Seminars in Oncology 47 (2020) 249–258

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/seminoncol

Risk-based Approaches for Optimizing Treatment in HER2-Positive Early Stage Breast Cancer

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ARTICLE INFO

Article history:
Received 28 May 2020
Accepted 9 July 2020

Keywords:
Early stage
HER2-positive breast cancer
Trastuzumab
Ado-trastuzumab emtansine
Pertuzumab
Neratinib

ABSTRACT

Advancements in the care for patients with early stage HER2-positive breast cancer is a story of incremental successes aimed at optimizing efficacy and reducing the toxicities of administered therapies. HER2 drives an aggressive breast cancer subtype that represents 15%–20% of breast cancers, for which HER2-targeted therapy is very active. In addition to trastuzumab, pertuzumab, neratinib, and ado-trastuzumab emtansine have been approved in recent years for the treatment of high-risk early stage HER2-positive breast cancer. As a result of both a high response rate to neoadjuvant therapy and the opportunity for response-adapted adjuvant therapy, the treatment paradigm has evolved so that most patients with stage II and III disease now receive neoadjuvant therapy. Additionally, the efficacy of HER2-therapy allows for de-escalation of treatment in many patients with stage I disease. As a result, multidisciplinary evaluation is essential for the optimal care of patients with HER2-positive breast cancer. Important areas of further research include tailoring the duration and intensity of therapy based on disease risk and response to neoadjuvant therapy. This article will review the evaluation of patients with early stage HER2-positive breast cancer and provide an evidence- and guideline-based summary of risk-based treatment strategies.

Background

HER2 protein overexpression, typically as a result of *ERBB2* gene amplification occurs in approximately 15%–20% of all invasive breast cancers [1]. HER2-positivity is associated with a highly proliferative subtype of breast cancer, usually with high-grade histology and an increased risk of lymph node involvement [2]. In the United States, breast cancer remains the second most common cause of cancer-related death among women, with around 40,000 new cases of HER2-positive breast cancer estimated in 2019 [3].

Without HER2-directed therapy, HER2-positive disease is associated with shorter disease-free survival (DFS) and breast cancer-specific survival, independent of other prognostic indicators including hormone-receptor (HR) status or lymph node involvement [2,4]. Risk factors for HER2-positive disease are less well understood than with HR-positive disease, however patients with germline mutations in TP53 (Li-Fraumeni syndrome) have been found to have a higher likelihood of HER2-positive disease [5].

The *HER2/ERBB2* oncogene located on chromosome 17 encodes for a 185kD transmembrane glycoprotein receptor. The HER2 receptor is a member of the epidermal growth factor receptor (EGFR) tyrosine kinase family, along with EGFR (HER1), HER3, and HER4. The HER2 protein forms homodimers or heterodimers with other HER family proteins, activating downstream tyrosine kinase signaling cascades. Activation of these pathways, including PI3K-AKT and RAS-MAPK, plays a crucial role in promoting cell proliferation, survival, and metastases [6,7].

Evaluation of patients with HER2-positive breast cancer

Compared to normal tissue, breast cancer cells with HER2 overexpression have up to a 40–100-fold increase in HER2 protein expression [8]. HER2 expression can be evaluated using immunohistochemical (IHC) analysis with anti-HER2 antibody staining. Negative results include IHC staining of 0-1+; IHC staining of 3+ is categorized as positive. IHC 2+ (weak to moderate complete membrane staining observed in >10% of tumor cells) is considered equivocal, and per ASCO/CAP 2018 guidelines, additional testing with either in-situ hybridization (ISH) on the same specimen or testing of a new specimen (with either IHC or ISH) is required. Results from ISH are defined as the ratio of gene amplification of *HER2* and the chromosome 17 enumeration probe (CEP17). Patients with 2+ IHC and subsequent dual-probe ISH testing demonstrating a *HER2*/CEP17 ratio of ≥2 with average HER2 copy number signals per cell ≥4 are considered HER2-positive [9]. Recount of ISH by an

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https://doi.org/10.1053/j.seminoncol.2020.07.007
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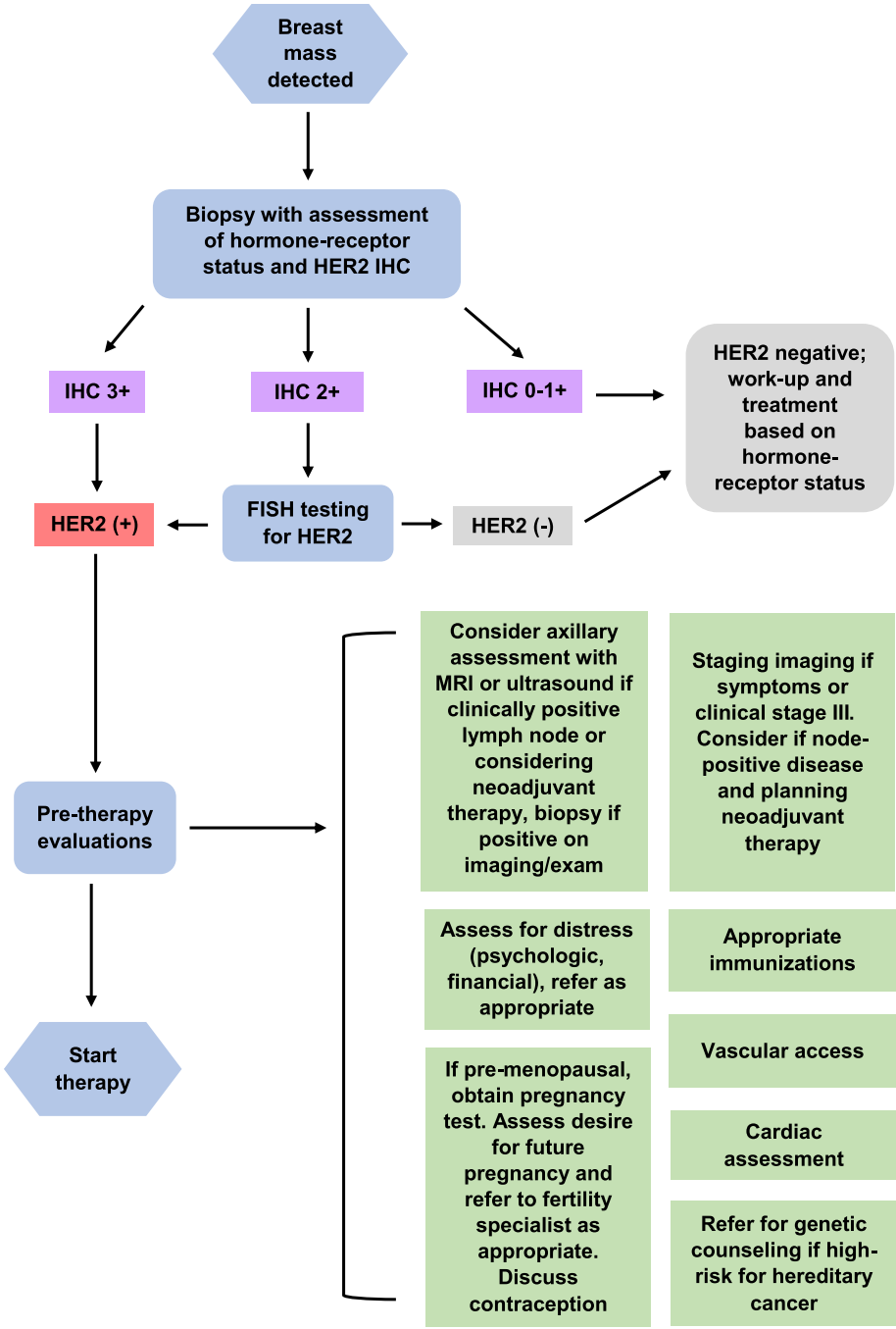

Fig. 1. Workup of HER2-positive early stage breast cancer.

additional, blinded observer is required if ISH testing meets only one of these criteria. If review confirms either *HER2*/CEP17 ratio of ≥2 with average *HER2* signals/cell <4 or *HER2*/CEP17 ratio <2 and average *HER2* signals/cell ≥4 (but less than 6), HER2 is considered negative with comment. However, if review confirms *HER2*/CEP17 ratio <2 and average *HER2* signals/cell ≥6, HER2 is considered positive.

For patients with a new diagnosis of invasive breast cancer, initial evaluation includes pathologic assessment for HR positivity as well as HER2 expression (Fig. 1). The tumor, node, metastasis staging system for breast cancers includes standard anatomic staging as well as a prognostic staging system which incorporates prognostic biomarkers such as tumor grade and HER2 and HR status [10]. Postneoadjuvant pathologic T and N categories (ypT and ypN) are also available, and residual cancer burden after neoadjuvant therapy has been used to further classify risk based on response to treatment [11,12] (Fig. 2).

Additional breast imaging with magnetic resonance imaging (MRI) is not universally recommended, although may be indicated in specific cases, including patients who have clinically positive axillary lymph nodes or occult primary disease, as well as in some cases to assess response to preoperative systemic therapy and to assess the potential for breast-conserving surgery. Routine systemic imaging is not indicated for most patients with early stage breast cancer (stage I or II) in the absence of signs or symptoms of metastatic disease. Systemic imaging with diagnostic chest and

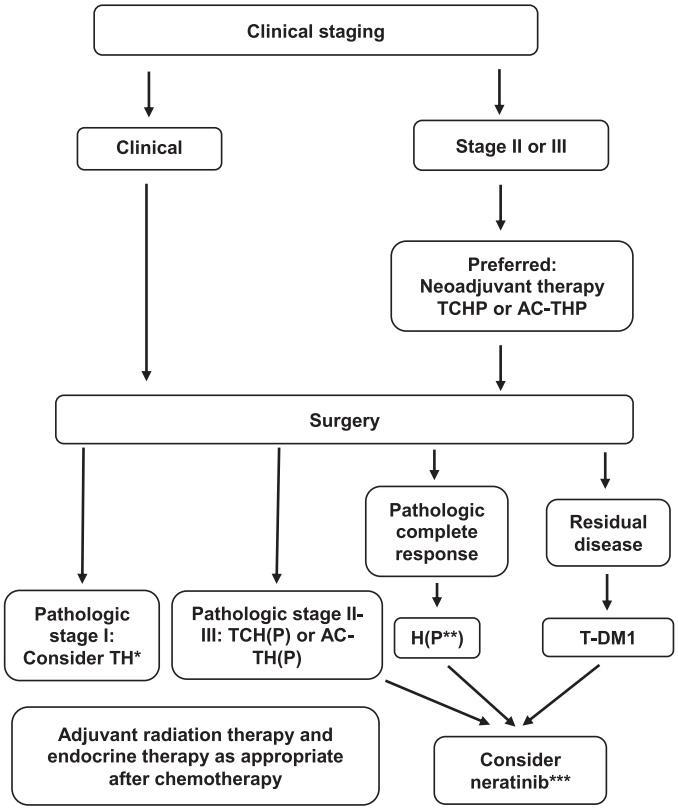

Fig. 2. Suggested treatment approach for HER2-positive early stage breast cancer. *Notes:* *Consider omission of chemotherapy and HER2-therapy for some small T1a tumors. **Benefit of adjuvant pertuzumab (P) primarily seen in lymph node positive breast cancer. ***Benefit of neratinib is seen primarily in HR-positive, node-positive breast cancer; efficacy after pertuzumab (P) or T-DM1 is unknown. AC-TH(P) = **A**driamycin (doxorubicin) + **C**yclophosphamide + **T**axol (paclitaxel) + trastuzumab (**H**erceptin) + **P**ertuzumab; TCH(P) = **T**axotere (docetaxel) + **C**arboplatin + **H**erceptin (trastuzumab) + **P**ertuzumab; T-DM1 = trastuzumab emtansine, **T**rastuzumab **DM1**; H = Herceptin (trastuzumab) P = pertuzumab (Perjeta).

abdominal/pelvic computed tomography (CT), as well as bone scan, may be considered for patients with locally advanced/stage III disease, or those with symptoms concerning for metastatic disease. FDG positron emission tomography (PET)/CT may be considered, and is most helpful in situations where standard staging studies are equivocal or suspicious. Other imaging, including brain magnetic resonance imaging, is recommended based on symptoms [12].

In addition to staging imaging, baseline cardiac assessment with either transthoracic echocardiogram or multigated acquisition scan is needed for patients being considered for treatment with HER2-targeted therapy and/or anthracycline-based chemotherapy. Genetic counseling should be offered to patients thought to be at high risk of hereditary breast cancer and all patients should be assessed for psychosocial distress related to their diagnosis. Patients should receive any appropriate immunizations if feasible before starting therapy and may be referred to social work or financial counseling if needs are identified [12].

All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies. Data regarding the impact of chemotherapy for breast cancer on fertility is limited, as rates of infertility and amenorrhea are highly impacted by patient specific factors, particularly age. It is known that alkylating agents such as cyclophosphamide can have significant impact on fertility, and the concomitant use of anthracyclines or taxanes may increase the risk of amenorrhea and infertility [13]. There is no clear added risk to fertility with HER2-targeted therapy. Patients who desire to bear children after systemic therapy should be referred to a fertility specialist prior to initiating systemic therapy. Premenopausal women should also undergo pregnancy testing and be counseled about the need for contraception during treatment and for 6 months after completion of treatment with HER2-targeted agents [14,15]. Contraception is also required during treatment with tamoxifen [16].

HER2-targeted therapy has been shown to significantly improve overall survival (OS) in early-stage HER2-positive breast cancer [17-19]. It has been studied in both the adjuvant and neoadjuvant settings, and has been used in conjunction with both anthracycline-based and non-anthracycline-based chemotherapy. HER2-directed therapy is thought to have a synergistic effect when combined with certain chemotherapeutic agents, with HER2 therapy enhancing chemosensitivity and increasing rates of pathologic complete response (pCR) when used in the neoadjuvant setting [20,21]. Therapy selection, sequence of care, and duration of therapy are decisions that need to be individualized based on stage, pathologic features, and patient factors, including comorbidities (such as underlying cardiac disease), desire for fertility preservation and performance status.

HER2-targeted drugs and regimens for early stage breast cancer

There are 4 HER2-targeted agents approved by the FDA for early stage HER2 positive breast cancer: trastuzumab, pertuzumab, trastuzumab-emtansine, and neratinib. These drugs along with frequently used perioperative chemotherapy regimens for HER2-positive breast cancer are summarized in Table 1.

Trastuzumab (Herceptin) is a monoclonal IgG1 humanized murine antibody which exhibits antitumor activity in HER2-positive breast cancer by binding to the extracellular domain IV of the HER2 receptor and inhibiting HER2 dimerization as well as causing antibody-dependent cell mediated cytotoxicity (ADCC) [14]. Trastuzumab has been associated with a decrease in left ventricular ejection fraction and congestive heart failure which are often reversible. Patients should have baseline assessment of left ventricular ejection fraction (LVEF) and extreme caution should be used if treating patients with pre-existing cardiac dysfunction.

Pertuzumab (Perjeta) is a monoclonal antibody with a unique HER2 binding domain (domain II) that inhibits HER2 homo- and heterodimerization with HER3, therefore inhibiting intracellular signaling through MAPK and PI3K pathways in addition to mediating ADCC [15]. In 2013 based on phase II neoadjuvant data it received FDA-accelerated approval for neoadjuvant therapy in tumors >2 cm or with involvement of lymph nodes. In 2017 it gained regular approval for use in combination with trastuzumab and chemotherapy as adjuvant treatment in patients with HER2-positive early breast cancer at high risk of recurrence. The most common added toxicity is diarrhea. Although it is recommended to hold therapy if significant decreases in LVEF are seen, no specific association with increased cardiotoxicity has been shown. Pertuzumab is pregnancy category D.

Trastuzumab emtansine/T-DM1 (Kadcyla) is an antibody drug conjugate that consists of the chemotherapy emtansine (DM-1), a microtubule toxin, combined with the HER2 monoclonal antibody trastuzumab. Upon binding to subdomain IV of the HER2 receptor, the drug undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1-containing toxic catabolites. Binding of DM1 to tubulin disrupts microtubule networks in the cell, resulting in cell cycle arrest and apoptosis [22]. T-DM1 also works to mediate ADCC. In 2019, it received approval for use in the adjuvant setting for patients with residual disease after neoadjuvant therapy [23]. The most common toxicities are thrombocytopenia, liver enzyme elevation, and pe-

Table 1
Common (neo)adjuvant therapies for HER2-positive early stage breast cancer.

Acronym	Dosing and schedule	Timing/sequence	Other notes and common toxicities
Dose dense AC-TH(P)			
• **A**driamycin + • **C**yclophosphamide + • **T**axol + • **H**erceptin + • (**P**ertuzumab)	• Doxorubicin 60 mg/m^2 d 1 of 14-d cycle with growth factor support + • Cyclophosphamide 600 mg/m^2, d 1 of 14-d cycle with growth factor support followed by • Paclitaxel 80 mg/m^2 weekly x 12 with trastuzumab and pertuzumab	• Neoadjuvant or adjuvant chemotherapy and HER2-therapy followed by HER2-targeted therapy every 3 wk to complete 1 yr	• Cytopenias, give with growth factor • Neuropathy • Diarrhea increased with pertuzumab • Risk for cardiac toxicity
TCH(P)			
• **T**axotere + • **C**arboplatin • **H**erceptin+ • (**pertuzumab**)	• Docetaxel 75 mg/m^2 + Carboplatin AUC 6 day 1 of 21-d cycle with growth factor support with trastuzumab and pertuzumab	• Neoadjuvant or adjuvant chemotherapy and HER2-therapy followed by HER2-targeted therapy every 3 wk to complete 1 yr	• Cytopenias, give with • growth factor • Neuropathy • Diarrhea increased with pertuzumab
TH			
• **T**axol + • **H**erceptin	• Paclitaxel 80 mg/m^2 weekly x 12 with trastuzumab followed by trastuzumab	• Adjuvant therapy with TH weekly, then trastuzumab every 3 wk to complete 1 yr	• Neuropathy • Mild cytopenias
Trastuzumab (Herceptin)	**Every 3 wk**		
• Binds extracellular subdomain IV of HER2 and inhibits HER2 dimerization • Also mediates ADCC	• Loading 8 mg/kg followed by 6 mg/kg **Weekly:** • Loading 4 mg/kg followed by 2 mg/kg	• Neoadjuvant and/or adjuvant	• Associated with decrease in LVEF and CHF which are often reversible • Perform baseline assessment of LVEF • Use extreme caution if treating patients with pre-existing cardiac dysfunction.
Pertuzumab (Perjeta)	**Every 3 wk:**		
• Binds domain II and inhibits HER2 homo- and heterodimerization with HER3 inhibiting intracellular signaling through MAPK and PI3K pathways • Also mediates ADCC	• Loading 840 mg followed by 420 mg with trastuzumab	• Neoadjuvant and/or adjuvant	• Diarrhea • Although recommend holding therapy with significant decreases in LVEF, no specific association with increased cardiotoxicity has been shown
Ado-trastuzumab emtansine (T-DM1) (Kadcyla)	**Every 3 wk:**		
• Binds to subdomain IV of HER2 receptor, and undergoes receptor-mediated internalization with subsequent lysosomal degradation, and release of DM1-containing toxic catabolites • DM1 binds to beta-tubulin and disrupts MT function • Also mediates ADCC	• 3.6 mg/kg every 3 wk x 14 cycles	• Adjuvant therapy in patients with residual disease after neoadjuvant chemotherapy and trastuzumab-based therapy	• Thrombocytopenia, neuropathy, transaminase elevation • Monitor serum transaminases and bilirubin before each dose • Similar cardiovascular monitoring as for trastuzumab
Neratinib (Neralyx)	**Daily:**		
• Irreversibly binds to EGFR, HER2 and HER4 • Thought to reduce EGFR and HER2 autophosphorylation, and downstream MAPK and AKT signaling	• 240 mg daily with food	• Adjuvant after 1 yr of chemotherapy-HER2 therapy	• Grade 3 diarrhea in 40% and any grade in 95% without prophylaxis • Give prophylactic loperamide for at least the first two cycles • Consider addition of budesonide, colestipol or other antidiarrhea regimens if needed • is significantly reduced with

ADCC = antibody-dependent cell mediated cytotoxicity; AKT = AKR mouse strain thymoma, also known as protein kinase B (PKB); CHF = congestive heart failure; DM1 = mertansine, emtansine; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; HER4 = human epidermal growth factor receptor 4; LVEF = left ventricular ejection fraction; MAPK = mitogen activated protein kinase; MT = microtubule; PI3K = phosphoinositide 3-kinase; T-DM1 = trastuzumab emtansine, trastuzumab DM1.

ripheral neuropathy. Serum transaminases and bilirubin should be monitored before each dose with dose reductions or discontinuation recommended based on severity of changes. Similar cardiovascular monitoring is recommended as for trastuzumab, and it is pregnancy category D.

Neratinib (Neralyx) is a tyrosine kinase inhibitor that irreversibly binds to EGFR, HER2, and HER4. It is thought to reduce EGFR and HER2 autophosphorylation, as well as downstream MAPK and AKT signaling [24]. It was approved in 2017 for extended adjuvant treatment after trastuzumab therapy with benefit primar-

ily seen in node-positive HR-positive breast cancer. Its efficacy in patients who have received prior pertuzumab or T-DM1 is not known. Grade 3 diarrhea in 40% and any grade in 95% without prophylaxis is significantly reduced with prophylactic loperamide for at least the first 2 cycles. The addition of budesonide or colestipol can further reduce diarrhea [25]. Concomitant use of proton-pump inhibitors or H2 receptor antagonists are contraindicated, and use should be avoided with strong or moderate CYP3A4 inhibitors and inducers as well as P-glycoprotein substrates. LFTs should be monitored prior to initiation and monthly for the first 3 months, then every 3 months afterwards while on treatment. Pregnancy should be avoided.

Evidence-based decision-making for systemic therapy in patients with HER2-positive breast cancer

Who needs systemic therapy?

HER2 drives an aggressive breast cancer subtype that carries a high risk for recurrence, thus the majority of patients with early stage disease benefit from systemic therapy [2]. Although the initial studies establishing the role for adjuvant chemotherapy in early breast cancer did not characterize HER2-status, meta-analyses of these studies established a clear benefit from adjuvant anthracycline-taxane containing chemotherapy for early breast cancer (primarily based on data from breast cancers larger than 1 cm) [26]. Additionally, in adjuvant chemotherapy studies, retrospective analysis after HER2-testing was completed on tissue blocks showed HER2-positivity predicted for greater benefit from anthracyclines and benefit from adjuvant paclitaxel (Table 2) [27-29].

In 2005, interim results from the HERA and BCIRG-006 trials, as well as the joint analysis of NSABP B-31 and NCCTG N9831 trials were reported, demonstrating the benefit of trastuzumab and chemotherapy over chemotherapy alone [17-19]. These studies included patients with HER2-positive tumors with node-positive disease (all trials) or high-risk node-negative disease (defined as tumor size >2 cm for N9831 and BCIRG-006 and >1 cm for HERA). BCIRG-006 also included patients whose lymph nodes were negative with ER/PR negative tumors, histologic and/or nuclear grade 2–3 or those <35 years of age regardless of tumor size [30]. These studies showed an approximately 50% reduction in the risk of recurrence and a 30% early improvement in OS was seen in the joint analysis report. Longer term follow-up demonstrated consistent improvement in DFS and OS (hazard ratio [HR] for OS compared to the control arm ranged 0.63–0.74), benefits which were seen despite a cross-over rate of up to 50% in the HERA trial, and smaller crossover rates in other studies [30-32]. This has established the benefit of combined chemotherapy plus HER2 therapy in patients with tumors >2 cm or lymph node involvement.

Randomized data is more limited in patients with node-negative tumors <2 cm and lacking in those with tumors <1 cm. However, recurrence rates of around 20% are seen in tumors ≤1 cm without adjuvant systemic therapy [33-35]. As a result of the high risk for recurrence seen with these limited retrospective and registry data as well as much more favorable outcomes with chemotherapy and HER2 therapy, guidelines recommend consideration of adjuvant chemotherapy plus HER2 therapy in patients with tumors ≥5 mm and can be considered in tumors 3–4 mm as well [36].

Take away: In candidates for systemic therapy, (neo)adjuvant chemotherapy and trastuzumab should be given in patients with invasive breast cancer 5 mm or larger and can be considered in some cases with smaller tumors (3–4 mm and/or multifocal tumors) as well.

What is the preferred sequence and duration of chemotherapy and HER2 therapy?

The landmark study establishing the value of trastuzumab in HER2-positive metastatic breast cancer showed remarkable efficacy of trastuzumab when given concurrently with anthracyclines; however, 27% of patients developed cardiotoxicity [37]. As a result of this toxicity, adjuvant trastuzumab studies were designed with sequential administration of anthracyclines and trastuzumab. The N9831 trial prospectively compared the sequential administration of chemotherapy and trastuzumab (AC-T followed by trastuzumab) with concurrent taxane-trastuzumab therapy (AC followed by paclitaxel-trastuzumab) with 5-year DFS of 80.1% versus 84.4% (HR 0.77, 99.9% confidence interval [CI] 0.53–1.11, P= .0216) [38]. This numerical trend toward improved outcomes and safety with concurrent taxane-trastuzumab led to our standard of concurrent administration.

The initial adjuvant trastuzumab trials established the benefit of an arbitrarily determined 1 year of therapy; subsequent studies have tested various durations to optimize the benefits and reduce risks of trastuzumab therapy.

The HERA trial included arms with 1 and 2 years of adjuvant trastuzumab. When compared directly there was no difference in 10-year DFS (69% in both arms, HR 1.02 95% CI 0.89–1.17) or OS (79*v* 80% with 1 and 2 years of trastuzumab, respectively), thus extending trastuzumab beyond 1 year has not shown benefit [31,39].

The FinHER trial demonstrated only 9 weeks of trastuzumab significantly improved DFS when added to chemotherapy (HR 0.29, 95% CI, 0.13–0.64) with a similar magnitude of improvement in absolute DFS at 3 years as shown in the joint analysis of NSABP-B31 and NCCTG-N9831. This raised interest and provided the rationale for evaluating shorter durations of adjuvant trastuzumab [40]. The phase III PHARE trial has the most mature data, and evaluated 3,380 women with breast cancers of at least 1 cm. DFS was 79.6% with 12 months compared to 78.8% with 6 months of trastuzumab, HR 1.08, 95% CI, 0.93–1.25. Because this did not meet the prespecified threshold for noninferiority of 1.15, the authors concluded 12 months remains the standard [41]. The PERSEPHONE trial was a similarly designed trial that included 4,089 patients with HER2-positive breast cancer who were candidates for adjuvant chemotherapy. DFS at 4 years was 89.8% with 12 months and 89.4% with 6 months of trastuzumab. The HR of 1.07 (95% CI, 0.93–1.21) was similar to the PHARE study. However, the prespecified threshold for noninferiority was higher at 1.25, thus authors concluded the 6 months was noninferior [42]. In the smaller HOGR trial, 481 women were randomized to 12 or 6 months of trastuzumab with 3-year DFS of 95.7% versus 93.3%, respectively (HR 1.57, 95% CI 0.89–2.10), also did not show noninferiority [43]. It is noteworthy that the vast majority of patients in all of these studies received anthracycline and taxane-based therapy. Only about 10% of patients in PHARE and PERSEPHONE and no patients in HOGR received anthracycline-free taxane-based chemotherapy. Thus, the generalizability of this data to anthracycline-free regimens such as TCH(P) or TH is not known. Even shorter durations of trastuzumab (9–12 weeks) were evaluated in the SOLD, Short-HER, and E2198 trials [44-46]. These studies did not demonstrate noninferiority of the brief trastuzumab course.

These trials have also demonstrated that longer duration of trastuzumab is directly related to a higher rate of cardiotoxicity, which is most often reversible. When adjuvant trastuzumab was extended from 1 year to 2 years, the risk for decreased left ventricular ejection fraction (drop by at least 10% from baseline and to a level <50% confirmed by repeat assessment) increased from 4.1% to 7.2%. Additionally, grade 3 and 4 adverse events increased from 16.3% to 20.4% [39]. In PERSEPHONE, serious adverse events occurred in 19 versus 24% and clinical cardiac dysfunction in 8 versus 11% in the 6-month compared to the 1-year arms [42]. Similarly,

Table 2
Major Phase III Adjuvant HER2 Therapy Trials

Trial	Sample Size	Node-Positive	Hormone-Receptor Positive	HER2 Agents	Chemotherapy Backbone	Median Follow-Up	DFS	OS	Other Notes
HERA [1–3]	5081	57%	50%	1 or 2 years of trastuzumab after adjuvant chemotherapy	94% received anthracycline-based chemotherapy	11y	63% vs 69% vs 69% (observation vs 1y vs 2y trastuzumab) HR = 0.76 (1y trastuzumab vs observation)	73% vs 79% vs 80% HR = 0.74	No difference between 1 and 2 years of trastuzumab Higher incidence of grade 3 or 4 adverse events with 2 years vs 1 year 52% crossover
NCCTG N9831 and NSABP B-31 (joint-analysis) [4,5]	4046	94%	52% ER+, 40% PR+	1 year of trastuzumab	AC-T vs AC-TH	8.4y	62.2% vs 73.7% HR = 0.60	75.2% vs 84% HR 0.63	20% crossover
BCIRG-006 [6,7]	3222	71%	54%	1 year of trastuzumab	AC-T vs AC-TH vs TCH	10.3y	67.9% vs 74.6% vs 73.0% HR for DFS at 10y (compared to AC-T): - AC-TH = 0.70 - TCH = 0.76	78.7% vs 85.9% vs 83.3% HR for OS at 10y: AC-TH = 0.64 TCH = 0.76	No difference in efficacy between AC-TH and TCH. Significant cardiac safety benefit in non-anthracycline-based regimen 3.1% crossover
APHINITY [8]	4805	63%	64%	Trastuzumab +/- pertuzumab with adjuvant taxane-based therapy	78% received adjuvant anthracycline containing regimen	6.1y	87.8% vs 90.6%* (trastuzumab vs trastuzumab + pertuzumab) HR = 0.76	93.9% vs 94.8% HR=0.85 (95% CI 0.67-1.07)	Diarrhea more common in pertuzumab group No statistically significant difference in OS
KATHERINE [9]	1486	68%	72%	Adjuvant trastuzumab vs T-DM1 × 14 cycles after taxane-based neoadjuvant chemotherapy	76.9% received anthracycline-containing regimen	41mo	77% vs 88.3%* (trastuzumab vs T-DM1) HR 0.50	92.5% vs 94.3% HR=0.70 (95% CI 0.47-1.05)	Increased thrombocytopenia, elevation in bilirubin/transaminases, peripheral neuropathy in T-DM1 group For patients with residual disease after neoadjuvant therapy Benefit primarily seen in node-positive
ExteNET [10,11]	2840	76%	57%	Neratinib for 1 year after neoadjuvant/adjuvant chemo/HER2 therapy	78% received anthracycline-containing regimen	5.2y	87.7% vs 90.2%* (control vs neratinib) HR 0.73		40% had grade 3 diarrhea Greater benefit in HR-positive, node-positive

* Invasive DFS

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in the PHARE trial, patients treated with 6 months of trastuzumab had a 2.5% absolute reduction in cardiac dysfunction [47].

Take away: The series of studies to optimize the sequence and duration of chemotherapy and HER2-therapy have led to our standard of anthracycline without HER2-therapy if anthracycline is given and concurrent taxane and trastuzumab administration followed by adjuvant HER2-therapy to complete 1 year of HER2-therapy. The majority of benefit is derived in the first 6 months of HER2 therapy. Thus, shorter durations of HER2-therapy may be reasonable in situations of toxicities, co-morbidities, or other restraints. Discussion of duration and sequence for HER2 therapies other than trastuzumab are discussed below.

What is the preferred chemotherapy backbone?

The EBCTCG meta-analysis established survival benefits with adjuvant anthracycline and taxane-based chemotherapy and initial trials confirming the benefit of adjuvant trastuzumab utilized an anthracycline-taxane backbone (AC-T) [18,48]. However, the concern for excess cardiotoxicity with anthracyclines and trastuzumab and the efficacy of trastuzumab created interest in de-escalating the chemotherapy backbone of adjuvant treatment, which was evaluated in the BCIRG-006 study. This trial included over 3,000 patients with HER2-positive disease that was either node-positive or high-risk node-negative (tumor >2 cm, grade 2 or 3, or ER/PR negative, age <35 years) [30]. Patients were randomized to either chemotherapy alone (AC-T), anthracycline-taxane and trastuzumab (AC-paclitaxel + trastuzumab), or docetaxel, carboplatin, trastuzumab (TCH). The estimated 5-year DFS was 75%, 84%, and 81%, respectively. Both trastuzumab regimens were superior to AC-T, but there was no statistically significant difference in DFS seen between the anthracycline and non-anthracycline arms. At the final analysis with a median of 10.5 years of follow-up, the benefit of trastuzumab continued to be seen (HR of 0.70 and 0.76 with AC-TH and TCH compared to AC-T, respectively). Although not powered to detect equivalence of the two chemotherapy backbones, there was no significant difference in DFS or OS between the two chemotherapy-trastuzumab arms. There were 10 more DFS events with TCH compared to AC-TH (75% *v*73%). However, this came at the cost of 17 more cases of grade 3 or 4 congestive heart failure, 7 more cases of therapy-related leukemia, and 103 more cases of sustained LVEF loss of >10%. When compared in the neoadjuvant setting with dual-HER2-targeted agents, anthracycline and nonanthracycline regimens produced similar pCR rates with somewhat higher toxicities noted in the anthracycline arms, supporting the use of anthracycline-sparing regimens [26,49].

Although not evaluated in a randomized phase III study, further de-escalation of the chemotherapy backbone is supported by the phase II, single-arm APT study. This trial included 410 patients with tumors up to 3 cm and negative or micrometastatic lymph node involvement. The majority of patients had stage I breast cancer: 49% of patients had tumors ≤1 cm, 42% had tumors 1–2 cm, and only 1.5% had micrometastatic lymph node involvement. Patients were treated with TH (paclitaxel 80 mg/m^2 and trastuzumab weekly for 12 weeks followed by trastuzumab to complete 1 year). At a follow-up of 6.5 years, only 5.7% ($n = 23$) had a DFS event. Of these 6 were new breast cancer diagnosis, 5 were locoregional recurrence, and 8 were nonbreast cancer related deaths. Only 4 patients (1%) had a distant recurrence [36]. A subsequent two-arm phase II study, the ATEMPT trial, randomized patients to TH or T-DM1 every 3 weeks for 1 year [50]. The TH arm had 7 events with a 3-year DFS of 92.8% and the T-DM1 arm had a 3-year DFS of 97.7%, 95% CI 96.2%–99.3%, each arm with 2 distant recurrences. TH caused more neuropathy but 23% of patients in the T-DM1 arm discontinued treatment early, with 66% of them receiving further therapy with adjuvant trastuzumab.

Take away: Studies support the efficacy of sequential therapy with anthracycline followed by taxane-trastuzumab ± pertuzumab therapy. However, when directly compared with an anthracycline-free taxane-based therapy, TCH(P) offers similar outcomes with fewer rare but severe toxicities (cardiac dysfunction, leukemia). Both are standard treatment regimens for stage II and III HER2-positive breast cancers. For many stage I breast cancers, TH is likely sufficient therapy.

Should treatment be given adjuvantly or neoadjuvantly?

Neoadjuvant therapy can offer several benefits that include tumor down-staging to convert nonoperable to operable breast cancer, breast conservation, and reduction in the extent of axillary involvement. These considerations are especially relevant as response rates are high to neoadjuvant therapy in HER2-positive breast cancers, with pCR rates after combination chemotherapy and dual-HER2 therapy over 50% [51]. Additionally, neoadjuvant therapy provides insight into chemotherapy and HER2-therapy sensitivity, allowing adjuvant therapy to be adapted. Caution should be utilized with neoadjuvant therapy in situations where the extent of tumor is difficult to assess to avoid over-treatment.

The importance of neoadjuvant therapy was increased with the results of the KATHERINE trial. This study, involving 1,486 patients, evaluated adjuvant T-DM1 or trastuzumab given for 14 cycles to women who had any degree of residual invasive disease after at least six cycles of neoadjuvant therapy (at least 9 weeks of both taxane-based chemotherapy and trastuzumab, slightly shorter duration permitted for dose-dense regimens) [23]. 72.3% of patients received an anthracycline-taxane regimen and 27.7% received a taxane-only regimen. In addition to trastuzumab, 19.5% of patients received dual-HER2 therapy (pertuzumab) neoadjuvantly. This trial showed that invasive DFS was significantly increased in those treated with T-DM1 (HR 0.50; 95% CI 0.39–0.64), with 88.3% of patients in the T-DM1 group free of invasive disease at 3 years compared with 77% in the trastuzumab group. In addition, the risk of distant recurrence was significantly lower in the T-DM1 group (HR 0.60; 95% CI 0.45–0.79). The benefit was seen even for patients with <1 cm of residual disease [23]. Although survival data are awaited at this early follow-up, given the difference noted in distant recurrence, this approach has been quickly adapted.

Take away: For stage II and III HER2-positive breast cancers, neoadjuvant therapy with multiagent chemotherapy and dual HER2-antibodies (AC-THP or TCHP) is the preferred approach. This allows for adjuvant risk-adapted HER2 therapy with administration of T-DM1 for those with residual disease and H(P) adjuvantly for those with pCR. Given the very low failure rates of TH in stage I HER2-positive breast cancers, upfront surgery for accurate staging, followed by adjuvant TH is an appropriate de-escalation approach.

What is the optimal use of HER2 agents for early stage breast cancer?

The past decade has seen a significant expansion in options for HER2-targeted therapies that enhance benefit from or overcome resistance to trastuzumab. In addition to trastuzumab, pertuzumab, trastuzumab-emtansine, and neratinib have been approved for early stage disease.

In the CLEOPATRA trial, pertuzumab showed remarkable efficacy for first-line therapy in metastatic HER2-positive breast cancer, improving OS by 16 months when added to a taxane and trastuzumab [52]. Subsequently, several phase II trials evaluated various combinations of chemotherapy, trastuzumab, and pertuzumab in the neoadjuvant setting. This included NeoSphere, in which the docetaxel-trastuzumab-pertuzumab arm had a pCR rate of 46% compared to 29% with docetaxel-trastuzumab and

only 17% with trastuzumab-pertuzumab [53]. Although not powered for evaluating differences in long-term outcomes, the 5-year PFS was 81% versus 86% with docetaxel-trastuzumab compared to docetaxel-trastuzumab-pertuzumab [54]. The TRYPHAENA study had a primary endpoint of cardiac toxicity and studied various schedules of multi-agent chemotherapy with trastuzumab and pertuzumab, with pCR rates of 57%–66% [26]. Other neoadjuvant studies including the WSG-ADAPT-HER2+/HR-trial, TRAIN-2, and BERENICE showed consistently high pCR rates around 60% with neoadjuvant chemotherapy and dual HER2 antibodies and even higher rates when patients were selected for HER2-enriched subtype or ER/PR negative disease [49,55,56]. Based on data from phase II neoadjuvant studies, pertuzumab received accelerated approval by the FDA in 2013 for use in neoadjuvant therapy for tumors >2 cm or with positive lymph nodes, and subsequent regular approval in 2017 based on the APHINITY study for use in HER2-positive high-risk disease.

The APHINITY trial evaluated the addition of pertuzumab to standard adjuvant chemotherapy and 1 year of trastuzumab. The study enrolled 4,805 patients with node-positive or high-risk node-negative HER2-positive operable breast cancer, including 64% who had HR-positive disease and 63% with lymph node involvement. Seventy-eight percent of patients were treated with anthracycline-based adjuvant chemotherapy. Results demonstrated an absolute improvement in invasive DFS at 6 years of 2.8% (90.6% *v*87.8%) and a HR of 0.76 (95% CI 0.64–0.91) at a median follow-up of 74 months. At the same follow-up the absolute benefit in invasive DFS in lymph node positive patients was 4.5% with a HR of 0.72 (0.59–0.87), with no difference seen in the lymph node negative patients. No difference is yet seen in OS. Although the initial publication suggested a greater benefit was seen in patients with HR-negative disease, with longer follow-up, the difference was seen regardless of HR-status [57].

T-DM1 has also been studied neoadjuvantly in the KRISTINE/TRIO-021 phase III trial where the pCR rate with T-DM1 and pertuzumab was 44% compared to 56% with TCHP [58]. In the Phase II WSG-ADAPT HR+ HER2+ arm, T-DM1, and T-DM1 with endocrine therapy demonstrated a pCR rate of 41% [59]. Additionally in the I-SPY platform, pertuzumab and T-DM1 compared to paclitaxel and trastuzumab improved pCR rate and updated results from the adjuvant phase III KAITLIN (NCT01966471) study are awaited [60]. Currently T-DM1 is approved for use as adjuvant therapy in patients with residual invasive disease after neoadjuvant taxane and trastuzumab-based treatments based on improvement in DFS compared to trastuzumab in the KATHERINE trial as discussed above.

Neratinib's approval for use as extended adjuvant therapy after 1 year of trastuzumab-based therapy in patients with early stage HER2-positive breast cancer is based on results from ExteNET which included 2,840 women who completed 1 year of trastuzumab therapy [61]. Patients could have completed therapy up to 2 years prior to randomization. When external results from NCCTG-N981 and BCIRG-006 trials demonstrated that patients with node-negative tumors or those who were farther from completion of trastuzumab had lower risk of recurrence, an amendment was made to only include higher risk (node-positive) patients who had completed therapy up to 1-year prior. Patients were randomized to receive either neratinib or placebo for 12 months. 24% of patients enrolled were node-negative, 57% were HR-positive, and 78% of patients received an anthracycline as part of their therapy. Results demonstrated an improvement in 5-year invasive DFS of 2.5% (90.2% *v*87.7%) in the neratinib and placebo groups, respectively with a HR of 0.73 (95% CI 0.57–0.92). Greater benefit was seen in HR-positive patients (HR 0.60 *v*0.95 for HR-positive *v*negative) [61]. The efficacy of neratinib after pertuzumab and/or T-DM1 is unknown. In the neratinib group, 40% of patients developed grade 3 diarrhea, which has been shown to be mitigated somewhat by prophylactic use of combination loperamide and either budesonide or colestipol as shown in the CONTROL trial [25].

Lapatinib is an oral tyrosine kinase inhibitor that reversibly binds HER1 and HER2 and has also been studied extensively for early stage and metastatic HER2-positive breast cancer disease with activity in the neoadjuvant setting. Three neoadjuvant phase III trials showed pCR rates were boosted by 10%–20% when lapatinib was added to paclitaxel and trastuzumab, albeit with increased toxicity [62-64]. However, when evaluated in randomized adjuvant phase III studies, adjuvant therapy with lapatinib was inferior to trastuzumab and had more toxicity, thus it is not used for early stage HER2-positive breast cancer [65].

Take aways: Neoadjuvantly, dual HER2-antibody therapy with trastuzumab and pertuzumab produces the highest pCR and response rates and should be utilized in the neoadjuvant setting in combination with chemotherapy. In the adjuvant setting, taxane and trastuzumab alone is likely sufficient for stage I HER2-positive breast cancers. In those with a complete response to neoadjuvant therapy, trastuzumab alone or trastuzumab with pertuzumab can be given adjuvantly. Pertuzumab offers benefit when given adjuvantly in node-positive breast cancers. For patients who received neoadjuvant therapy and have residual disease, adjuvant T-DM1 should be given. Neratinib offers benefit in some high-risk breast cancers after 1 year of initial chemotherapy-HER2 therapy, particularly node positive, HR-positive breast cancers.

How should HR status influence decision-making?

Over half of HER2-positive breast cancers also are positive for the estrogen and/or the progesterone receptor. Preclinical data show evidence of ER-HER2 pathway crosstalk, with upregulation of the ER pathway as HER2 resistance is acquired [66-68]. In the landmark HER2-positive adjuvant clinical trials, endocrine therapy was initiated after the completion of chemotherapy along with HER2-therapy continuing after its completion. This approach has remained our standard of care. However, there are limitations in data regarding optimal endocrine therapy in HER2-positive patients because the early studies establishing the role of endocrine therapy for ER-positive breast cancer patients were completed prior to standard HER2 testing [69]. More recent studies optimizing endocrine therapy through extension of duration of endocrine therapy or ovarian suppression excluded HER2-positive patients [70].

Take away: In HR-positive HER2-positive breast cancer, endocrine therapy should be initiated after completion of chemotherapy. Choice of endocrine therapy and duration of administration is determined by extrapolation from studies in HR-positive HER2-negative breast cancer.

How should systemic therapy be approached in patients who may not be candidates for chemotherapy?

With the efficacy of HER2 therapy and toxicity of chemotherapy, there remains interest in chemotherapy-free regimens especially in patients with comorbidities. The RESPECT trial was a randomized control trial of trastuzumab and chemotherapy or trastuzumab-alone in patients over 70 years old with early stage HER2-positive breast cancer [71]. Over 5 years, 275 patients were randomized, the majority of whom had stage II breast cancer. At a median follow-up of 3.5 years, the 3-year DFS was 94.8% versus 89.2% for chemotherapy and trastuzumab compared to trastuzumab, respectively.

Patients with cardiac comorbidities should be referred for a cardiology evaluation when possible and have close monitoring of cardiac function during and after therapy. Although the role for beta-blockers, ace-inhibitors, angiotensin receptor blockers, or "goal-directed therapies" as potentially "cardioprotective" agents

has not been established, optimizing cardiac risk factors may be helpful. Additionally, given the data presented above, in some situations shorter durations of HER2-therapy can be considered.

Future directions and conclusions

There are still notable gaps in our knowledge and areas of active research. De-escalation strategies continue to be an area of interest. For these approaches, molecular subtype and tumor heterogeneity has implications for response to therapy and thus may impact identification of appropriate candidates [62,72]. Anticipated further evolution of therapy includes the more frequent utilization of trastuzumab biosimilars and subcutaneous administration of trastuzumab. Despite advances, our therapies still fail to benefit some patients as much as we would like. Strategies for noninvasive monitoring (eg, circulating tumor DNA) as well the potential role for novel therapies (including tucatinib, trastuzumab-deruxtecan, and immunotherapy) are also likely to be areas of further research. Nevertheless, two decades of advances in optimizing therapy for early stage HER2-positive breast cancer has resulted in substantial improvements in outcomes and ongoing research promises to continue to move the needle forward.

Conflicts of interest

Ami Shah: Honorarium – Taiho, Daiichi-Sankyo; Advisory Board – Abbvie Lauren Chiec: none.

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