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REVIEW

Risk Factors for Disease Recurrence in Patients with HER2+ Early Breast Cancer and Implications for Therapy: A Narrative Review

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ABSTRACT

Human epidermal growth factor receptor 2 (HER2) overexpression or amplification of the human *ERBB2* oncogene occurs in approximately one-fifth of breast cancers and, of these, two-thirds are hormone receptor (HR)-positive (HR+). The introduction of HER2-targeted therapies in recent years has significantly improved survival outcomes in patients with this tumor subtype. However, disease recurrence risk is 10–30% at 5 years with a different pattern between patients with HER2+/HR+ and HER2+/HR-negative (HR–) early breast cancer, with HR+ patients having a lower risk than those with HR– disease in the first 5 years, but a slightly higher risk at 5–10 years post-surgery. This highlights a crucial need to explore the underlying mechanisms for these differences to address specific treatment needs and to optimize systemic adjuvant treatment outcomes. Therefore, this narrative review provides an overview of published data regarding the recognized factors and ongoing challenges associated with the risk of relapse in women with HER2+ early breast cancer and proposes potential adjuvant treatment strategies to minimize risk of recurrence in high-risk patients.

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Key Summary Points

In patients with human epidermal growth factor receptor 2 amplified (HER2+) early breast cancer, relapse patterns after surgery and neoadjuvant and/or adjuvant therapy differ between those with hormone receptor (HR)-positive (HR+) or HR-negative disease, as patients with HR+ tumors are more likely to experience late relapse.

Cross-talk between HER2 and estrogen receptor signaling pathways means that patients with HER2+/HR+ disease require both HER2-directed therapy and endocrine therapy.

In premenopausal patients with early-stage HER2+/HR+ disease, the addition of ovarian function suppression to adjuvant endocrine therapy improved disease-free survival and overall survival irrespective of trastuzumab treatment in a retrospective analysis of the HERA trial, while in metastatic HER2+/HR+ disease, the addition of cyclin-dependent kinase inhibitors to endocrine therapy and HER2-directed treatment may further improve outcomes.

Extended adjuvant treatment with the tyrosine kinase inhibitor neratinib has been shown to improve outcomes in patients with HER2+/HR+ breast cancer, if started within 1 year of completing trastuzumab-based post-neoadjuvant or adjuvant therapy, especially in patients with residual disease.

Tumor size, nodal status at diagnosis, and residual cancer after neoadjuvant therapy are key determinants of relapse risk, and risk stratification based on these characteristics—along with other potential biomarkers—may help to individualize therapy in HER2+/HR+ early breast cancer.

INTRODUCTION

Overexpression of the human epidermal growth factor receptor 2 protein (HER2+) or amplification of the *ERBB2* oncogene occurs in approximately 15–20% of breast cancers (BC) [1, 2]. It is now evident that HER2+ BC cannot be assumed as a single entity since there is significant biologic and clinical heterogeneity within the HER2+ BC subtype [3]. HER2+ BC has been classically distinguished into two distinct diseases based on the expression of hormone receptor (HR). Approximately one-third of HER2+ tumors are HR-negative (HR–) and two-thirds are HR-positive (HR+) [1, 2].

Surgical resection is the primary treatment for early BC [4], but most patients with HER2+ disease will also receive neoadjuvant and/or adjuvant treatment. The European Society of Medical Oncology (ESMO) guidelines for early BC recommend neoadjuvant therapy in patients with HER2+ BC with tumors ≥ 2 cm and/or node-positive disease [4], and the American Society of Clinical Oncology (ASCO) guidelines recommend neoadjuvant therapy to reduce the extent of surgery when delays to surgery are preferable or unavoidable or in high-risk HER2+ patients whose postoperative treatment decisions will be guided by any residual disease [5]. Neoadjuvant systemic treatment with trastuzumab ± pertuzumab in combination with chemotherapy is recommended in patients with early-stage, node-positive (or high-risk node-negative), HER2+ BC, irrespective of HR expression [4, 5]. In the ESMO and ASCO guidelines, adjuvant therapy recommendations include HER2-directed therapy plus chemotherapy, with endocrine therapy added in patients with estrogen receptor-positive (ER+) or HR+ disease [4, 5]. In addition, adjuvant trastuzumab emtansine (T-DM1) is recommended for patients with residual invasive disease after anti-HER2-based neoadjuvant treatment.

Numerous studies have demonstrated an advantage of longer versus shorter endocrine therapy, although the optimal duration and regimen of adjuvant endocrine therapy is currently unknown. Of note, there is minimal benefit associated with the use of aromatase inhibitors (AIs) for > 5 years, with no significant

improvement in overall survival (OS) with prolonged AI therapy reported among patients with HR+ early BC in the MA-17R, NSABP-B42, and AERAS trials [6–8]. Moreover, most data on the use of extended endocrine therapy come from studies in patients with HER2-negative (HER2–) disease, and the optimal duration of endocrine therapy in patients with HER2+ BC who have received HER2-directed therapy remains unclear [9], although the median 11-year disease-free survival (DFS) data from the HERA trial support current standard-of-care (≥ 5 years of adjuvant endocrine therapy) in patients with HER2+ BC [10]. A retrospective analysis of patient-level data from the HERA trial indicated that the addition of ovarian function suppression (OFS) to adjuvant endocrine therapy (with or without trastuzumab) significantly improved 10-year DFS and OS in premenopausal women with HER2+/HR+ early BC [11]. Preliminary results from the phase 3 PATINA trial involving patients with metastatic HER2+/HR+ disease have shown that the addition of a cyclin-dependent kinase (CDK) inhibitor to endocrine therapy and HER2-directed treatment prolonged median progression-free survival (PFS) by over 15 months compared with endocrine therapy and anti-HER2 therapy alone [12]. These results emphasize the relevance of ER-targeting in luminal B/HER2+ disease and suggest a potential role for CDK4/6 inhibitors in the adjuvant setting.

Despite the use of anti-HER2 strategies, patients with HER2+ BC have a 10–30% risk of relapse at up to 7 years, depending upon their baseline risk and the duration of follow-up [10, 13–15]. However, disease recurrence patterns appear to differ between patients with HER2+/HR+ and HER2+/HR– early BC, with HR+ patients having a significantly lower risk of recurrence than those with HR– disease during the first 5 years after surgery, but a slightly higher risk at 5–10 years after surgery [16]. HER2-low expression may also be associated with an increased risk of disease recurrence, although retrospective studies conducted in the USA, China, and South Korea show conflicting data [17–19]. There was minimal prognostic difference between HER2-low and HER2– BC in the US study [17], and no difference in the 5-year rates of DFS, OS, or recurrence-free survival (RFS) between HER2-low and HER2– disease were observed in the South Korean study [18]. However, the Chinese study reported an increase in the 10-year risk of local recurrence with HER2-low versus HER2– early BC [19].

Given the heterogeneity of the HER2+ BC subtype, it is crucial to explore the underlying mechanisms of these differences in recurrence risk to optimize systemic adjuvant treatment. Herein, we review the recognized risk factors associated with the risk of recurrence in women with HER2+ early BC, and propose potential adjuvant treatment strategies to manage these high-risk patients.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RISK FACTORS FOR DISEASE RECURRENCE

Substantial clinical and biological heterogeneity exists in HER2+ BC, which affects patient prognosis and the risk of disease recurrence [20, 21]. Several patient- and disease-related factors are recognized as being predictive of recurrence in patients with HER2+ BC, including residual disease, HR status, lymph node status, tumor size, biomarkers, and other factors (e.g., age at diagnosis and body mass index [BMI]) [22].

Residual Disease

Residual disease is a known risk factor for recurrence of HER2+ BC [22]. The achievement of pathologic complete response (pCR) after neoadjuvant therapy is a recognized surrogate for long-term outcomes [15, 23]. Data from 3710 patients randomly assigned in 11 neoadjuvant trials for HER2+ early BC revealed higher 5-year event-free survival (EFS) and OS among patients achieving pCR compared with those who did not [15]. A meta-analysis of 11 studies in patients with HER2+ BC who received neoadjuvant HER2-directed therapies found that the weighted mean 3-year DFS was 91.5% (95% confidence interval [CI] 90.7, 93.5) in the group

with pCR versus 79.7% (95% CI 77.4, 80.9) in those with residual disease [24]. According to the Residual Cancer Burden (RCB) evaluation system, each tumor can be categorized as RCB-0 (no residual tumor or pCR), RCB-I (minimal residual tumor), RCB-II (moderate residual tumor), or RCB-III (extensive residual tumor), with the RCB-I, -II, or -III categories indicating partial response to treatment [25]. When evaluated by the RCB system, Neoadjuvant Response Index (NRI), and Neo-Bioscore, patients with stage II–III HER2+ BC who had minimal residual disease after treatment with surgery plus trastuzumab-based neoadjuvant therapy (i.e., RCB-I, NRI ≥ 0.75, or Neo-Bioscore 0–1) had a similar 5-year recurrence-free interval to those with pCR [23]. In the Cher-LOB study in 121 patients with stage II–IIIA HER2+ BC who received neoadjuvant HER2-targeted therapy with trastuzumab and/or lapatinib, pCR was significantly associated with improved RFS and OS after a median follow-up of 9 years [26]. A multicenter pooled analysis of 5161 patients with different phenotypic BC subyptes similarly showed that RCB score was an independent predictor of prognosis for EFS across multiple subtypes of BC, including HER2+ disease [27]. Although the RCB score has the potential to be included in standard pathology following neoadjuvant therapy, it is not yet commonly used in clinical practice.

Of note, although residual disease may be prognostic of poorer outcomes, some patients who achieve pCR are still at risk of recurrence due to high-risk features at diagnosis. A study of individual patient data from 11 clinical trials of neoadjuvant systemic treatment in HER2+ early BC found clinical tumor size (cT; cT1–2 vs cT3–4) and clinical node status (cN; cN0 vs cN+) were independent prognostic factors for EFS and cT alone was prognostic for OS in 1497 patients with pCR, while cT, cN, and HR status were prognostic for both EFS and OS in 2213 patients without pCR [15].

HR Status

Patients with HER2+/HR− BC are more likely to achieve pCR than those with HR+ tumors [28]. This is particularly evident among patients who receive HER2-directed therapy, which is less effective in HR+ disease because of bidirectional cross-reactivity between endocrine receptors and the HER2 pathway [28]. For example, a retrospective study of 283 patients with stage II or III HER2+ BC found that those with HER2+/ER− BC were more likely to achieve pCR after neoadjuvant therapy with chemotherapy plus HER2-directed therapy than patients with ER+ disease, although the patient population was too small to draw conclusions from the subgroups with ER+ versus ER− disease [24]. Similarly, in the prospective TRYPHAENA [29] and NeoSphere [30] trials involving patients with HER2+ BC, patients with HR− disease were more likely than those with HR+ disease to achieve pCR following neoadjuvant HER2-directed therapy with or without chemotherapy. In the phase 3 ALLTO study in patients with stage I–III HER2+ BC who received chemotherapy plus 1 year of dual- versus single-agent HER2-directed therapy, subgroup analyses showed patients with HR− disease had a numerically better DFS in favor of dual-agent therapy than patients with HR+ disease (median follow-up 6.9 years) [31]. Furthermore, an exploratory subgroup analysis of patients with HR+ versus HR− disease in the ALTTO study found that HR status had a strong impact on the type of first DFS event (with bone and liver metastases being more common in patients with HR+ tumors, while lung and brain metastases were more common in those with HR− disease) and the risk factors for overall DFS over 0–5 and 6–8 years, although 5- and 8-year DFS rates were similar in the HR+ and HR− subgroups [32].

When considering differences in relapse rate between patients with HR+ and HR− BC within the first 5 years after diagnosis and beyond, HR+ and HR− BCs appear to behave differently over time [10, 33]. For example, estimated annualized hazard ratios for BC-free intervals among 4105 patients in the International Breast Cancer Study Group (IBSCG) trials I–V demonstrated that both ER+ and ER− tumors showed an initial peak in recurrence during the first 2–3 years after surgery, with persistent risk for up to 24 years [33]. However, during the first 5 years, patients with ER+ tumors had a lower annualized hazard rate than those with ER− tumors (9.9% vs 11.5%; $p = 0.01$) [33]. In terms of prognosis, HR− disease is associated with worse outcomes over the first

5 years, but similar outcomes to HR+ at 10 years [10]. Data from the IBSCG have also demonstrated that HR+ and HR− BCs appear to behave differently over timeframes of >5 years [33]. Patients with ER+ BC had a higher risk of recurrence than those with ER− BC (5–10 years, 5.4% vs 3.3%; 10–15 years, 2.9% vs 1.3%; 15–20 years, 2.8% vs 1.2%; and 20–25 years, 1.3% vs 1.4%; $p<0.001$). Of note, annualized hazard rates of recurrence in patients with ER+ disease remained elevated beyond 10 years, even in those with N0 (2.0%, 2.1%, and 1.1% at 10–15, 15–20, and 20–25 years, respectively) or N1–3 tumor status at diagnosis (3.0%, 3.5%, and 1.5%, respectively) [33]. Thus, even among women with small, node-negative (T1N0), low-grade tumors (assumed to be very low-risk patients), the risk of recurrence remained present for up to 20 years. Of note, associations between tumor diameter and nodal status with the risk of distant relapse appeared to be additive for those with ER+ disease, highlighting a clinically unmet need in these patients.

Lymph Node Status and Tumor Size

Lymph node-positivity is a risk factor for distant metastasis, recurrence, and relapse of HER2+ BC in both the neoadjuvant and adjuvant treatment setting [34–36]. In a real-world study of 217 patients with HER2+ BC and pCR after dual-agent HER2-directed neoadjuvant therapy, patients with node-positive disease at diagnosis remained at increased risk for disease recurrence, with a 4-year invasive DFS (iDFS) rate of 86.2% (vs 96.0% for node-negative disease) [34]. This was also the case in a pooled analysis of nine prospective neoadjuvant BC trials, where node-positive disease was associated with a significantly greater risk of locoregional recurrence compared with node-negative disease [37]. Lymph node metastasis has also been associated with an increased risk of distant recurrence in patients with HER2+ early BC, with a 5-year RFS rate of 85.9% when treated with chemotherapy alone, although adjuvant HER2-directed therapy appears to have reduced this risk [35].

Large tumor size correlates with an increased risk of disease recurrence across all treatment settings [22, 38–40]. A retrospective analysis of 529 Polish patients with BC found that tumor size and lymph node metastases were significant negative prognostic factors at 5 years among patients with HER2+ disease [38]. In addition, very large tumor size (>5 cm) was associated with an increased risk of relapse within 3 years in a retrospective study of 1136 Asian patients with HER2+ BC [39], and failure to achieve pCR after neoadjuvant therapy in another retrospective study of 163 US patients with HER2+ BC [40].

In the patient-level Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of data from 88 trials of 62,923 patients with ER+ BC (of whom 4131 had known HER2+ disease), tumor size and lymph node status were strong predictors of distant metastasis for up to 20 years in women who were disease-free after 5 years of endocrine therapy [36]. During long-term follow-up, the annual risk of disease recurrence increased as the number of positive lymph nodes increased, with the 20-year risk being 20% in patients with nodal status of N0, 31% in patients with N1–N3, and 52% with those with N4–N9 [36]. Furthermore, the risk of recurrence increased steadily over 15 years' follow-up after the completion of 5-year endocrine therapy depending on baseline tumor size and lymph node status [36].

Biomarkers

Several studies have indicated that a higher tumor-infiltrating lymphocyte (TIL) density is associated with a reduced risk of HER2+ BC recurrence [41–44]. In a pooled analysis of data from six randomized trials conducted by the German Breast Cancer Group, increased TILs was predictive of response to neoadjuvant therapy among 1244 patients with HER2+ disease (median follow-up 63.3 months), with pCR being achieved by 48% of patients with high TILs (≥60% immune cells in tumor stromal tissue), 39% of those with intermediate TILs (11–59% immune cells), and 32% of those with low TILs (≤10% immune cells) [41]. In

the ShortHER adjuvant study in 1253 patients with HER2+ early BC, higher TILs were independently associated with improved distant DFS (DDFS) following chemotherapy plus HER2-directed therapy, with 5-year DDFS rates of 91.1% for patients with < 20% TILs versus 95.7% for those with ≥ 20% TILs ($p = 0.025$) [43]. This study found that 10% increments in TILs were significantly prognostic for DDFS for patients who received 9 weeks of HER2-directed treatment, but not for those treated for 1 year [43]. Similarly, the PREDIX HER2 study in 197 patients with HER2+ BC showed after a median follow-up of 5.2 years that baseline TILs ≥ 10% was an independent predictor of pCR after adjusting for HR status, treatment, tumor size, and lymph node status ($p = 0.006$), with higher rates of pCR in patients with TILs ≥ 10% versus < 10% (51.4% vs 28.1%) [44]. Low TIL density may also be a risk factor for late recurrence of HER2+ early BC. A single-center study that included 129 patients with HER2+ BC also reported that low TILs prior to neoadjuvant therapy were associated with significantly lower pCR rates than intermediate/high TILs (26.0% vs 51.9%) after a median follow-up of 98 months [42].

Low baseline expression of the proliferation cell nuclear antigen (Ki67) biomarker has been associated with an increased risk of recurrence in patients with HER2+ BC across all treatment settings [22, 45–47]. Also, low baseline Ki67 expression (≤ 38%) was associated with lower rates of pCR in a Spanish observational study in 108 patients with HER2+/ER+ BC, in which only 16% of patients with low Ki67 expression achieved pCR following neoadjuvant therapy [45]. In the NA-PHER2 study in patients with HER2+/ER+ BC and high baseline Ki67 expression (geometric mean 32%) who received neoadjuvant HER2-targeted therapy plus RB1 blockade (with or without fulvestrant), downregulation of Ki67 expression at 2 weeks was predictive of efficacy at 16 weeks, with clinical response rates of 89–97% after 16 weeks and pCR rates of 19–27% at surgery [46, 47]. These results suggest that Ki67 expression may be a potential predictor of neoadjuvant success in HER2+ early BC; however, more studies are needed to validate its potential for use in routine clinical practice.

BRCA mutations may also be considered when assessing the risk of recurrence and prognosis in HER2+ BC. A multicenter observational study in patients with HER2+ BC with or without *BRCA* mutations evaluated iDFS and OS [48]. Patients with HER2+/*BRCA*-mutated BC had a similar 5-year iDFS rate to those with HER2+/*BRCA* wild-type disease (88% vs 86%; $p = 0.08$), while the 5-year OS rate was significantly lower in patients with *BRCA*-mutated tumors (93% vs 97%; $p = 0.04$) [48]. The authors of this study indicated that HER2 positivity and *BRCA* mutation co-occurrence were predictive for poor prognosis in patients with early or locally advanced BC, suggesting an actionable role for *BRCA* mutations in HER2+ disease.

The current ASCO guidelines do not recommend the use of biomarkers (including TILs, Ki67 expression, programmed cell death ligand 1 levels, circulating tumor cells, and circulating tumor DNA) to guide adjuvant treatment decisions regarding endocrine therapy or chemotherapy in patients with HER2+ early BC because of a lack of mature evidence [49]. However, they note that with additional research, many of these biomarkers may yet prove to have clinical utility in early BC, and encourage researchers to include them in clinical trials of adjuvant or neoadjuvant therapy [49].

Of note, the use of a new HER2DX assay for predicting pCR and survival outcomes in patients with HER2+ early BC is being investigated in a prospective study [50]; this genomic assay, which incorporates tumor size, lymph node status, and four gene expression signatures (tracking immune infiltration, tumor cell proliferation, luminal differentiation, and HER2 expression), could be used to accurately estimate the risk of recurrence, along with the likelihood of achieving pCR, in patients with HER2+ early BC, and thereby guide the path to individualized strategies of escalation and de-escalation [50].

Other biomarkers in the HER family may also be potential predictors of prognosis and/or treatment response, including epidermal growth factor receptor (EGFR or HER1), HER3, and HER4. EGFR is a long-established therapeutic target in BC [51], and EGFR overexpression is a marker of poor prognosis in patients with HER2+ BC [52]. HER3 and HER4 also have unique roles in

tumorigenesis and the emergence of treatment resistance [53–55]. Although HER3 lacks intrinsic kinase activity, after binding to one of its preferred ligands (neuregulin [NRG] 1 or 2), it can heterodimerize with other HER family members (e.g., HER2 or EGFR) to initiate potent oncogenic signaling [53, 54]. HER3 overexpression is associated with poor prognosis and resistance to HER2- or EGFR-targeted therapies, with the presence of *NRG1* fusions (rare oncogenic driver alterations that lead to HER3 overexpression) being potential predictors of good response to HER3-targeted therapies, whereas loss of HER3 is associated with reduced tumor cell proliferation [53, 54]. Having intrinsic kinase activity, HER4 can signal independently or via heterodimerization with HER family members, including HER3 [55]. HER4 may act as either an oncogene or tumor suppressor in BC, depending on its isoform and cellular environment [55].

Other Factors

Across the neoadjuvant and adjuvant setting, younger age at diagnosis (≤ 50 years) is associated with an increased risk of recurrence in patients with HER2+ BC [22]. The NCCTG N9831 and NSABP B-31 studies found that among patients with HER2+ BC who received chemotherapy alone, younger age (≤ 40 years) was associated with poorer outcomes than older age (> 40 years), with 8-year RFS rates in younger versus older patients of 63.5% versus 71.1%, respectively, in NCCTG N9831 and 46.3% versus 60.3%, respectively, in NSABP B-31 [56]. In addition, younger patients with HER2+/HR+ BC had poorer outcomes when treated with chemotherapy alone than younger patients with HER2+/HR− BC. This study also found that HR+ disease and a higher tumor grade were more common in younger patients [56]. Significantly improved prognosis has been observed in premenopausal women with HER2+/HR+ early BC receiving adjuvant endocrine therapy with the addition of OFS, suggesting that young patients with HER2+/HR+ BC benefit from intensified endocrine treatment [11]. Of note, older age may also be an important factor in patients with HER2+ BC. A retrospective single-center Chinese study in patients with T1, node-negative HER2+ BC found that older age (≥ 65 years) was associated with improved 10-year rates of DFS and distant RFS with adjuvant chemotherapy (± trastuzumab) compared with younger age (< 65 years), but was a negative prognostic factor for OS [57].

Patients with a high BMI are also at an increased risk of HER2+ BC recurrence. In an Italian retrospective study in patients with surgically resected, stage I–III HER2+ BC, higher BMI (≥ 27.8 kg/m^2) was associated with reduced RFS rate in patients with HR− BC treated with standard-of-care adjuvant HER2-directed therapy, but not in those with HR+ disease (median follow-up 76.7 months) [58]. In this study, baseline hyperglycemia was also associated with a trend towards reduced RFS in patients with HER2+/HR+ BC [58]. Interestingly, the randomized controlled BENEFIT trial found that aerobic and resistance exercise during neoadjuvant chemotherapy may provide tumor shrinkage and pCR benefits and reduce the need for axillary lymph node dissection in patients with HR+ BC (including those with HER2+ disease) [59].

TREATMENT STRATEGIES TO PREVENT RECURRENCE

Because of the risk of late recurrence in patients with HER2+/HR+ tumors, there is a need for prolonged follow-up and careful therapeutic decision-making in this setting. As HER2+/HR+ and HER2+/HR− disease do not have the same genetic profile, different therapeutic approaches are needed to optimize clinical outcomes. The evidence for adjuvant treatment strategies in patients with HER2+ early BC is summarized in Table 1. While the risk of recurrence in patients with HR+ BC reaches almost the same level as in HR− BC after 10 years' follow-up, patients with HER2+/HR+ disease should be regarded as high-risk when additional poor prognosis factors are present. Therefore, there is an ongoing need for physicians to define this at-risk population and understand its implications on contemporary therapeutic decisions.

Trastuzumab First-in-Class

The EBCTCG meta-analysis comprising patients with HER2+ early BC showed that adding trastuzumab to chemotherapy reduced the risk of disease recurrence for up to 5 years compared with chemotherapy alone [60]. Long-term follow-up data from the EBCTCG meta-analysis in patients with HER2+ early BC also demonstrated a significant reduction in the absolute 10-year risk of recurrence by 9.0% with trastuzumab plus chemotherapy versus chemotherapy alone [60]. The HERA trial in 5102 patients with HER2+ early BC showed that DFS rates at 10 years in the 1- and 2-year trastuzumab groups were 69% and higher than that reported in the observation group (63%), with an absolute benefit in 10-year DFS rate of 6% [10]. In patients with HR+ disease, 1 year of adjuvant trastuzumab was associated with significantly improved DFS compared with observation after a median of 11 years' follow-up (hazard ratio 0.80; 95% CI 0.68, 0.96) [10].

Adjuvant trastuzumab treatment for 1 year is associated with an increased risk for cardiac events, but these are generally limited to asymptomatic or mildly symptomatic decreases in left ventricular ejection fraction (LVEF) [61]. In the EBCTCG meta-analysis, the incidences of congestive heart failure and asymptomatic LVEF reduction were low, but higher with trastuzumab plus chemotherapy versus chemotherapy alone and usually led to treatment discontinuation [60].

Newer Treatment Options

Pertuzumab Plus Trastuzumab

The primary analysis of the APHINITY trial, which involved 4805 patients with HER2+ early BC, demonstrated a significantly improved 3-year iDFS with adjuvant pertuzumab plus trastuzumab versus trastuzumab alone in all patients (94.1% vs 93.2%; hazard ratio 0.81; 95% CI 0.66, 1.00) and in those with node-positive BC (92.0% vs 90.2%; hazard ratio 0.77; 95% CI 0.62, 0.96) [62]. These data led to the approval of pertuzumab as adjuvant therapy in combination with trastuzumab and chemotherapy in patients with HER2+ early BC [63]. In interim analyses of APHINITY at 6 and 8 years' follow-up, the iDFS benefit of adjuvant pertuzumab plus trastuzumab in HER2+ early BC was maintained in all patients, and in the node-positive and HR+ cohorts [64, 65]. At a median 11.3 years of follow-up, the iDFS benefit of adjuvant dual HER2 blockade was maintained in all patients (10-year iDRS rates were 87.2% vs 83.8% for pertuzumab plus trastuzumab vs trastuzumab alone, respectively), with clinically meaningful benefits for the node-positive disease (hazard ratio 0.74; 95% CI 0.62, 0.88) and the HR+ (hazard ratio 0.75; 95% CI 0.62, 0.91) cohorts [66]. Data from APHINITY illustrate the challenge of demonstrating a clinical benefit of a new strategy in a BC population with a good prognosis. Continued follow-up of patients is needed to determine any possible survival benefit with the addition of adjuvant pertuzumab to trastuzumab.

Adjuvant treatment with pertuzumab plus trastuzumab is also associated with a small increase in the risk of cardiac events. In the APHINITY trial, the incidence of primary cardiac events (defined as New York Heart Association [NYHA] class III or IV heart failure and decrease in LVEF of ≥ 10% from baseline and to < 50% or cardiac death) was 0.7% with adjuvant pertuzumab plus trastuzumab versus 0.3% with trastuzumab alone after a median follow-up of 45 months [62] and 0.8% versus 0.3% in the respective treatment arms after 74 months of follow-up [65]. Secondary cardiac events, defined as asymptomatic or mildly symptomatic (NYHA class II) LVEF decrease (assessed by multiple-gated acquisition and confirmed within 3 weeks by repeat assessment or cardiac advisory board) was reported in 2.7% of patients receiving pertuzumab plus trastuzumab versus 2.8% of those receiving trastuzumab alone at both timepoints [62, 65].

Trastuzumab Emtansine

The randomized, open-label, phase 3 KATHERINE study evaluated adjuvant T-DM1 versus trastuzumab in patients with HER2+ early BC (in which 72% of patients had HR+ disease)

Table 1 Evidence for adjuvant treatment strategies in patients with HER2+ early breast cancer

Treatment	Study	Number of patients	Comparator	Duration of follow-up	DFS outcome
Trastuzumab	EBCTCG meta-analysis	13,864	CT alone	≥ 10 years	First recurrence: 4.6% vs 8.0% in 0–1 year, 3.4% vs 4.4% in 2–4 years, 1.2% vs 1.5% in 5–9 years, 0.5% vs 0.7% at ≥ 10 years 10-year risk of recurrence reduced by 9.0% ($p < 0.0001$) [60]
	HERA	5102	Observation	11 years	10-year DFS absolute benefit: 6% (hazard ratio 0.80; 95% CI 0.68, 0.96) [10]
Pertuzumab + trastuzumab	APHINITY	4805	Trastuzumab alone	3 years	iDFS: 94.1% vs 93.2% (hazard ratio 0.81; 95% CI 0.66, 1.00) [62]
				6 years	iDFS: 88% vs 83% (hazard ratio 0.72; 95% CI 0.59, 0.87) [65]
				8 years	iDFS: 88.4% vs 85.8% (all patients) hazard ratio 0.75; 95% CI 0.61, 0.92 (HR+ cohort) [64]
				11.3 years	iDFS: 87.2% vs 83.8% (all patients) hazard ratio 0.75; 95% CI 0.62, 0.91 (HR+ cohort) [66]
T-DM1	KATHERINE	1486	Trastuzumab	3 years	iDFS: 88.3% vs 77.0% (hazard ratio 0.50; 95% CI 0.39, 0.64; $p < 0.001$) [14]
				8.4 years	Landmark 7-year iDFS: 80.8% vs 67.1% (difference 13.7%) [68]

CI confidence interval, *CT* chemotherapy, *DFS* disease-free survival, *EBCTCG* Early Breast Cancer Trialists' Collaborative Group, *HR+* hormone receptor-positive, *HER2+* human epidermal growth factor receptor 2-positive, *iDFS* invasive disease-free survival, *T-DM1* trastuzumab emtansine

with residual invasive disease at surgery after receiving neoadjuvant chemotherapy plus trastuzumab [14]. The primary analysis of KATHERINE reported that 3-year iDFS was significantly improved with T-DM1 versus trastuzumab (hazard ratio 0.50; 95% CI 0.39, 0.64; $p<0.001$) [14], forming the basis for the approval of adjuvant T-DM1 in patients with residual invasive disease after HER2-directed neoadjuvant therapy [67]. Long-term follow-up data (median 8.4 years) from the KATHERINE study showed sustained improvement with T-DM1 over trastuzumab,

with an iDFS event at 7 years reported in 19.7% and 32.2% of patients in the respective treatment groups (unstratified hazard ratio 0.54; 95% CI 0.44, 0.66; $p<0.0001$) [68]. The landmark 7-year iDFS rate was 80.8% with T-DM1 and 67.1% with trastuzumab (difference 13.7%) [68]. The most common first iDFS events were distant recurrence (14.7% with T-DM1 vs 21.5% with trastuzumab), locoregional recurrence (2.2% vs 6.2%), and contralateral breast cancer (0.9% vs 2.6%); death without prior event was reported for 1.9% patients in each treatment group [68]. Distant recurrence iDFS events included central nervous system (CNS) metastases, which occurred in 7.0% and 5.1% of patients treated with T-DM1 and trastuzumab, respectively [68], highlighting this clinical challenge in some high-risk patients.

In the safety analysis of the KATHERINE study, the most common grade ≥ 3 adverse events (AEs) with T-DM1 (in ≥ 2% of patients) were decreased platelet count (5.7% vs 0.3% with trastuzumab) and hypertension (2.0% vs 1.2%) after a median of 41 months of follow-up; adjudicated cardiac events were rare (0.1% vs 0.6% in the respective groups) [14].

Neratinib

As an irreversible pan-HER inhibitor [69, 70], neratinib has been approved as an extended adjuvant treatment in patients with HER2+ early BC after an adjuvant trastuzumab-based therapy in the USA, Europe, China, and many other countries; in Europe, neratinib is registered as extended adjuvant treatment for adults with HER2+/HR+ early BC who initiate treatment within 1 year of completing trastuzumab-based therapy [71–73]. These approvals were based on data from the ExteNET double-blind, placebo-controlled phase 3 study, which showed an improvement in survival with neratinib [74, 75]. Although there was no significant difference in the 8-year OS rate with neratinib versus placebo in the intention-to-treat (ITT) population (90.1% vs 90.2%) [75], descriptive analyses showed a numerical (but non-significant) improvement in OS (median follow-up 8.3 years) with neratinib versus placebo in patients with HER2+/HR+ tumors who initiated neratinib within 1 year of completing trastuzumab (absolute benefit 2.1%; hazard ratio 0.79; 95% CI 0.55, 1.13; $p=0.203$) [74]. Moreover, neratinib significantly improved iDFS at 2 years compared with placebo in patients with HER2+ early BC after adjuvant trastuzumab therapy (hazard ratio 0.67; 95% CI 0.50, 0.91; $p=0.0091$) [76]. Of note, a prespecified subgroup analysis revealed improved iDFS benefit with neratinib in patients with HER2+/HR+ BC (hazard ratio 0.51; 95% CI 0.33, 0.77; $p=0.0013$) that was not significant in those with HER2+/HR− disease (hazard ratio 0.93; 95% CI 0.60, 1.43; $p=0.74$; $p=0.054$ for interaction) [76]. In HER2+/HR+ patients who initiated neratinib within 1 year of completing adjuvant trastuzumab (≤ 1 year) the absolute iDFS benefit was 4.5% at 2 years (hazard ratio 0.49; 95% CI 0.30, 0.78; $p=0.002$) and was 5.1% at 5 years (hazard ratio 0.58; 95% CI 0.41, 0.82; $p=0.002$) [74].

A trend was observed towards a lower cumulative incidence of first CNS recurrence at 5 years with neratinib versus placebo (0.7% vs 2.1%) among patients with HER2+/HR+BC who initiated treatment ≤ 1 year post-trastuzumab [74]. Furthermore, a high proportion of patients were alive and without CNS recurrence at 5 years in both treatment groups (98.4% and 95.7%, respectively) [74]. The ITT population consisted of 2840 patients (1420 per treatment group), 1631 (57%) of whom had HR+ disease (neratinib, $n=816$; placebo, $n=815$). Among those with HR+ tumors, 1334 (82%) patients had initiated study treatment within 1 year of completing trastuzumab therapy (neratinib, $n=670$; placebo, $n=664$).

The ExteNET study initially enrolled all patients who completed neoadjuvant and/or adjuvant chemotherapy plus trastuzumab therapy regardless of response at surgery (pCR and non-pCR patients); however, the study protocol was subsequently amended to restrict recruitment to higher-risk patients who completed neoadjuvant therapy and had residual invasive cancer present in the breast and/or axilla (non-pCR only) after completing 1 year of trastuzumab [74]. In a subgroup analysis of 295 patients (HER2+/HR+, ≤ 1 year) with non-pCR, the 5-year iDFS rate was 85.0% and 77.6% in

the neratinib and placebo groups, respectively (absolute benefit 7.4%; hazard ratio 0.60; 95% CI 0.33, 1.07) [74] and the 8-year OS rate was 91.3% and 82.2% in the neratinib and placebo groups, respectively (absolute benefit 9.1%; hazard ratio 0.47, 95% CI 0.23, 0.92) [74].

In the ExteNET study, neratinib treatment was commonly associated with diarrhea [74], a known adverse effect of tyrosine kinase inhibitors (TKIs), with grade ≥ 3 diarrhea occurring in 40% of patients [77]. However, most grade 3 diarrhea events were reported in the first month of treatment (median time to onset 8 days) and were transient (median cumulative duration 5 days) [74]. The subsequent CONTROL study (described below) demonstrated that antidiarrheal prophylaxis and gradual neratinib dose escalation can be used to effectively manage treatment-related diarrhea [78].

THE ONGOING CHALLENGES OF MANAGING HIGH-RISK HER2+ EARLY BC

Despite the availability of trastuzumab and the newer treatment options (pertuzumab and T-DM1), many patients with HER2+ early BC are at persistent high risk for recurrent disease after adjuvant trastuzumab-based therapy. Therefore, further strategies are needed to manage these high-risk patients.

The ESMO guidelines for the management of early BC recommend a standard 1-year duration of adjuvant trastuzumab-based therapy for patients with HER2+ early BC, and ≥ 5 years of endocrine therapy, tailored to menopausal status and risk profile, for those with ER+ tumors [4], and the ASCO guidelines recommend neoadjuvant HER2-directed therapy with trastuzumab in patients with node-positive or high-risk node-negative HER2+ disease [5]. Patients with high-risk HR+ tumors may be considered for extended treatment with neratinib (concurrent with endocrine therapy) for 1 year after completion of 1 year of trastuzumab or trastuzumab-based therapy [Level I, B; ESMO-Magnitude of Clinical Benefit Scale v1.1 score: no evaluable benefit; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-A] [4]. The use of neratinib after trastuzumab and pertuzumab or post T-DM1 is an extrapolation of the ExteNET data.

It is well documented that poor treatment adherence in patients with BC has direct consequences with regard to disease recurrence and mortality [79]. Treatment adherence is defined as the extent to which the patient takes the medication in terms of the prescribed interval and dosage [80]; the World Health Organization (WHO) has identified non-adherence to treatment as the most crucial factor that can dramatically alter treatment outcomes [81]. Adherence to endocrine therapy in adjuvant BC trials is relatively high, but only around 50% of patients complete 5-year adjuvant therapy in the clinical setting [82].

Dose escalation and optimization of prophylactic interventions may improve treatment adherence with extended adjuvant neratinib therapy for HER2+ early BC by reducing the severity of diarrhea and related treatment discontinuations, although discontinuation is still an issue with neratinib. In the open-label, phase 2 CONTROL study of patients with HER2+ early BC who received neratinib after completing trastuzumab-based adjuvant therapy, pre-emptive anti-diarrheal prophylaxis (e.g., loperamide) and/or gradual dose escalation of neratinib reduced the rate, severity, and duration of treatment-emergent grade ≥ 3 diarrhea [78]. Compared with the ExteNET study, in which grade 3 diarrhea was reported in 40% of patients [76], all preventive strategies reduced the incidence of grade 3 diarrhea, with patients in the 2-week neratinib dose-escalation cohort having the lowest incidence (13%) [78]. In addition, the proportion of patients who discontinued neratinib as a result of treatment-emergent diarrhea was 3% in the 2-week dose-escalation cohort from CONTROL, while it was 17% in ExteNET [78]. Similarly, the real-world observational ELEANOR study in patients with stage I–III HER2+/HR+ BC showed that patients who initiated lower-dose neratinib had lower incidences of grade ≥ 3 diarrhea (16.2% vs 22.7%) and diarrhea-related permanent treatment discontinuations (10.3% vs 14.3%) than those who initiated treatment at the full dose, with a lower proportion of patients

permanently discontinuing treatment within the first 3 months (20.6% vs 31.9%) [83].

FUTURE DIRECTIONS

Ongoing research is evaluating further potential strategies to improve outcomes in patients with HER2+ early BC, particularly among high-risk patients with residual disease. When evaluating potential new strategies and novel agents in this setting, it will be crucial to consider the risk–benefit profile of these treatments in order to optimize the patients' quality of life.

The DESTINY-Breast05 study is investigating whether trastuzumab deruxtecan, which is currently approved for treatment of patients with advanced HER2+ BC, may be an alternative to T-DM1 in patients with HER2+ early BC who have residual invasive disease in breast or axillary lymph nodes following neoadjuvant therapy (NCT04622319; estimated primary completion 2025). Two other studies are investigating whether adding treatments to T-DM1 may provide benefits in patients with HER2+ BC at high risk of recurrence; the ASTEFANIA study is comparing T-DM1 plus atezolizumab with T-DM1 plus placebo (NCT04873362; estimated primary completion 2028) and the CompassHER2 RD study is comparing T-DM1 plus tucatinib with T-DM-1 plus placebo (NCT04457596; estimated primary completion 2028). In both of these studies, the primary endpoint is iDFS.

Novel agents are also being evaluated in this setting, including GLSI-100, an investigational vaccine consisting of GP2 (a nine amino acid HER2-derived peptide) plus granulocyte–macrophage colony stimulating factor. In a phase 2b study, GLSI-100, administered as four booster injections at 6-month intervals, was associated with a potent immune response and minimal injection site response [84]. This study confirmed that GLSI-100 is generally well tolerated, with the majority of patients reporting only mild local (erythema, induration, and pruritic) and systemic (fatigue, headache, and myalgia/arthralgia) AEs [85]. The phase 3 FLAMINGO-01 study is investigating whether immunization with GLSI-100 can improve invasive DFS in high-risk patients with HER2+ BC who have completed the standard neoadjuvant and adjuvant treatment sequence (NCT05232916; estimated primary completion December 2026). The GLSI-100 regimen consists of a primary immunization series (monthly intradermal injections for 6 months) and five booster injections given 6 months apart.

Other new drugs being explored as HER2-targeted therapies in breast cancer include the novel monoclonal antibody (mAb) inetetamab (also known as cipterbin), which binds to the HER2 subdomain IV [86]. A retrospective Chinese study of inetetamab in combination with vinorelbine plus pyrotinib after trastuzumab-based treatment in patients with HER2+ metastatic BC showed good treatment response and a manageable safety profile, with the most common grade ≥ 3 AEs being leukopenia and neutropenia [87]. Ongoing clinical trials are investigating inetetamab in the neoadjuvant setting in combination with pertuzumab and chemotherapy (NCT05749016), and inetetamab combined with pyrotinib and chemotherapy in the metastatic setting, in first or subsequent lines (NCT05823623, NCT04681911, NCT05823623, NCT05621434, and NCT04963595); all of these studies posted estimated primary completion dates by December 2024 at the latest, but have not been updated with study results as at the time of writing this review.

Bispecific antibodies have been developed that target different domains in the HER2 receptor, optimizing its blockade [86]. For example, the humanized immunoglobulin (Ig) G1 mAb zanidatamab simultaneously targets the HER2 subdomains II and IV, and is being evaluated both as monotherapy in the neoadjuvant setting (NCT05035836; estimated primary completion December 2025), and in combination with antibody–drug conjugates (NCT05027139; estimated primary completion April 2025) or CDK4/6 inhibitors (NCT04224272; estimated study completion October 2025). Primary results from the latter study, a phase 2a trial in patients with HR+/HER2+ metastatic BC indicated that zanidatamab plus palbociclib and fulvestrant had promising antitumor activity and manageable tolerability, with neutropenia being the

most common treatment-related grade ≥ 3 AE [88]. Another bispecific antibody is anbenitamab, which is derived from trastuzumab and pertuzumab, and is in ongoing clinical trials in the neoadjuvant (NCT04881929) and metastatic (NCT04165993) settings in combination with chemotherapy. Preliminary data from these trials have indicated that anbenitamab plus docetaxel had promising clinical benefit and acceptable safety in both settings [89, 90]. The most common grade ≥ 3 treatment-emergent AEs in the neoadjuvant setting were decreased neutrophil, white blood cell, and lymphocyte counts [89]. Similarly, in patients with metastatic disease, the most common grade ≥ 3 treatment-related AEs were decreased neutrophil count, leukopenia, and increased alanine aminotransferase levels [90].

Poziotinib is an irreversible pan-HER TKI that has been evaluated in patients with HER2+ metastatic BC in the third-line setting and beyond, which appears to have similar OS and toxicity to other TKIs [86]. In the phase 2 NOV120101-203 trial in heavily pretreated patients with HER2+ metastatic BC, poziotinib had clinical meaningful antitumor activity and the most common treatment-related AEs were diarrhea, stomatitis, skin disorders, and decreased appetite [91, 92].

CONCLUSIONS

Patients with HER2+/HR+ early BC have a similar risk of disease recurrence at 10 years after diagnosis compared with those with HER2+/HR− disease. Despite the recent introduction of novel anti-HER2 therapies, there is a need for reducing the risk of late relapse in patients with HER2+/HR+ early BC. Extended adjuvant endocrine therapy is an option that can be considered for high-risk patients and ongoing trials may provide some new options for adjuvant treatment in the near future. Additional research should specifically focus on the risk for intracranial recurrences as the first site of progression, with the aim of improving extracranial disease control. Without longer-term data for HER2+ BC, treatment decisions should be guided by current knowledge of recognized risk factors for recurrent disease and available therapies to minimize this risk in patients with HER2+/HR+ tumors. When considering the need for additional adjuvant treatment in HER2+/HR+ early BC, current evidence suggests that physicians should consider high-risk factors, such as tumor size and nodal status at diagnosis, and residual disease after neoadjuvant therapy, which remain the decisive determinants of recurrence.

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Declarations

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