels **should not** be used to guide treatment decisions in EBC [I, E].
- Germline testing and subsequent genetic counselling for PVs in *BRCA1/2* should be offered to patients who meet the respective national criteria and to those who are candidates for adjuvant olaparib therapy [I, A; ESCAT score: I-A].

STAGING AND RISK ASSESSMENT

Summary details on staging and risk assessment are included in the Supplementary Material Section 5 and Supplementary Tables S2-S4, available at https://doi.org/10.1016/j.annonc.2023.11.016.

Recommendations

- Disease stage and final pathological assessment of surgical specimens should be made according to the World Health Organization classification of tumours and the eighth edition of the Union for International Cancer Control TNM (tumour—node—metastasis) staging system [V, A].
- Minimum blood work-up (a full blood count, liver and renal function tests, alkaline phosphatase and calcium

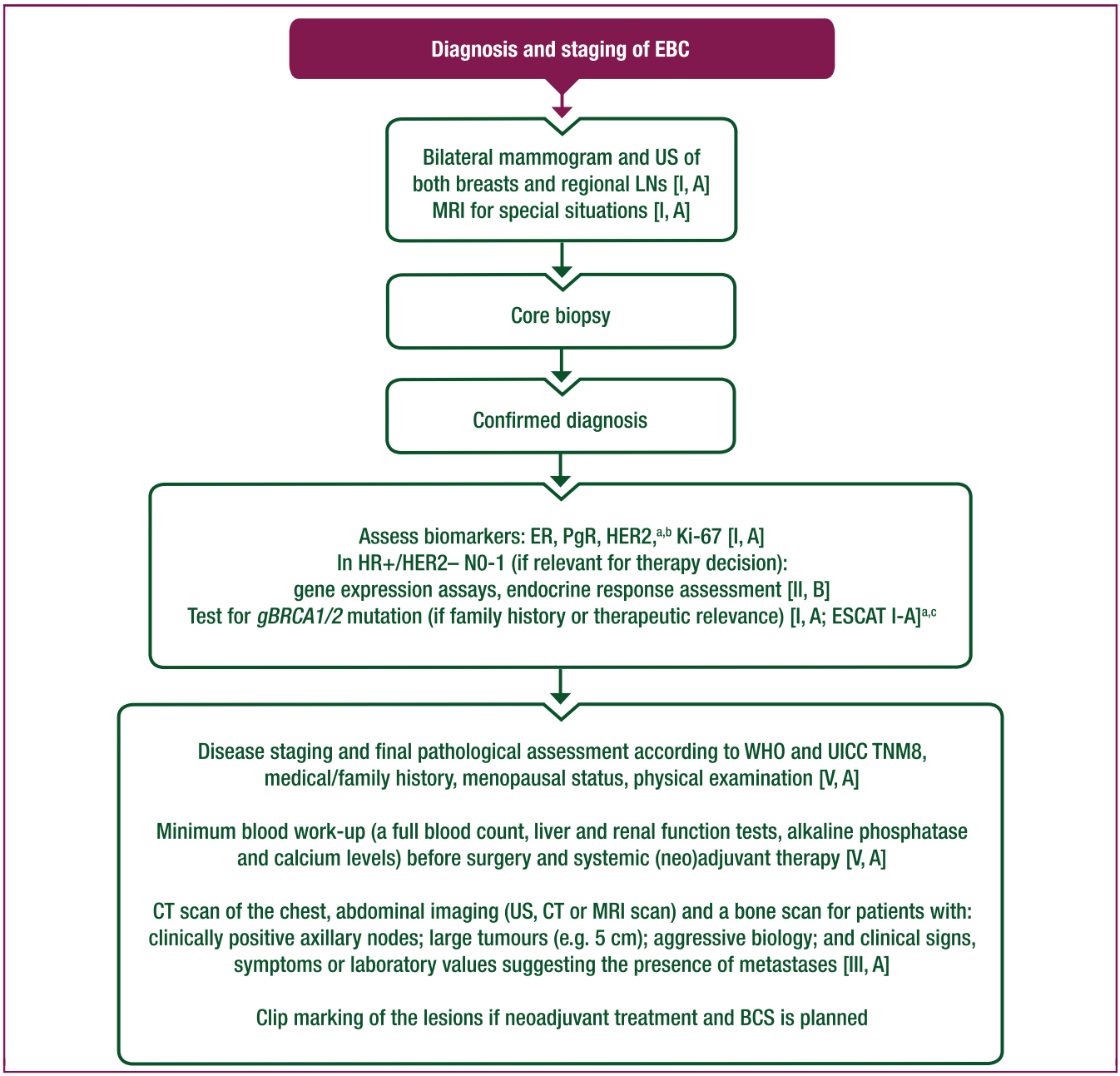

Figure 1. Diagnostic work-up and staging of EBC.
Purple: general categories or stratification; white: other aspects of management.
BCS, breast-conserving surgery; CISH, chromogenic *in situ* hybridisation; CPG, Clinical Practice Guideline; CT, computed tomography; EBC, early breast cancer; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; *gBRCA1/2*; germline *BRCA1/2*; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LN, lymph node; MRI, magnetic resonance imaging; N, node; PgR, progesterone receptor; TNM8, tumour—node—metastasis eighth edition; UICC, Union for International Cancer Control; US, ultrasound; WHO, World Health Organization.
[a]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.[114] See Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.11.016, for more information on ESCAT scores.
[b]ESCAT score only applicable if HER2 gene amplification assessed by FISH/CISH.
[c]Detailed rationale for *gBRCA*1/2 mutation testing is covered in the ESMO CPG for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes.[4]

levels) is recommended before surgery and systemic (neo)adjuvant therapy [V, A].

- A computed tomography (CT) scan of the chest, abdominal imaging (US, CT or MRI scan) and a bone scan can be considered for patients with:
  - o clinically positive axillary nodes
  - o large tumours (e.g. 5 cm)
  - o aggressive biology
  - o clinical signs, symptoms or laboratory values suggesting the presence of metastases [III, A]
- The complete medical and family history must be evaluated, including menopausal status (if in doubt, serum estradiol and follicle-stimulating hormone levels should be measured) [V, A].

- [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)—positron emission tomography (PET)—CT scanning may be used instead of CT and bone scintigraphy particularly for high-risk patients and when conventional methods are inconclusive [II, B].

MANAGEMENT OF EBC

General treatment principles

The recommendations in this guideline provide a framework to promote optimal patient care. However, treatment decisions for each patient should be based on an individual risk—benefit analysis considering patient/disease characteristics, comorbidities and patient preferences. All treatment decisions should be made as part of a shared decision-making process with the patient. Clinical trial participation is preferred whenever available.

Supplementary Material Section 6, available at https://doi.org/10.1016/j.annonc.2023.11.016, provides further details on general treatment principles.

For a general overview of EBC management, see Figure 2.

Patient communication and shared decision making

Supplementary Material Section 7, available at https://doi.org/10.1016/j.annonc.2023.11.016, provides details on patient communication and shared decision making.

Locoregional treatment

Surgery. Breast-conserving surgery (BCS) is an appropriate surgical option for most patients with breast cancer. For patients undergoing BCS, typically with post-operative radiotherapy (RT), also known as breast-conserving therapy (BCT), optimal oncological and cosmetic outcomes are important. It is, therefore, recommended that breast surgeons should either work with plastic surgeons or be trained in oncoplastic approaches themselves. Shared decision making should be facilitated using appropriate patient-oriented information tools.[5]

Margin status should be reported; for invasive cancer, no tumour at the inked margin is required; for *in situ* disease, $\geq$2 mm is preferred.[6]

Marking the tumour bed with clips facilitates an accurate planning of either the radiation boost field or for partial breast irradiation, if indicated.[7] The aim should be to achieve local recurrence rates of $<$0.5% per year and $\leq$5% overall per 5 years. Nipple-sparing mastectomy and skin-sparing mastectomy are generally considered oncologically safe while improving cosmetic outcomes for cases where primary breast conservation cannot be achieved.

Immediate or delayed breast reconstruction should be offered to most women requiring mastectomy. Oncological reasons to advise against immediate reconstruction include inflammatory breast cancer or situations where the risk of locoregional recurrence is high to avoid delays in initiating post-operative RT.[8] Autologous tissue-based reconstructive

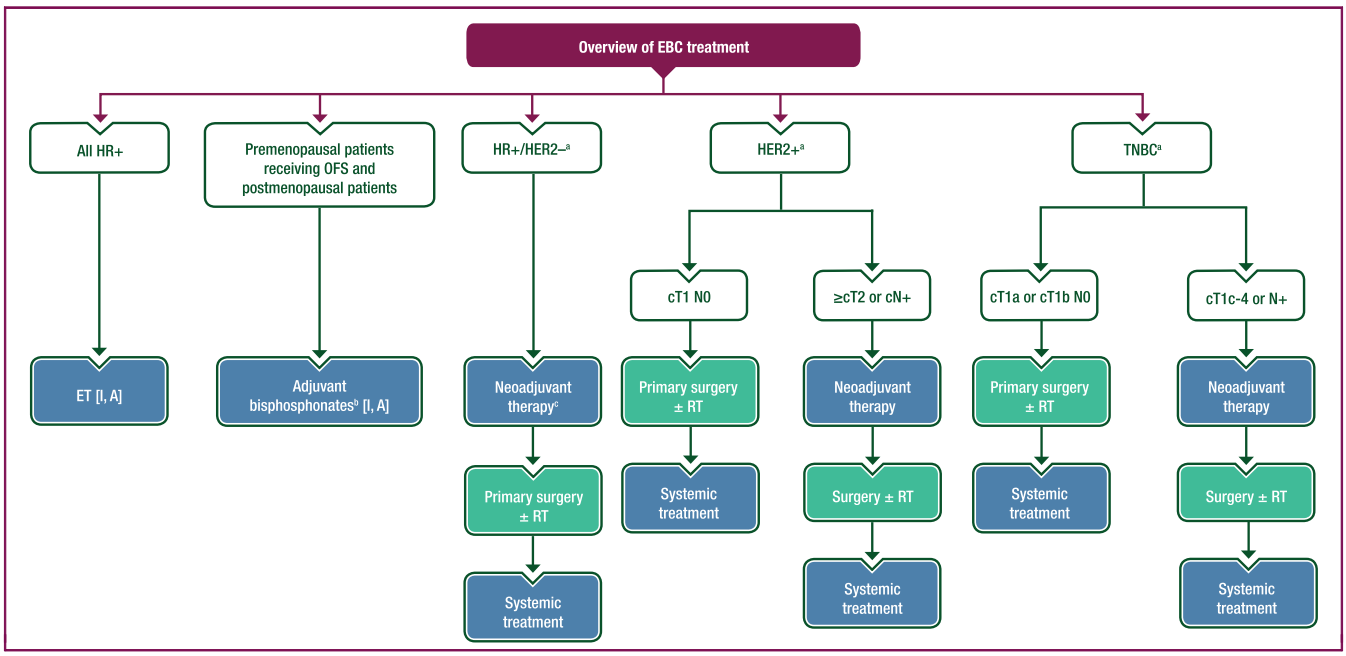

Figure 2. EBC treatment overview.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.
ALN, axillary lymph node; c, clinical; ChT, chemotherapy; CPG, Clinical Practice Guideline; DCIS, ductal carcinoma *in situ*; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; N, node; OFS, ovarian function suppression; T, tumour; TNBC, triple-negative breast cancer; RT, radiotherapy.
[a]See Figure 3 for management of ALN involvement and Figures 4-7 for systemic therapy according to breast cancer subtype. Recommendations for special situations (elderly patients, male breast cancer and DCIS) are described in the CPG text.
[b]Bisphosphonates are approved for treating bone metastases and osteoporosis and not for prevention of relapse.
[c]If ChT is indicated it may be given in the neoadjuvant setting.

techniques generally tolerate post-operative RT better than implant-based reconstruction, both preceding and following post-mastectomy RT (PMRT).[9]

For breast reconstruction, many immediate or delayed surgical options are available. Silicone gel implants are generally safe, but patients should be informed about the small risk of anaplastic large-cell lymphoma with certain implants.[10]

The optimal reconstruction technique should be discussed individually, considering anatomical, treatment- and patient-related factors and preferences.

Advances in management of axillary LNs. See Figure 3 for a treatment algorithm on the management of axillary LN (ALN) involvement with primary surgery or primary systemic/neoadjuvant therapy.

Regional LN status remains one of the strongest prognosticators of long-term outcome in EBC. Sentinel LN biopsy (SLNB) is the standard staging approach for clinically negative ALNs at diagnosis or after neoadjuvant ChT. SLNB is associated with less shoulder stiffness, pain and arm swelling morbidity than complete ALN dissection (ALND). With appropriate training, high identification rates (≥97%), low false-negative rates and favourable ALN recurrence rates following SLNB are achievable.[11] Notably, isolated ALN recurrence occurs in <1% of negative SLNBs despite a false-negative rate of 5%-10%.[12]

Micrometastases (0.2-2.0 mm) (N1mic) or isolated tumour cells (N0itc+) in treatment-naïve ALNs are prognostically equivalent to N0 disease, with local and systemic treatment options selected based on other tumour- and patient-based parameters. Based on the IBCSG 23-01 trial, further ALN treatment is not required if a sentinel LN (SLN) has micrometastases unless neoadjuvant therapy was given.[13] Routine IHC or PCR for the evaluation of SLNs in patients unexposed to neoadjuvant ChT is therefore not recommended.[14]

Micrometastases after neoadjuvant ChT indicate a non-pathological complete response (pCR) which is associated

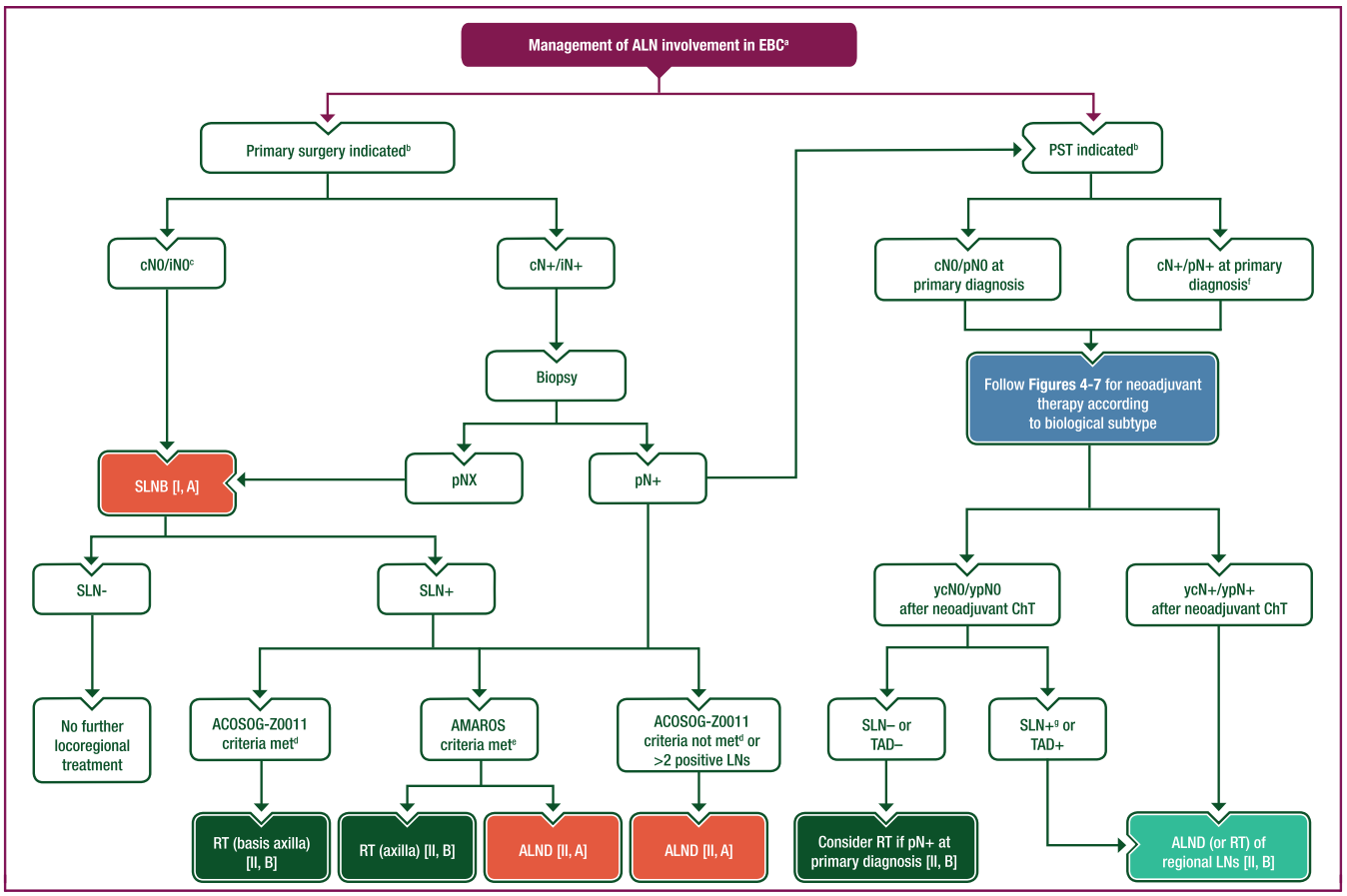

Figure 3. Management of ALN involvement in EBC.
Purple: general categories or stratification; red: surgery; turquoise: combination of treatments or other systemic treatments; blue: systemic anticancer therapy; dark green: RT; white: other aspects of management.
ALN, axillary lymph node; ALND, axillary lymph node dissection; c, clinical; ChT, chemotherapy; CT, computed tomography; EBC, early breast cancer: i, imaging; ITC, isolated tumour cell; LN, lymph node; MDT, multidisciplinary team; MRI, magnetic resonance imaging; N, node; p, pathological; PET, positron emission tomography; PST, primary systemic therapy; RT, radiotherapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection; US, ultrasound.
[a]Discuss in MDT whether number of LNs is important for systemic therapy allocation.
[b]See Figure 2 for an overview of primary surgery and neoadjuvant therapy indications.
[c]Imaging (axillary US is preferred but MRI and PET—CT may be used in specific cases where more detailed imaging is required).
[d]Refers to ACOSOG-Z0011 trial eligibility criteria.[12]
[e]Refers to AMAROS trial eligibility criteria.[117] OTOASOR trial criteria can also be considered.[17]
[f]Inflammatory breast cancer and patients with N2 or N3 stage disease should receive ALND unless otherwise defined in a clinical trial.
[g]If ITCs are detected, consider axillary and locoregional RT as an alternative to ALND if an impact on adjuvant systemic treatments is not anticipated.

with worse prognosis than micrometastases in treatment-naïve LNs.[15]

For cases with macrometastatic spread to the SLN, the ACOSOG Z0011 trial reported similar outcomes without ALND for patients with clinical T1-T2 cN0 invasive breast cancer who had 1-2 SLNs containing metastases but no gross extracapsular extension (treated with BCS, tangential post-operative RT including part of the axilla and adjuvant systemic therapy).[12] For patients who do not meet these criteria, and for patients with more than two positive SLNs, ALND remains the standard of care. Another option for patients with cN0 disease and SLN metastases is axillary RT, as demonstrated by the AMAROS and OTOASOR studies.[16,17] Nodal involvement-based indications for systemic therapy options (e.g. abemaciclib, olaparib) need to be considered by a multidisciplinary team (MDT) when choosing between ALND and RT in case of positive SLNs. The question of whether patients who have undergone mastectomy with or without an indication for PMRT (low-risk tumours, T <5 cm) can forego ALND after positive SLNB remains unresolved.[18] The benefit of ALND in patients with micrometastatic and macrometastatic SLNs after neoadjuvant ChT is currently being investigated. Thus, until outcomes are reported from randomised trials, ALND is recommended for ypN1mi as well as any macrometastatic disease (ypN+) regardless of other features. There are currently no available data on isolated tumour cells in ALND after neoadjuvant ChT.

Occult breast cancer presents as regional LN metastases without an identifiable primary lesion within the breast. It constitutes <0.5% of all new breast cancer cases. Routine diagnosis requires breast MRI and systemic staging, preferably by FDG—PET—CT. ALND with whole-breast RT (WBRT) and regional RT is the preferred treatment. Systemic therapy, including neoadjuvant therapy, should be according to recommendations by subtype and stage.[19]

Surgery after primary systemic/neoadjuvant therapy. Before primary systemic therapy (PST), it is recommended to mark the primary site (using a marker clip or carbon localisation) to facilitate accurate surgery when BCS is anticipated. In case of a positive ALN (cN1), marking the positive LN will allow ALND to be avoided for patients who are cN0 after PST. Although not mandatory, breast MRI is the most accurate modality for assessing the extent of residual disease following PST but only when coupled with pretreatment baseline MRI.

After PST, breast surgery must follow the same principles of oncological safety, low morbidity and good cosmesis as primary breast surgery. Downsizing of a large unifocal primary tumour with PST will allow BCS in a substantial proportion of patients. Even in cases with multifocal disease or when tumour shrinkage is limited, patients may still be eligible for BCS. Surgery following PST should usually be planned according to the new tumour extent and not the original tumour bed.[20]

In patients with clinically and imaging-negative axilla, SLNB after PST is the method of choice. In patients with biopsy-proven limited initial nodal involvement (pN1) who convert to clinically negative (ycN0), SLNB can be carried out safely, as shown by the results from the SENTINA, ACOSOG Z1071, SN FNAC and GANEA 2 trials.[21-24] In these studies, false-negative rates of SLN following PST ranged from 8% to 14%. False-negative rates can be decreased to <5% by marking the biopsied positive node(s) to verify their removal, as well as using a dual tracer and removing ≥3 SLNs—comparable to targeted axillary dissection involving removal of the clipped node plus ≥1 SLN. According to current evidence, any tumour deposits in SLNs following PST prompt ALND. Furthermore, available data from trials do not support the routine use of SLNB in patients with initial bulky nodal involvement [cN2-3 (detected clinically or on PET—CT)] or in inflammatory breast cancer, even if converted to ycN0 after PST.

WBRT after BCS. WBRT after BCS results in an absolute reduction in the 10-year risk of any first recurrence (locoregional or distant) and the 15-year risk of breast cancer-related mortality of 15.7% and 3.8%, respectively.[25] Boost RT reduces local recurrence rates compared with no boost (relative reduction of 41% and 35% at 10 and 20 years, respectively) and is indicated for patients with unfavourable risk factors for local control.[26]

Excellent results equivalent to WBRT are reported after accelerated partial breast irradiation (APBI) for well-selected patients with low-risk disease according to the European Society for Radiotherapy and Oncology (ESTRO) consensus recommendations.[27-29] Low-risk features suitable for partial breast irradiation are: luminal-like subtypes, small tumour (≤3 cm), absence of lymphovascular space invasion, non-lobular invasive carcinoma, tumour grade 1-2, low-to-intermediate-grade ductal carcinoma *in situ* (DCIS) (sized ≤2.5 cm with clear surgical margins ≥3 mm), age at diagnosis ≥50 years, unicentric or unifocal lesion, clear surgical margins (>2 mm), node negative (including isolated tumour cells) and no use of PST. Any technique, including external beam RT, brachytherapy, endocavitary and intraoperative RT with electron techniques, allowing full coverage of the entire target volume, is suitable.[28,30]

Omission of RT after BCS remains investigational. However, women at advanced age and/or with comorbidities, who intend to take ≥5 years of adjuvant endocrine therapy (ET), may forego RT if they accept an increased risk for local recurrences especially at long term as well as the possible side-effects of the ET.

PMRT. For patients with node-positive disease, PMRT results in an absolute reduction in first recurrence of 10.6% at 10 years and an absolute reduction in breast cancer-related mortality of 8.1% at 20 years.[31] PMRT is recommended for high-risk disease (including involved resection margins, ≥4 involved ALNs and T3-T4 tumours) independent of the nodal status. It should also be considered in patients with intermediate-risk features (e.g. lymphovascular invasion, age), including those with 1-3 positive ALNs.[31]

Regional RT. The use of comprehensive locoregional RT encompassing the chest wall and all regional LNs improves

outcomes, especially for patients with ALN involvement. Modern locoregional RT, based on CT-planned locoregional targets, will result in reduced recurrence with the main effect being on distant recurrence. RT has been shown to significantly reduce breast cancer mortality [rate ratio 0.87, 95% confidence interval (CI) 0.80-0.94, $P = 0.0010$], with no significant effect on non-breast-cancer mortality (0.97, 0.84-1.11, $P = 0.63$), leading to significantly reduced all-cause mortality (0.90, 0.84-0.96, $P = 0.0022$).[32]

In the case of PST, indications and target volumes can be individualised based on the clinical tumour stage combined with the tumour response. The ESTRO guidelines for target volume delineation in breast cancer precisely describe the LN location to be treated, specifying that in regionally advanced disease, individualisation is required.[33]

After ALND, the resected part of the axilla should not be irradiated, except in cases of clear residual disease after surgery. After a positive SLNB without subsequent ALND, regional RT is advised, the extent being defined by other risk factors (e.g. lowest risk: no RT; intermediate risk: exclusive level 1-2 RT; highest risk: full level 1-4 RT including the internal mammary nodes).[25,31,34]

RT and breast reconstruction. PMRT can be administered after immediate breast reconstruction. Better outcomes are usually obtained with autologous tissue reconstruction.[9]

RT doses and fractionation. Doses used for local and/or regional adjuvant irradiation have historically been 45-50 Gy in 25-28 fractions of 1.8-2.0 Gy with a typical boost dose of 10-16 Gy in 2 Gy single doses. Moderate hypofractionation (e.g. 15-16 fractions of 2.50-2.67 Gy single dose) has shown equivalent effectiveness and comparable side-effects. The FAST-Forward trial demonstrated that after 6 years' median follow-up, ultra-hypofractionation of 26 Gy in five fractions in 1 week results in the same oncological and safety outcomes for breast and chest wall irradiation.[35] In terms of outcomes after ultra-hypofractionation for locoregional RT, data from a prospective sub-study are awaited. The ESTRO Advisory Committee in Radiation Oncology Practice consensus recommends shorter regimens whenever indicated.[29] Another ultra-hypofractionation regimen using fraction sizes of 5.7-6.0 Gy, delivered once a week over 5 weeks, can be used for frail patients with difficulties of daily transportation.[36]

(Neo)adjuvant systemic treatment

General aspects of systemic therapy. The decision regarding systemic treatment should be based on the opportunities for pathological response-guided post-operative systemic therapy and the benefit from its use as well as an individual's risk of relapse and predicted sensitivity to treatment types. The final decision should also incorporate the short- and long-term toxicities and the patient's biological age, general health status, comorbidities and preferences. Neoadjuvant therapy should start as soon as diagnosis and staging are completed (ideally within 2-4 weeks). Adjuvant systemic therapy should be started without undue delays (ideally within 4-6 weeks), as data show a decrease in efficacy when it is administered >12 weeks after surgery.[37] Whenever systemic adjuvant ChT is indicated, neoadjuvant use of the same regimen can also be considered. ET should be used in all patients with HR-positive breast cancer unless contraindicated.[38]

HR-positive, HER2-negative EBC. Figures 4 and 5 provide treatment algorithms and Supplementary Table S5,

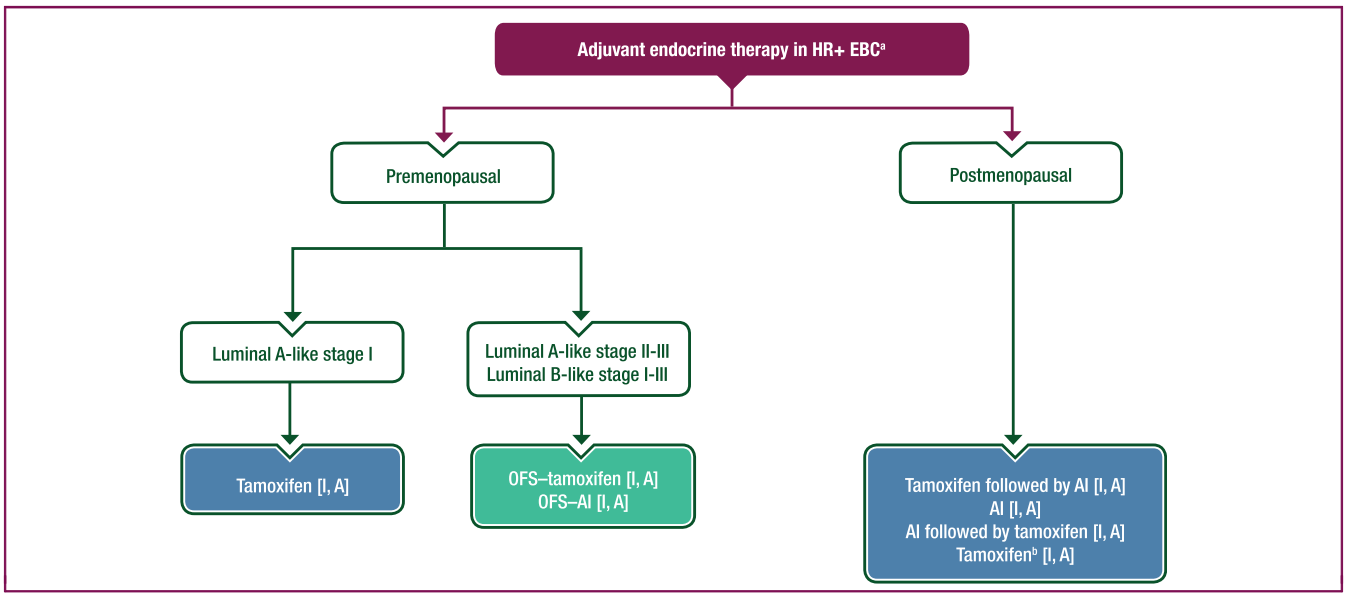

Figure 4. Role of adjuvant endocrine therapy in HR-positive EBC.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.
AI, aromatase inhibitor; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OFS, ovarian function suppression.
[a]See Figure 2 for the role of surgery in HR-positive, HER2-negative EBC.
[b]Tamoxifen can be given for lower-risk tumours or if AIs are not tolerated [I, A].

available at https://doi.org/10.1016/j.annonc.2023.11.016, provides an overview of adjuvant therapy for patients with HR-positive, HER2-negative EBC.

HR-positive, HER2-negative tumours are the most common type of EBC, accounting for >70% of all cases worldwide. Risk factors for recurrence of HR-positive cancers are well established (see the 'Screening, diagnosis, pathology and molecular biology' section of this guideline).

Treatment is individualised based on tumour stage and biology [subtype (Supplementary Material Section 4, available at https://doi.org/10.1016/j.annonc.2023.11.016, provides details on subtype classification)], menopausal status and the several classes of therapeutic interventions available, including ET, ChT and targeted therapy. Although the relative benefit of ChT and ET might be the same in different subgroups, the absolute benefit depends on the individual risk of recurrence. The absolute benefit should be considered in conjunction with the side-effects of each treatment in an informed decision-making process with the patient.

Anatomic risk variables (tumour size, nodal status) do not influence treatment sensitivity or the relative benefit from

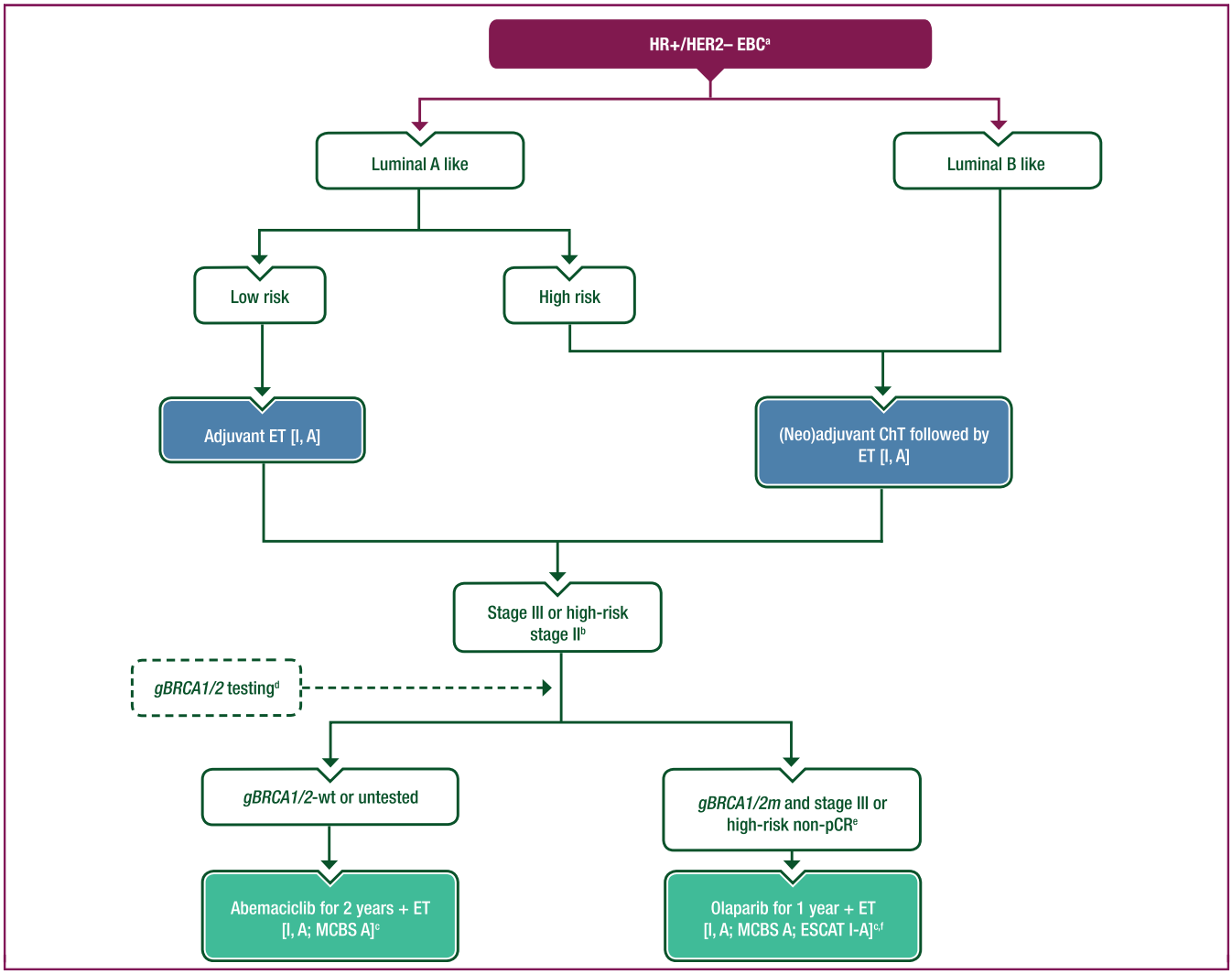

Figure 5. Systemic treatment of HR-positive, HER2-negative EBC.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy; dashed line: optional recommendation.
ChT, chemotherapy; CPS + EG, pretreatment clinical stage and post-treatment pathological stage, estrogen receptor and tumour grade; EBC, early breast cancer; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; *gBRCA1/2*, germline *BRCA1/2;* HER2, human epidermal growth factor receptor 2; HR, hormone receptor; m, mutation; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; pCR, pathological complete response; wt, wild type.
[a]See Figure 2 for the role of surgery in HR-positive, HER2-negative EBC.
[b]Stage N1 with primary tumour >5 cm, and/or grade 3 and/or Ki-67 ≥20%.
[c]ESMO-MCBS v1.1[115] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[d]If *gBRCA1/2* testing is appropriate and feasible.
[e]Patients with HR-positive tumours and non-pCR after neoadjuvant ChT require a CPS + EG score ≥3 to receive olaparib.[118]
[f]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.[114] See Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.11.016, for more information on ESCAT scores.

adjuvant therapy; however, by guiding therapy selection, they can have a major impact on absolute risk reduction. Higher-risk HR-positive tumours generally warrant aromatase inhibitor (AI)-based therapy, consideration of ChT, targeted treatments, extended adjuvant ET and, for premenopausal women, ovarian function suppression (OFS) and ChT.

For most HR-positive, HER2-negative, screening-detected breast cancer, surgery is the initial treatment modality. For women with larger tumours or clinical nodal involvement, neoadjuvant systemic therapy may be preferred. Neoadjuvant ChT can be effective for surgical downstaging of HR-positive, HER2-negative cancers; however, pCR is uncommon although it occurs more frequently in young patients and/or patients with high-grade tumours.[39] For selection of appropriate neoadjuvant treatments, similar considerations as for adjuvant therapy apply.

Adjuvant ChT reduces the relative recurrence risk and improves survival in women by 25%-30% irrespective of the subtype.[40-44] Defining cohorts most appropriate for ChT increasingly depends on classifying tumours based on genomic signatures as well as other biological factors (i.e. ER, PgR, HER2 and Ki-67) that refine prognosis beyond pathology alone. The combination of low grade and/or low Ki-67 level with strong ER/PgR expression and endocrine response to a short course of preoperative ET may serve as surrogates for a sufficiently favourable biology.[45,46] Among postmenopausal women with node-negative disease or with 1-3 positive nodes and low-risk genomic signature scores/low-risk biology, adjuvant ChT did not further reduce recurrence rates compared with ET alone.[47-49] Among premenopausal women with node-negative disease or 1-3 positive nodes and low-risk genomic signature scores, adjuvant ChT did reduce recurrence rates compared with ET alone.[47,49] Some of this benefit may be due to ChT-induced amenorrhoea, though it is unclear precisely how much of the difference is accounted for by direct cytotoxicity against micrometastatic cancer versus secondary endocrine effects of ChT. Endocrine response assessment using Ki-67 response (Ki-67 $\leq$10%) after a 4-week preoperative ET regimen may be used to estimate benefit from adjuvant ChT in patients with 0-3 involved LNs.[45,46] For women with HR-positive, HER2-negative breast cancer warranting ChT, anthracycline, taxane and alkylator-based ChT regimens are standard but non-anthracycline-based regimens may be appropriate for stage I and II cancers with limited nodal involvement.

Adjuvant ET is almost universal for patients with HR-positive invasive breast cancer of any stage and HER2 status and reduces the risk of locoregional recurrence, distant metastatic recurrence and contralateral breast cancer, while improving overall survival (OS).[50,51]

Among premenopausal women with higher-risk HR-positive cancers, OFS paired with an AI or tamoxifen reduces the likelihood of recurrence and improves OS versus tamoxifen alone. OFS with an AI reduces recurrences compared with OFS with tamoxifen.[51] In postmenopausal women, AIs, used either upfront or sequentially after 2-3 years of tamoxifen, offer lower risk of recurrence compared with tamoxifen alone, especially in higher-stage cancers.[51] Standard treatment duration is 5 years but extended durations to 7 or 10 years further lower recurrence risk and increase survival, particularly in higher-stage cancers.[52,53]

The use of adjuvant bisphosphonate therapy in postmenopausal women with EBC, as well as premenopausal women receiving OFS, can lower the risk of tumour recurrence and mitigate the side-effects of osteopenia/osteoporosis seen with AIs. A meta-analysis published by The Early Breast Cancer Trialists' Collaborative Group indicates a benefit irrespective of the HR status and bisphosphonate type or regimen. Large randomised trials of adjuvant denosumab have had mixed results in terms of impact on breast cancer outcomes and it is therefore not recommended.[54,55]

Targeted therapy with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in addition to ET has been widely studied in EBC. The addition of abemaciclib for 2 years reduced the absolute risk of recurrence at 4 years by 6.4% (hazard ratio 0.664, 95% CI 0.578-0.762, $P < 0.0001$) in a cohort of women with HR-positive, HER2-negative breast cancer with either $\geq$4 involved LNs, 1-3 positive nodes with either T3 (>5 cm) tumours or grade 3 histology or Ki-67 expression $\geq$20%.[56] The NATALEE trial evaluated the addition of ribociclib 400 mg/day (days 1-21 of every 28-day cycle) for 3 years to adjuvant ET in women with American Joint Committee on Cancer (eighth edition) stage II (either N0 with grade 2-3 and/or Ki-67 $\geq$20% or N1) or stage III HR-positive, HER2-negative breast cancer. It reached its primary endpoint with a 3.3% improvement in 3-year invasive disease-free survival (iDFS) (hazard ratio 0.748, 95% CI 0.618-0.906, $P = 0.0014$).[57] Pending approval by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA), this could potentially be another option for intermediate- and high-risk disease.

In patients with *gBRCA1/2m* and high-risk HER2-negative tumours, adjuvant olaparib for 1 year improves DFS (hazard ratio 0.63, 95% CI 0.5-0.78) and OS (hazard ratio 0.68, 95% CI 0.47-0.97, $P = 0.009$) irrespective of HR status. At 4 years, the absolute differences in iDFS and distant DFS were 7.3% (95% CI 3.0% to 11.5%) and 7.4% (95% CI 3.6% to 11.3%), respectively. Patients with HR-positive tumours had to have $\geq$4 involved LNs at diagnosis or a clinical and pathological stage plus ER and nuclear grade (CPS + EG) score $\geq$3 to be eligible for inclusion in the trial.[58]

Though supportive interventions can reduce many therapy-related side-effects, considering the modest reductions in recurrence or improvement in OS with many common treatments for ER-positive breast cancer, especially in lower-risk tumours, patient preferences are an important part of the equation governing adjuvant treatment recommendations.

HER2-positive EBC. The addition of trastuzumab to ChT improves OS by approximately one-third. The relative magnitude of the survival benefit for patients with HR-positive EBC is the same as for those with HR-negative

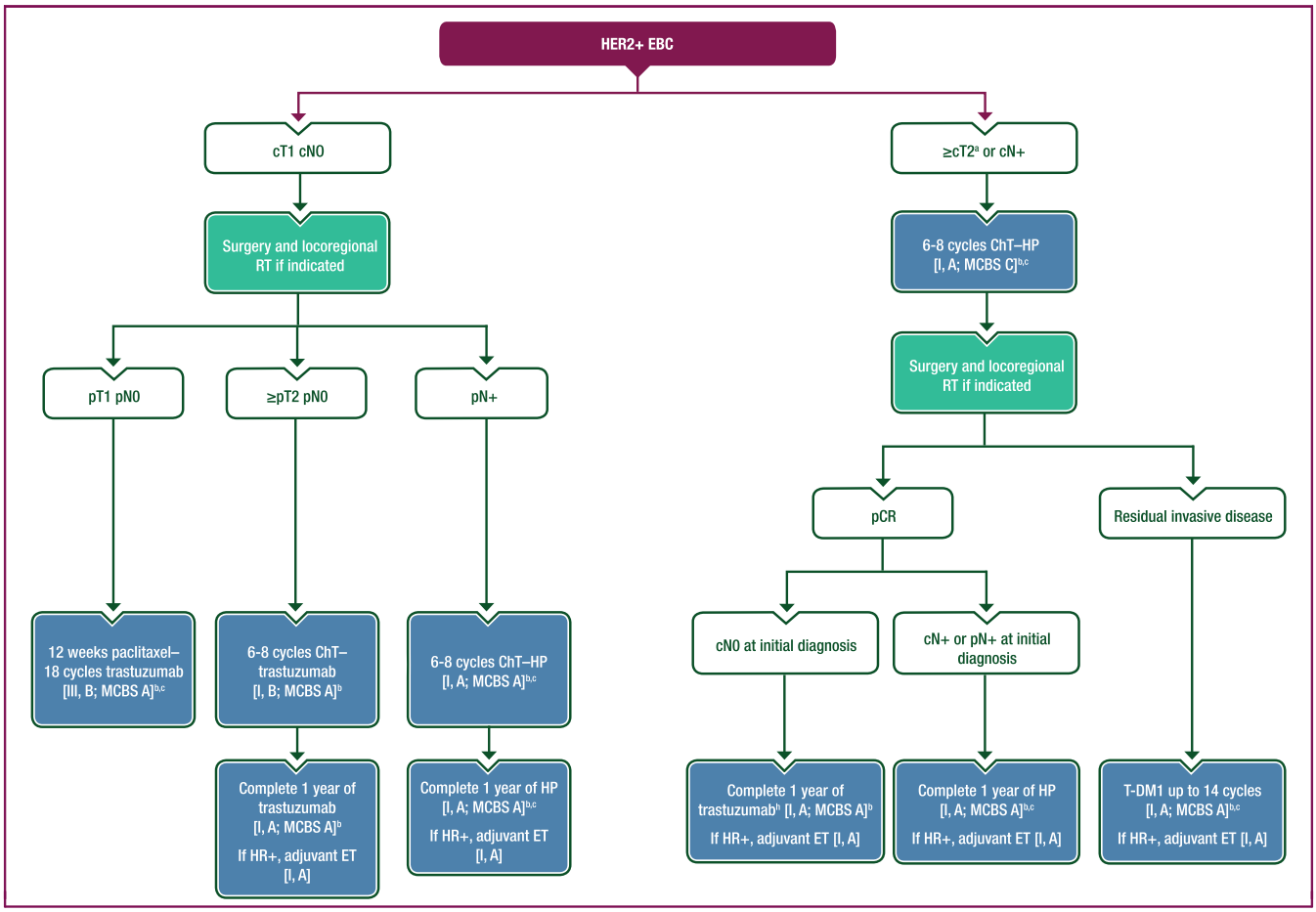

Figure 6. Management of HER2-positive EBC.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.
c, clinical; CISH, chromogenic *in situ* hybridisation; ChT, chemotherapy; EBC, early breast cancer; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HP, trastuzumab—pertuzumab; HR, hormone receptor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; p, pathological; pCR, pathological complete response; RT, radiotherapy; T, tumour; T-DM1, trastuzumab emtansine.
[a]Tumours <2 cm can be considered for neoadjuvant therapy.
[b]ESMO-MCBS v1.1[115] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[c]ESCAT score I-A if HER2 gene amplification by FISH/CISH. ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.[114] See Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.11.016, for more information on ESCAT scores.

EBC after 10 years of follow-up; however, the latter have earlier recurrences.[59] Figure 6 provides a treatment algorithm for patients with HER2-positive EBC.

Neoadjuvant and post-neoadjuvant systemic treatment based on pCR. In patients with clinical stage II-III disease, the preferred option is initial preoperative systemic therapy followed by local therapy, with the aim of evaluating treatment efficacy by pathological response assessment, guiding risk stratification, reducing the extent of surgical need and determining the adjuvant treatment plan. Patients with a pCR after neoadjuvant treatment demonstrate a substantially lower risk of disease recurrence.[39] However, patients with a high initial tumour burden are still at elevated risk of relapse even with a pCR.[60,61] The presence of residual invasive tumour in the breast or nodes indicates poorer outcomes.[39] Anthracycline—taxane-based combinations with HER2-targeted agents have been a backbone of (neo)adjuvant ChT in patients with HER2-positive disease[62] but are associated with a very low, but potentially serious risk of cardiac toxicity and secondary acute myeloid leukaemia (one additional treatment-induced leukaemia per 400-500 patients).[63,64] Anthracycline-free regimens comprising carboplatin with taxanes have been tested in phase II (PREDIX HER2, TRAIN2, TRYPHAENA) and III (BCIRG-006) clinical trials, reporting similar outcomes to anthracycline-containing regimens and improved cardiac safety.[65-68] Neoadjuvant ChT combined with dual HER2 blockade [trastuzumab—pertuzumab (HP)] results in higher pCR rates compared with trastuzumab alone, translating into improved outcomes, particularly among patients with LN-positive cancers.[69] In low-to-intermediate-risk HER2-positive, HR-negative disease, 12 weeks of paclitaxel in combination with HP without post-operative anthracyclines showed a pCR rate of >90% and an iDFS at 5 years of ~98% in highly selected patients in a single-arm phase II

study.[70] This regimen is currently being evaluated in other optimisation trials.[71]

Patients with pCR after standard neoadjuvant systemic therapy should continue anti-HER2 therapy for a total duration of 1 year.[70] The phase III KATHERINE trial reported improved outcomes in patients who had residual invasive cancer and received adjuvant trastuzumab emtansine (T-DM1) instead of trastuzumab; the proportion of patients free of invasive disease at 3 years was 88.3% versus 77.0%, respectively.[72] T-DM1 significantly decreased the risk of recurrence of invasive breast cancer or death (hazard ratio 0.50, 95% CI 0.39-0.64, $P < 0.001$). T-DM1 was effective irrespective of the HER2 status in the non-pCR specimen.[73] Adjuvant RT and ET may safely be given concurrently with T-DM1 but data are limited for patients having extensive nodal irradiation including internal mammary nodes.[74] For patients with a pCR who were clinically node negative at initial diagnosis, the addition of pertuzumab to trastuzumab should not be considered on a routine basis in the post-neoadjuvant treatment setting. There is potential benefit in patients who are suspected to have been node positive at baseline (∼30% of patients[11]).[75]

Adjuvant therapy for HER2-positive breast cancer. Patients with HER2-positive breast cancer treated with initial surgery should receive adjuvant treatment with HER2-directed therapy plus ChT and ET if HR positive. ESCAT scores apply only in the case of HER2 gene amplification by FISH/chromogenic *in situ* hybridisation.

De-intensification of adjuvant treatment can be considered for pathological stage pT1 pN0 disease, using a regimen of weekly paclitaxel for up to 12 doses along with 12 months of trastuzumab. This de-intensified regimen provided low recurrence rates in a prospective single-arm phase II trial, reporting 10-year iDFS, breast cancer-specific survival and OS rates of 91.3%, 98.8% and 94.3%, respectively.[76]

The APHINITY trial compared adjuvant HP with trastuzumab—placebo, both in combination with anthracycline-based (78%) or non-anthracycline-based ChT. The initial report demonstrated that HP significantly improved 3-year iDFS (hazard ratio 0.81, 95% CI 0.66-1.00, $P = 0.045$).[77] With longer follow-up, the N+ subgroup maintained a clear iDFS benefit favouring HP, with an 8-year iDFS of 86% versus 81% (hazard ratio 0.72, 95% CI 0.60-0.87) without significantly improving OS; no benefit was seen in the node-negative subgroup.[75] The HR-positive cohort derived at least the same benefit as the HR-negative group.[75]

Duration of adjuvant treatment with HER2-targeted therapy. The length of trastuzumab administration in the adjuvant setting has been established based on the results of pivotal trials, which have arbitrarily chosen a duration of 12 months.[59] The HERA trial reported no additional benefit from 2 years of treatment.[78] Clinical studies have investigated the non-inferiority of a shorter duration of trastuzumab of 6 months versus 12 months. The PERSEPHONE trial claimed non-inferiority for 6 months versus 12 months of trastuzumab treatment,[79] while others could not rule out non-inferiority.[80] While these results are considered inconclusive, the benefit of 12 months versus 6 months of trastuzumab may need to be balanced against the baseline risk of recurrence in resource-constrained settings with limited ability to provide 12 months of treatment.[81] It remains unknown whether patients who achieve a complete response to neoadjuvant ChT plus HER2-targeted therapy need to complete 12 months of trastuzumab.

Tyrosine kinase inhibitors as adjuvant therapy. Adjuvant tyrosine kinase inhibitors have been evaluated in clinical trials in HER2-positive EBC. None of the trials evaluating lapatinib in EBC significantly improved outcomes. The phase III ExteNET trial evaluated 1 year of extended therapy with neratinib after completion of 1 year of adjuvant trastuzumab. This trial showed that neratinib significantly improved iDFS overall (hazard ratio 0.73, 95% CI 0.57-0.92, $P = 0.0083$) but largely in the subgroup of HR-positive tumours (hazard ratio 0.60, 95% CI 0.43-0.83, $P = 0.063$).[82,83] The study was conducted before the advent of pertuzumab- or T-DM1-based therapies, which are now standard. Neratinib is associated with high rates of moderate to severe diarrhoea; however, implementation of a dose escalation schedule and optimisation of prophylactic interventions can result in lower grade 3 diarrhoea rates, better therapeutic adherence and lower discontinuation rates.[84]

TNBC. Figure 7 provides a treatment algorithm for patients with early TNBC.

Neoadjuvant ChT is the standard for T1c/N0 or greater TNBC. The majority of patients with pT1a pN0 disease do not benefit from adjuvant ChT while data on the efficacy of adjuvant ChT in pT1b pN0 are unclear. Patients with low-grade TNBC of specific histologies (e.g. adenoid cystic, secretory, medullary) seem to derive little or no benefit from adjuvant ChT, particularly in those with low-risk clinical features, although confidence in these results is limited by small numbers and the retrospective nature of the data.[85,86]

The agents in the ChT regimens do not differ between neoadjuvant and adjuvant treatment other than the use of pembrolizumab in the neoadjuvant setting for high-risk patients. However, neoadjuvant treatment allows pathological response-guided adjuvant treatment that can improve survival, and is therefore the preferred strategy. Evidence-based regimens without immune checkpoint inhibitors (ICIs) are sequential: anthracycline-based therapy followed by a taxane or taxane—carboplatin or vice versa. The benefit from carboplatin is independent of *gBRCA1/2m* status.[87,88] The standard anthracycline-based regimens are doxorubicin—cyclophosphamide (AC) or epirubicin—cyclophosphamide (EC) given for four cycles over 8 or 12 weeks followed by a taxane given for four cycles over 8 or 12 weeks. Dose-dense therapies, including dose-dense AC or EC and weekly paclitaxel, are preferred.[41] Six cycles of a non-anthracycline, taxane-based regimen, such as docetaxel—cyclophosphamide or a taxane plus carboplatin,

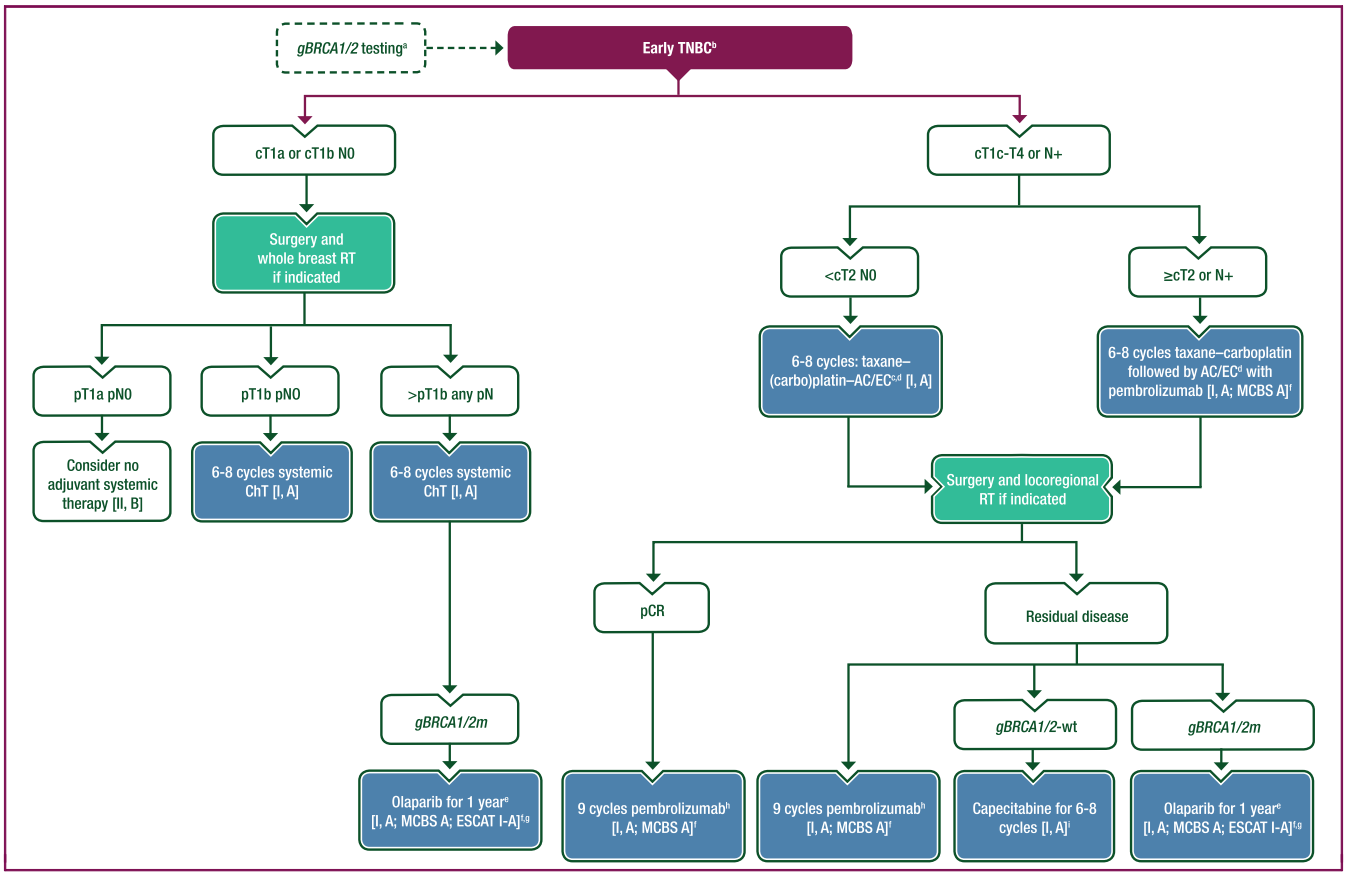

Figure 7. Management of early TNBC.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy; dashed line: optional recommendation.
AC, doxorubicin—cyclophosphamide; c, clinical; ChT, chemotherapy; CPG, Clinical Practice Guideline; EC, epirubicin—cyclophosphamide; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; *gBRCA1/2,* germline *BRCA1/2*; G-CSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICI, immune checkpoint inhibitor; m, mutation; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; p, pathological; pCR, pathological complete response; PgR, progesterone receptor; RT, radiotherapy; T, tumour; TNBC, triple-negative breast cancer; wt, wild type.
[a]See the ESMO CPG for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes.[4]
[b]HER2− tumours with 1%-9% ER and/or PgR expression (ER-low/PgR-low) are a heterogenous group, some of which behave biologically similarly to TNBC; therapeutic strategies should be adjusted to this specific situation since this might lead to a higher response to ChT and to reduced efficacy of ET compared with classical HR+ breast cancer [II, B].
[c]These evidence-based regimens without ICIs are sequential: anthracycline-based therapy followed by a taxane or taxane—carboplatin or vice versa.
[d]The use of dose-dense schedules of ChT, with G-CSF support, should be considered given their documented benefit over non-dose-dense schedules [I, A].
[e]Indicated as adjuvant therapy for patients with *gBRCA1/2m* tumours and non-pCR or ≥pT2 or ≥pN1 if treated with initial surgery.
[f]ESMO-MCBS v1.1[115] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[g]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.[114] See Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.11.016, for more information on ESCAT scores.
[h]Only if pembrolizumab was given preoperatively.
[i]Only for ICI-naïve patients.

may be used as an alternative in patients for whom anthracyclines are contraindicated. Adding carboplatin to the taxane improves pCR rates and event-free survival (EFS) but its impact on OS is less certain. Patients with *gBRCA1/2m* respond very well to standard anthracycline—taxane-based ChT irrespective of platinum use. Single-agent poly (ADP-ribose) polymerase (PARP) inhibitors induce high (>40%) pCR rates, but are not considered standard of care as neoadjuvant therapy and may be best reserved for adjuvant therapy for patients with residual disease after PST. pCR remains a prognostic factor regardless of *gBRCA1/2m* status.[87-89]

In patients with stage II-III TNBC, a four-drug ChT regimen of taxane—carboplatin followed by AC or EC, all combined with pembrolizumab, improved pCR rate and EFS at 3 years (hazard ratio 0.63, 95% CI 0.48-0.82, $P < 0.001$). Pembrolizumab was continued after surgery for nine 3-week cycles. The benefit from pembrolizumab was independent of PD-L1 status.[90] In a phase III trial using a nab-paclitaxel—anthracycline backbone, neoadjuvant atezolizumab also improved pCR rate regardless of PD-L1 status.[91] A randomised phase II study using nab-paclitaxel and EC as ChT backbone with or without durvalumab (only given in the neoadjuvant setting) resulted in a numerical non-significant

improvement in pCR rate but significantly improved EFS and OS.[92]

Residual disease after neoadjuvant therapy. In the CREATE-X trial, adjuvant capecitabine improved DFS (hazard ratio 0.70, 95% CI 0.53-0.92, $P = 0.01$) and OS (hazard ratio 0.59, 95% CI 0.39-0.90, $P = 0.01$); this benefit was only significant in patients with TNBC tumours.[93] Two recent reviews found that adjuvant capecitabine improved OS, by a relative reduction of 12%-30% in patients with TNBC but little evidence of impact in those with HR-positive disease.[94,95] Low-dose capecitabine also improves outcomes after standard non-platinum-containing adjuvant ChT.[96]

It is unknown whether post-neoadjuvant capecitabine adds benefit in patients receiving post-neoadjuvant continuation of their ICI or olaparib (indicated as adjuvant therapy for patients with *gBRCA1/2m* tumours and non-pCR or ≥pT2 or ≥pN1 if treated with initial surgery). No efficacy results are available for either of these combinations in the adjuvant setting. The understanding of safety of olaparib—capecitabine is also insufficient to support use of this combination.

Special situations

Refer to the Supplementary Material Section 8, available at https://doi.org/10.1016/j.annonc.2023.11.016, for further details on elderly patients, male breast cancer and other special populations.

Adjuvant therapy for DCIS

Surgery. Breast surgery for DCIS should follow the recommendations for invasive carcinoma, as discussed in the Locoregional treatment—Surgery section of this document. For *in situ* disease, margins of ≥2 mm are preferred.[6]

ALN evaluation with SLNB is not routinely required in DCIS. To exclude microinvasive disease, SLNB should be considered if mastectomy is undertaken or for large (>5 cm) or high-risk DCIS. The likelihood of a positive SLN with pure DCIS is low (∼5%).[97]

RT. WBRT after BCS for DCIS halves the risk of local recurrence without impact on survival.[98] Total mastectomy with clear margins in DCIS is curative.[99] Young age, inadequate margins and greater disease volume are associated with higher risk of local recurrence after BCS with or without RT, while young age, high grade and microinvasion are associated with higher risk of local recurrence after mastectomy. In patients with low-risk DCIS (tumour size <10 mm, low or intermediate nuclear grade, adequate surgical margins), omitting RT can be an option.[100] Hypofractionated regimens can be used instead of longer treatment schedules; in intermediate-/high-risk patients, the addition of a boost dose to the primary tumour bed lowers recurrence rates.[101] APBI is an alternative to WBRT for low-risk DCIS, as defined in the 'WBRT after BCS' subsection of this guideline.[29]

Systemic therapy. In patients treated with BCT for HR-positive DCIS, both tamoxifen and AIs (postmenopausal patients only) reduce the risk of invasive and non-invasive recurrences and reduce the incidence of second primary (contralateral) breast cancer, albeit without an effect on OS.[102-104] In the TAM-01 trial, low-dose tamoxifen (5 mg daily) also decreases the risk of recurrence after DCIS.[105]

Recommendations

General treatment principles

- Where available, treatment should be carried out in specialised breast units/centres by a specialised MDT that can refer patients to other specialties [III, A].
- Participation in clinical trials is recommended [V, A].
- The treatment strategy for each patient should be based on an individual risk—benefit analysis considering the tumour burden (size and location of the primary tumour, number of lesions and extent of LN involvement) and biology (pathology, including biomarkers and gene expression), as well as age, menopausal status, general health status and patient preferences [I, A].
- Age should be considered in relation to other factors and should not be the primary determinant for treatment decisions [IV, A].
- Fertility and fertility preservation should be discussed with younger premenopausal patients (irrespective of stage of disease) before the initiation of any systemic treatment [V, A].[106]

Patient communication and shared decision making

- Information on diagnosis and treatment choice should be given repeatedly (both verbally and in writing) in a comprehensive and easily understandable manner [V, A].
- The use of reliable, patient-centred websites or similar sources of information is recommended [V, A].
- Patients should be actively involved in all management decisions and should have equitable access to the full range of reproductive care options including pregnancy counselling, contraception and fertility preservation [V, A].

Locoregional treatment

- BCS with post-operative RT is the preferred local treatment option for the majority of patients with EBC [I, A].
- If mastectomy is indicated/preferred, breast reconstruction should be offered, except for primary inflammatory and other high-risk tumours where delays in systemic/radiation treatment would compromise care [V, A].
- SLNB is the standard axillary surgery in all cN0 patients [I, A].
- In the absence of prior PST, patients with micrometastatic spread and those with limited SLN involvement (1-2 affected SLNs) in cN0, following BCS with subsequent WBRT, eventually including the lower part of axilla and adjuvant systemic treatment, do not need further axillary surgery [II, A].
- ALND following positive SLNB with <3 involved SLNs is generally recommended only in case of expected high axillary disease burden or impact on further adjuvant systemic treatment decisions [II, A].

- Surgical planning following PST should consider the post-PST situation [II, A].
- WBRT is recommended after BCS [I, A].
- Hypofractionated schedules are recommended: moderate (i.e. 15-16 fractions of $\leq$3 Gy per fraction daily for all indications of post-operative RT) and ultra-hypofractionated [i.e. 26 Gy in five daily fractions for whole-breast or chest wall (without reconstruction) irradiation] [I, A].
- APBI is an alternative treatment to WBRT in patients with invasive and *in situ* breast cancer at low local recurrence risk [I, A].
- PMRT is recommended for high-risk EBC, including involved resection margins, $\geq$4 involved ALNs, T3-T4 tumours and in the presence of combinations of other risk factors [I, A].
- PMRT should be considered in patients with intermediate-risk features (e.g. lymphovascular invasion, age), including those with 1-3 positive ALNs [I, A].
- Nodal RT is recommended for patients with involved LNs (the extent of target volumes depends on risk factors including the number of involved LNs, N-stage and response to PST) [I, B].
- If indicated, PMRT can be administered after immediate breast reconstruction [III, A].

HR-positive, HER2-negative EBC

- All luminal-like cancers should be treated with ET [I, A].
- Most luminal A-like tumours do not require ChT, except those with high disease burden [I, A].
- In cases of uncertainty about indications for adjuvant ChT (after consideration of all clinical and pathological factors), gene expression assays or endocrine response assessment can be used to guide decisions on adjuvant ChT [I, A].
- Luminal B-like HR-positive, HER2-negative tumours should be treated with ChT followed by ET. ChT should be considered in cases of high clinical risk (e.g. multinode positive, premenopausal node positive, locally advanced) and 0-3 involved LNs with high-risk features (e.g. high-risk gene expression assay result) [I, A].
- Premenopausal patients should receive either tamoxifen alone (luminal A like, stage I) [I, A], or in case of a high risk of recurrence, ovarian suppression with either OFS—tamoxifen [I, A] or OFS—AI [I, A].
- Postmenopausal patients should receive an AI or tamoxifen followed by an AI [I, A].
  - o Tamoxifen can be given for lower-risk tumours or if AIs are not tolerated [I, A].
- Bisphosphonates (up to 5 years) are recommended in women without ovarian function (postmenopausal or undergoing OFS), especially if at high risk of relapse [I, A] or treatment-related bone loss [I, A].
- Abemaciclib for 2 years in addition to ET after completion of locoregional therapy should be considered in patients with stage III or high-risk stage II EBC [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: A].
- Extended ET beyond 5 years should be considered in high-risk EBC [I, A]; 7-8 years' treatment duration seems sufficient for most patients at high risk [I, A].
- Following completion of (neo)adjuvant and locoregional therapy, 1 year of adjuvant olaparib is recommended for patients with *gBRCA1/2m* and HER2-negative, HR-positive EBC with multiple positive LNs after primary surgery or residual high-risk EBC after neoadjuvant ChT [I, A; ESMO-MCBS v1.1 score: A; ESCAT: I-A].
- ET should be given concomitantly with adjuvant olaparib in *gBRCA1/2m* carriers [I, A].
- Olaparib and abemaciclib should not be combined due to overlapping toxicities but may be considered sequentially with olaparib first [V, A].

HER2-positive EBC

- HER2-directed therapy (with initial concurrent ChT) should be given for 12 months, covering both the neoadjuvant and/or adjuvant phases of treatment [I, A; ESCAT score: I-A].
  - o Administration can be combined—if indicated—with RT and ET [I, A]. In selected low-risk situations, 6 months of anti-HER2 therapy may be non-inferior.
  - o Regular cardiac assessments are recommended (before, during and following therapy) with the option of additional assessments before the start of any ChT treatment [II, B].
- For patients with clinical stage II-III HER2-positive breast cancer (e.g. T $>$2 cm or node positive), neoadjuvant systemic ChT with anti-HER2 therapy comprising HP is the preferred option [I, A; ESCAT score: I-A].
- For the ChT backbone, a regimen of anthracycline—taxane or taxane—carboplatin is evidence-based independent of neoadjuvant or adjuvant use [I, A].
- Dual blockade with HP (versus trastuzumab alone) combined with ChT achieves higher pCR rates and is recommended for neoadjuvant therapy [I, A; ESMO-MCBS v1.1 score: C; ESCAT score: I-A].
- Patients with residual invasive disease (non-pCR after neoadjuvant ChT and anti-HER2 therapy) should receive adjuvant treatment with T-DM1 for up to 14 cycles [I, A; ESMO-MCBS v1.1 score: A; ESCAT score: I-A].
- For patients with stage I (T1a-b N0) HER2-positive EBC, primary surgery may be carried out [III, B], followed by adjuvant administration of 12 weeks of paclitaxel plus 1 year of trastuzumab if clinical stage is confirmed by pathology [III, B; ESMO-MCBS v1.1 score: A; ESCAT score: I-A].
- For patients with pathological stage II or III cancer treated with initial surgery, adjuvant ChT combined with 1 year of anti-HER2 therapy should be given [I, A; trastuzumab ESMO-MCBS v1.1 score: A; HP ESMO-MCBS v1.1 score: A; ESCAT score: I-A].
- In patients with node-positive disease, the addition of pertuzumab to trastuzumab should be strongly considered in the adjuvant setting irrespective of HR status [I, A; ESMO-MCBS v1.1 score: A; ESCAT score: I-A].

- Patients with high-risk HR-positive tumours may be considered for extended treatment with neratinib (concurrent with ET) for 1 year after completion of 1 year of trastuzumab or trastuzumab-based therapy [I, B; ESMO-MCBS v1.1 score: no evaluable benefit; ESCAT score: I-A].

TNBC

- HER2-negative tumours with 1%-9% ER and/or PgR expression (ER-/PgR-low) are a heterogenous group, some of which behave biologically similarly to TNBCs; therapeutic strategies should be adjusted to this specific situation since this might lead to a higher response to ChT and to reduced efficacy of ET compared with classical HR-positive breast cancer [II, B].
- TNBC tumours should be treated with ChT with or without an ICI (pembrolizumab) [I, A], except for some node-negative special histological subtypes such as secretory or adenoid cystic carcinomas or very low clinical risk (pT1a pN0) tumours [II, B].
- ChT should be administered for 12-24 weeks (4-8 cycles) depending on the stage of the disease, type of selected regimen and regardless of whether an ICI is added [I, A].
- The use of dose-dense schedules of ChT, with granulocyte colony-stimulating factor support, should be considered given their documented benefit over non-dose-dense schedules [I, A].
- For cT1c-4 N0, or any N-positive TNBC, neoadjuvant treatment is preferred [I, A].
- cT2-4 N0 or any N-positive (stage II-III) TNBC should be treated with neoadjuvant ChT plus pembrolizumab unless there are risk factors for excessive ICI-associated immune toxicity [I, A; ESMO-MCBS v1.1 score: A].
- Pembrolizumab should be administered every 3 weeks throughout the neoadjuvant phase [I, A] and for nine 3-week cycles during the adjuvant phase, regardless of pCR status [I, A; ESMO-MCBS v1.1 score: A].
- Patients receiving pembrolizumab should be monitored very closely for the risk of immune-related adverse events throughout treatment and following the ESMO CPG for the management of toxicities from immunotherapy [V, A].[107]
- An ICI **should not** be given solely in the adjuvant setting without prior neoadjuvant ICI treatment [V, D].
- In patients with *gBRCA1/2m* and high-risk TNBC (non-pCR or pathological stage II-III), 1 year of adjuvant olaparib should be administered [I, A; ESMO-MCBS v1.1 score: A; ESCAT: I-A].
  - The combination of ICIs and olaparib may be considered on an individual basis [V, C].
- Patients with residual disease who did not receive ICIs should be offered adjuvant capecitabine for 6-8 cycles [I, A].
  - The combination of olaparib and capecitabine in patients with *gBRCAm* should not be used [V, C].
  - The combination of ICI and capecitabine may be considered on an individual basis [V, C].

Special situations

- Treatment of elderly patients should be adapted to biological (not chronological) age, with consideration of less aggressive regimens in frail patients. In patients suitable for standard ChT, a standard multidrug regimen should be used [II, B].
- A geriatric assessment should be carried out before making treatment decisions [II, A].
- Tamoxifen is the standard adjuvant ET for male patients with breast cancer [IV, A].
- As with premenopausal women with breast cancer, a gonadotropin-releasing hormone agonist (GnRHa) may be added in higher-risk male patients with breast cancer, and a combination of AI—GnRHa should be considered in cases where tamoxifen is contraindicated [IV, B].
- An AI must be administered with a GnRHa when used as adjuvant ET in male patients with breast cancer [IV, A].
- In male patients with breast cancer, ChT, ET, anti-HER2, ICI, CDK4/6 inhibitor and PARP inhibitor therapy indications and regimens should follow the same recommendations as those for breast cancer in female patients [IV, A].
- DCIS should be preferentially treated with BCS and WBRT or, in cases of extensive or multicentric DCIS, mastectomy [I, A].
- Both tamoxifen and AIs may be used after local BCT for DCIS to prevent local recurrence and to decrease the risk of developing a second primary breast cancer [I, B].
- Following mastectomy for DCIS, tamoxifen or AIs might be considered to decrease the risk of contralateral breast cancer in patients with a high risk of new breast tumours [II, B].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

General follow-up considerations

The aims of follow-up are:

- To detect local and/or regional recurrences or contralateral breast cancers that are potentially curable
- To evaluate and treat therapy-related side-effects and complications
- To promote adherence to adjuvant systemic treatment
- To provide support to enable a return to normal life after breast cancer
- To detect second primary cancers

Even though no data exist from recent randomised trials involving modern imaging to support any particular follow-up sequence or protocol, surveillance should balance patient needs, follow-up costs and burden on the health care system. The follow-up strategy should consider differential recurrence patterns as determined by tumour biology.

Reproductive and sexual health considerations

The number of survivors following treatment for an initial presentation is increasing. Therefore, long-term

consequences related to the different treatment modalities must be recognised and followed (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2023.11.016).

Premature menopause and infertility represent extremely important potential consequences of EBC treatment, particularly affecting premenopausal women and with significant impact on quality of life (QoL). Side-effects of ET and sexual dysfunction affect women of all ages and should be addressed to improve QoL and ensure treatment adherence. Although a few patients experience temporary amenorrhoea, a subset will experience treatment-related permanent ovarian dysfunction, with risk increasing with age.[108] Even in patients who recover ovarian function, premature menopause and infertility represent significant concerns. Addressing these possibilities before therapy, and involving a fertility specialist to consider preservation strategies, is indicated in all premenopausal women considering a future pregnancy. Available data suggest that pregnancy is safe after breast cancer treatment.[109]

Psychosocial considerations

Long-term survivorship issues need particular attention and involve all the implications of living after a breast cancer diagnosis. Patients should be encouraged to adopt a healthy lifestyle, exercise regularly and avoid being overweight. Psychological and other practical consequences of the disease and its treatment are an extremely important part of long-term care. Patients should be followed and managed for issues such as anxiety, depression, uncertainty about the future, sleep disturbances, sexuality, chronic fatigue, neurocognitive dysfunction and direct or indirect consequences on their ability to work and care for their families. While addressing long-term care and follow-up, the broader dimensions of culture and context that impact implementation of follow-up strategies should be considered. Long-term survivorship considerations should include all psychosocial needs of patients once treatment ends.

Ultimately, these issues have a significant influence on the QoL of individual patients and deserve the organisation of a diagnostic, educational and management infrastructure with adequate human resources and a close multidisciplinary follow-up.

Recommendations

General follow-up considerations

- Regular follow-up visits are recommended every 3 months in the first 3 years post-treatment (every 6 months for low-risk EBC), every 6 months from years 4 to 5 and annually thereafter. The interval of visits can be adapted to the risk of relapse and patient needs [V, A].
- Annual bilateral (after BCT) or contralateral mammography (after mastectomy) is recommended, plus US and breast MRI, when needed [II, A].
- Breast cancer survivors should participate in national screening programmes for other cancers [V, B].
- In asymptomatic patients, laboratory tests (e.g. blood counts, routine chemistry, tumour marker assessment) or other imaging are not recommended [I, D].[110]
- Symptom-directed investigations should be considered as indicated [V, B].
- Regular bone density evaluation is recommended for patients on AIs or undergoing OFS [I, A].
- In asymptomatic patients with normal cardiac function who have received potentially cardiotoxic treatment, cardiac follow-up should be carried out as clinically indicated [III, B].[111,112]
- For patients on tamoxifen, an annual gynaecological examination is recommended [V, B]; however, routine transvaginal US is not recommended [V, D].[2]

Reproductive and sexual considerations

- Premature menopause, infertility and potential sexual dysfunction should be discussed and addressed with each patient, when appropriate, before the start of adjuvant therapy [V, A].
- Premenopausal women considering pregnancy should be informed that available evidence suggests that pregnancy seems to be safe after breast cancer treatment [III, A].
- For women desirous of pregnancy, temporary interruption of adjuvant ET after 18-30 months of ET, allowing a wash-out period of 3 months, and attempting to get pregnant during a period of up to 2 years, followed by resumption of ET, does not appear to impact short-term breast cancer outcomes in lower-risk HR-positive, HER2-negative EBC [III, A].[113]

Psychosocial considerations

- Patients should be encouraged to adopt a healthy lifestyle, exercise regularly, avoid being overweight and minimise alcohol intake [II, A].
- Long-term survivorship considerations, including psychological needs and issues related to work, family and sexuality, should be addressed [V, A].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. A table of ESCAT scores is included in Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.11.016. ESCAT scores have been defined by F. André and G. Curigliano on behalf of the authors and assisted, as needed, by the ESMO Translational Research and Precision Medicine Working Group.[114] A table of ESMO-MCBS scores is included in Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2023.11.016. ESMO-MCBS v1.1[115] was used to calculate scores for therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The

scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S9, available at https://doi.org/10.1016/j.annonc.2023.11.016.[116] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website (https://www.esmo.org/guidelines/guidelines-by-topic/breast-cancer/early-breast-cancer).

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DT reports non-remunerated roles as a member of the EMA Healthcare Professional Working Party and of the World Health Organization [Essential Medicines List (EML)] Cancer Medicines Working Group. AT reports employment as Head of the Division of Breast Cancer Research and Director of the Breast Cancer Now Research Centre at the Institute of Cancer Research (ICR); employment as honorary consultant clinical oncologist at Royal Marsden Hospital and Guy's and St Thomas' NHS Foundation Trust; employment as Director of Breast Cancer Now Research Unit at King's College London; personal fees for advisory board membership for Gilead and MD Anderson; personal fees as an invited speaker for AstraZeneca, Cancer Panel, Global Breast Cancer Conference (GBCC), Penn Medicine and San Antonio Breast Cancer Symposium (SABCS) 2021; personal fees for expert testimonies for EM Partners; personal fees for completion of a survey for Research to Practice; personal honorarium from American Association for Cancer Research (AACR) for the Team Science Prize; personal stocks or shares in Inbiomotion; personal royalties from AstraZeneca through the ICR rewards to inventor's scheme payments to Andrew Tutt's research accounts at ICR and to personal accounts; institutional fees for advisory board membership for AstraZeneca, Gilead and PAGE Therapeutics; institutional fees as an invited speaker for AstraZeneca, Gilead, Innovation in Breast Cancer Symposium 2022, Livingston Memorial Symposium, SABCS 2022, Vall d'Hebron Institute of Oncology and The Video Journal of Oncology; institutional fees for expert testimonies for Cancer Research UK (CRUK) and GE Healthcare; institutional funding as a coordinating PI for AstraZeneca; institutional compensation from Aicme; institutional research grants from Breast Cancer Now, CRUK, Medivation and Merck KGaA; non-remunerated product samples from Guy's Hospital; non-remunerated membership of ESMO 2023 Scientific Committee, ESMO Guidelines author group, National Cancer Research Institute Strategy Group and St Gallen Consensus panel. 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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Autier P, Boniol M, La Vecchia C, et al. Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database. *Br Med J*. 2010;341:c3620.
3. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet*. 2015;385(9972):977-1010.
4. Sessa C, Balmaña J, Bober SL, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. *Ann Oncol*. 2023;34(1):33-47.
5. Josfeld L, Keinki C, Pammer C, et al. Cancer patients' perspective on shared decision-making and decision aids in oncology. *J Cancer Res Clin Oncol*. 2021;147(6):1725-1732.
6. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma In Situ. *J Clin Oncol*. 2016;34(33):4040-4046.
7. Aznar MC, Meattini I, Poortmans P, et al. "To clip or not to clip. That is no question!". *Eur J Surg Oncol*. 2017;43(7):1145-1147.
8. Nair AG, Giannakeas V, Semple JL, et al. Contemporary trends in breast reconstruction use and impact on survival among women with inflammatory breast cancer. *Ann Surg Oncol*. 2022;29(13):8072-8082.
9. Wu ZY, Han J, Kim HJ, et al. Breast cancer outcomes following immediate breast reconstruction with implants versus autologous flaps: a propensity score-matched study. *Breast Cancer Res Treat*. 2022;191(2):365-373.
10. Cardoso MJ, Wyld L, Rubio IT, et al. EUSOMA position regarding breast implant associated anaplastic large cell lymphoma (BIA-ALCL) and the use of textured implants. *Breast*. 2019;44:90-93.
11. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11(10):927-933.
12. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA*. 2017;318(10):918-926.
13. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol*. 2013;14(4):297-305.
14. Lyman GH, Somerfield MR, Bosserman LD, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35(5):561-564.
15. Moo TA, Edelweiss M, Hajiyeva S, et al. Is low-volume disease in the sentinel node after neoadjuvant chemotherapy an indication for axillary dissection? *Ann Surg Oncol*. 2018;25(6):1488-1494.
16. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15(12):1303-1310.
17. Savolt A, Peley G, Polgar C, et al. Eight-year follow up result of the OTOASOR trial: the Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: a randomized, single centre, phase III, non-inferiority trial. *Eur J Surg Oncol*. 2017;43(4):672-679.
18. Goyal A, Mann GB, Fallowfield L, et al. POSNOC-POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus clearance or axillary radiotherapy: a randomised controlled trial of axillary treatment in women with early-stage breast cancer who have metastases in one or two sentinel nodes. *BMJ Open*. 2021;11(12):e054365.
19. Hessler LK, Molitoris JK, Rosenblatt PY, et al. Factors influencing management and outcome in patients with occult breast cancer with axillary lymph node involvement: analysis of the National Cancer Database. *Ann Surg Oncol*. 2017;24(10):2907-2914.
20. Dubsky P, Pinker K, Cardoso F, et al. Breast conservation and axillary management after primary systemic therapy in patients with early-stage breast cancer: the Lucerne toolbox. *Lancet Oncol*. 2021;22(1):e18-e28.
21. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol*. 2013;14(7):609-618.
22. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;310(14):1455-1461.
23. Morency D, Dumitra S, Parvez E, et al. Axillary lymph node ultrasound following neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: results from the SN FNAC study. *Ann Surg Oncol*. 2019;26(13):4337-4345.
24. Classe JM, Loaec C, Gimbergues P, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. *Breast Cancer Res Treat*. 2019;173(2):343-352.
25. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707-1716.
26. Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol*. 2015;16(1):47-56.
27. Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet*. 2017;390(10099):1048-1060.
28. Strnad V, Yashar C. Breast brachytherapy. *Brachytherapy*. 2021;20(5):976-983.
29. Meattini I, Becherini C, Boersma L, et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. *Lancet Oncol*. 2022;23(1):e21-e31.
30. Fastner G, Gaisberger C, Kaiser J, et al. ESTRO IORT Task Force/ACROP recommendations for intraoperative radiation therapy with electrons (IOERT) in breast cancer. *Radiother Oncol*. 2020;149:150-157.
31. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), McGale P, Taylor C, Cutter D, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014;383(9935):2127-2135.
32. Early Breast Cancer Trialists' Collaborative Group. Radiotherapy to regional nodes in early breast cancer: an individual patient data

meta-analysis of 14 324 women in 16 trials. *Lancet*. 2023;402(10416):1991-2003.
33. Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1. *Radiother Oncol*. 2016;118(1):205-208.
34. de Wild SR, de Munck L, Simons JM, et al. De-escalation of radiotherapy after primary chemotherapy in cT1-2N1 breast cancer (RAPCHEM; BOOG 2010-03): 5-year follow-up results of a Dutch, prospective, registry study. *Lancet Oncol*. 2022;23(9):1201-1210.
35. Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet*. 2020;395(10237):1613-1626.
36. Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: a randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. *J Clin Oncol*. 2020;38(28):3261-3272.
37. Lohrisch C, Paltiel C, Gelmon K, et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol*. 2006;24(30):4888-4894.
38. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO Guideline. *J Clin Oncol*. 2021;39(13):1485-1505.
39. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164-172.
40. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687-1717.
41. Early Breast Cancer Trialists' Collaborative Group. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet*. 2019;393(10179):1440-1452.
42. Early Breast Cancer Trialists' Collaborative Group, Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379(9814):432-444.
43. Early Breast Cancer Trialists' Collaborative Group. Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. *Lancet*. 2023;401(10384):1277-1292.
44. Early Breast Cancer Trialists' Collaborative Group. Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. *Lancet*. 2008;371(9606):29-40.
45. Smith I, Robertson J, Kilburn L, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(11):1443-1454.
46. Nitz UA, Gluz O, Kummel S, et al. Endocrine therapy response and 21-gene expression assay for therapy guidance in HR+/HER2- early breast cancer. *J Clin Oncol*. 2022;40(23):2557-2567.
47. Kalinsky K, Barlow WE, Gralow JR, et al. 21-Gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med*. 2021;385(25):2336-2347.
48. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *Lancet Oncol*. 2021;22(4):476-488.
49. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379(2):111-121.
50. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386(10001):1341-1352.
51. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. *Lancet Oncol*. 2022;23(3):382-392.
52. Gnant M, Fitzal F, Rinnerthaler G, et al. Duration of adjuvant aromatase-inhibitor therapy in postmenopausal breast cancer. *N Engl J Med*. 2021;385(5):395-405.
53. Del Mastro L, Mansutti M, Bisagni G, et al. Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(10):1458-1467.
54. Coleman R, Finkelstein DM, Barrios C, et al. Adjuvant denosumab in early breast cancer (D-CARE): an international, multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2020;21(1):60-72.
55. Gnant M, Frantal S, Pfeiler G, et al. Long-term outcomes of adjuvant denosumab in breast cancer. *NEJM Evidence*. 2022;1(12):EVIDoa2200162.
56. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24(1):77-90.
57. Slamon DJ, Stroyakovskiy D, Yardley DA, et al. Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer: primary results from the phase III NATALEE trial. *J Clin Oncol*. 2023;41(suppl 17):LBA500.
58. Geyer CE Jr, Garber JE, Gelber RD, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol*. 2022;33(12):1250-1268.
59. Early Breast Cancer Trialists' Collaborative Group. Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. *Lancet Oncol*. 2021;22(8):1139-1150.
60. Huober J, van Mackelenbergh M, Schneeweiss A, et al. Identifying breast cancer patients at risk of relapse despite pathological complete response after neoadjuvant therapy. *NPJ Breast Cancer*. 2023;9(1):23.
61. van Mackelenbergh MT, Loibl S, Untch M, et al. Pathologic complete response and individual patient prognosis after neoadjuvant chemotherapy plus anti-human epidermal growth factor receptor 2 therapy of human epidermal growth factor receptor 2-positive early breast cancer. *J Clin Oncol*. 2023;41(16):2998-3008.
62. Untch M, Jackisch C, Schneeweiss A, et al. NAB-paclitaxel improves disease-free survival in early breast cancer: GBG 69-GeparSepto. *J Clin Oncol*. 2019;37(25):2226-2234.
63. Praga C, Bergh J, Bliss J, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. *J Clin Oncol*. 2005;23(18):4179-4191.
64. Romond EH, Jeong JH, Rastogi P, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2012;30(31):3792-3799.
65. Schneeweiss A, Chia S, Hickish T, et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. *Eur J Cancer*. 2018;89:27-35.
66. Slamon DJ, Eiermann W, Robert NJ, et al. Abstract S5-04: Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with

docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer. *Cancer Res*. 2016;76(suppl 4):S5-S04.
67. van der Voort A, van Ramshorst MS, van Werkhoven ED, et al. Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual ERBB2 blockade in patients with ERBB2-positive breast cancer: a secondary analysis of the TRAIN-2 randomized, phase 3 trial. *JAMA Oncol*. 2021;7(7):978-984.
68. Matikas A, Johansson H, Gryback P, et al. Survival outcomes, digital TILs, and on-treatment PET/CT during neoadjuvant therapy for HER2-positive breast cancer: results from the randomized PREDIX HER2 trial. *Clin Cancer Res*. 2023;29(3):532-540.
69. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016;17(6):791-800.
70. Nitz U, Gluz O, Graeser M, et al. De-escalated neoadjuvant pertuzumab plus trastuzumab therapy with or without weekly paclitaxel in HER2-positive, hormone receptor-negative, early breast cancer (WSG-ADAPT-HER2+/HR-): survival outcomes from a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2022;23(5):625-635.
71. Piccart MJ, Hilbers FS, Bliss JM, et al. Road map to safe and well-designed de-escalation trials of systemic adjuvant therapy for solid tumors. *J Clin Oncol*. 2020;38(34):4120-4129.
72. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380(7):617-628.
73. Loibl S, Huang CS, Mano MS, et al. Adjuvant trastuzumab emtansine in HER2-positive breast cancer patients with HER2-negative residual invasive disease in KATHERINE. *NPJ Breast Cancer*. 2022;8(1):106.
74. Mamounas EP, Untch M, Mano MS, et al. Adjuvant T-DM1 versus trastuzumab in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer: subgroup analyses from KATHERINE. *Ann Oncol*. 2021;32(8):1005-1014.
75. Loibl S, Jassem J, Sonnenblick A, et al. VP6-2022: Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. *Ann Oncol*. 2022;33(9):986-987.
76. Tolaney SM, Tarantino P, Graham N, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial. *Lancet Oncol*. 2023;24(3):273-285.
77. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(2):122-131.
78. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet*. 2013;382(9897):1021-1028.
79. Earl HM, Hiller L, Vallier AL, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet*. 2019;393(10191):2599-2612.
80. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab in early breast cancer (PHARE): final analysis of a multicentre, open-label, phase 3 randomised trial. *Lancet*. 2019;393(10191):2591-2598.
81. Gulia S, Kannan S, Badwe R, et al. Evaluation of 1-year vs shorter durations of adjuvant trastuzumab among patients with early breast cancer: an individual participant data and trial-level meta-analysis. *JAMA Netw Open*. 2020;3(8):e2011777.
82. Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1688-1700.
83. Chan A, Moy B, Mansi J, et al. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. *Clin Breast Cancer*. 2021;21(1):80-91.e87.
84. Barcenas CH, Hurvitz SA, Di Palma JA, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. *Ann Oncol*. 2020;31(9):1223-1230.
85. Kulkarni N, Pezzi CM, Greif JM, et al. Rare breast cancer: 933 adenoid cystic carcinomas from the National Cancer Data Base. *Ann Surg Oncol*. 2013;20(7):2236-2241.
86. Mills MN, Yang GQ, Oliver DE, et al. Histologic heterogeneity of triple negative breast cancer: a National Cancer Centre Database analysis. *Eur J Cancer*. 2018;98:48-58.
87. Geyer CE, Sikov WM, Huober J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. *Ann Oncol*. 2022;33(4):384-394.
88. Hahnen E, Lederer B, Hauke J, et al. Germline mutation status, pathological complete response, and disease-free survival in triple-negative breast cancer: secondary analysis of the GeparSixto randomized clinical trial. *JAMA Oncol*. 2017;3(10):1378-1385.
89. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol*. 2018;19(4):497-509.
90. Schmid P, Cortes J, Dent R, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med*. 2022;386(6):556-567.
91. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet*. 2020;396(10257):1090-1100.
92. Loibl S, Schneeweiss A, Huober J, et al. Neoadjuvant durvalumab improves survival in early triple-negative breast cancer independent of pathological complete response. *Ann Oncol*. 2022;33(11):1149-1158.
93. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376(22):2147-2159.
94. Hoon SN, Lau PK, White AM, et al. Capecitabine for hormone receptor-positive versus hormone receptor-negative breast cancer. *Cochrane Database Syst Rev*. 2021;5(5):CD011220.
95. van Mackelenbergh MT, Seither F, Mobus V, et al. Effects of capecitabine as part of neo-/adjuvant chemotherapy - a meta-analysis of individual breast cancer patient data from 13 randomised trials including 15,993 patients. *Eur J Cancer*. 2022;166:185-201.
96. Wang X, Wang SS, Huang H, et al. Effect of capecitabine maintenance therapy using lower dosage and higher frequency vs observation on disease-free survival among patients with early-stage triple-negative breast cancer who had received standard treatment: the SYSUCC-001 randomized clinical trial. *JAMA*. 2021;325(1):50-58.
97. El Hage Chehade H, Headon H, Wazir U, et al. Is sentinel lymph node biopsy indicated in patients with a diagnosis of ductal carcinoma in situ? A systematic literature review and meta-analysis. *Am J Surg*. 2017;213(1):171-180.
98. Goodwin A, Parker S, Ghersi D, et al. Post-operative radiotherapy for ductal carcinoma in situ of the breast–a systematic review of the randomised trials. *Breast*. 2009;18(3):143-149.
99. Montero-Luis A, Aristei C, Meattini I, et al. The Assisi Think Tank Meeting Survey of post-mastectomy radiation therapy in ductal carcinoma in situ: suggestions for routine practice. *Crit Rev Oncol Hematol*. 2019;138:207-213.
100. Kindts I, Laenen A, Depuydt T, et al. Tumour bed boost radiotherapy for women after breast-conserving surgery. *Cochrane Database Syst Rev*. 2017;11(11):CD011987.
101. Chua BH, Link EK, Kunkler IH, et al. Radiation doses and fractionation schedules in non-low-risk ductal carcinoma in situ in the breast (BIG 3-07/TROG 07.01): a randomised, factorial, multicentre, open-label, phase 3 study. *Lancet*. 2022;400(10350):431-440.
102. Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in

postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. *Lancet*. 2016;387(10021):866-873.
103. Margolese RG, Cecchini RS, Julian TB, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. *Lancet*. 2016;387(10021):849-856.
104. Staley H, McCallum I, Bruce J. Postoperative tamoxifen for ductal carcinoma in situ. *Cochrane Database Syst Rev*. 2012;10:CD007847.
105. Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized placebo controlled trial of low-dose tamoxifen to prevent recurrence in breast noninvasive neoplasia: a 10-year follow-up of TAM-01 study. *J Clin Oncol*. 2023;41(17):3116-3121.
106. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). *Ann Oncol*. 2022;33(11):1097-1118.
107. Haanen J, Obeid M, Spain L, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33(12):1217-1238.
108. Poorvu PD, Hu J, Zheng Y, et al. Treatment-related amenorrhea in a modern, prospective cohort study of young women with breast cancer. *NPJ Breast Cancer*. 2021;7(1):99.
109. Lambertini M, Blondeaux E, Bruzzone M, et al. Pregnancy after breast cancer: a systematic review and meta-analysis. *J Clin Oncol*. 2021;39(29):3293-3305.
110. Moschetti I, Cinquini M, Lambertini M, et al. Follow-up strategies for women treated for early breast cancer. *Cochrane Database Syst Rev*. 2016;2016(5):CD001768.
111. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol*. 2020;31(2):171-190.
112. Lyon AR, Lopez-Fernandez T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J Cardiovasc Imaging*. 2022;23(10):e333-e465.
113. Partridge AH, Niman SM, Ruggeri M, et al. Interrupting endocrine therapy to attempt pregnancy after breast cancer. *N Engl J Med*. 2023;388(18):1645-1656.
114. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2018;29(9):1895-1902.
115. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol*. 2017;28(10):2340-2366.
116. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2001;33(2):139-144 [adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. Clin Infect Dis. 1994;18(3):421].
117. Comparison of complete axillary lymph node dissection with axillary radiation therapy in treating women with invasive breast cancer (AMAROS). Available at https://clinicaltrials.gov/ct2/show/NCT00014612. Accessed March 23, 2023.
118. Mittendorf EA, Jeruss JS, Tucker SL, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. *J Clin Oncol*. 2011;29(15):1956-1962.