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REVIEW

# Trastuzumab-induced cardiotoxicity: a review of clinical risk factors, pharmacologic prevention, and cardiotoxicity of other HER2-directed therapies

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## Abstract

**Purpose** Despite great success as a targeted breast cancer therapy, trastuzumab use may be complicated by heart failure and loss of left ventricular contractile function. This review summarizes the risk factors, imaging, and prevention of cardiotoxicity associated with trastuzumab and other HER2-targeted therapies.

**Findings** Cardiovascular disease risk factors, advanced age, and previous anthracycline treatment predispose to trastuzumab-induced cardiotoxicity (TIC), with anthracycline exposure being the most significant risk factor. Cardiac biomarkers such as troponins and pro-BNP and imaging assessments such as echocardiogram before and during trastuzumab therapy may help in early identification of TIC. Initiation of beta-adrenergic antagonists and angiotensin converting enzyme inhibitors may prevent TIC. Cardiotoxicity rates of other HER2-targeted treatments, such as pertuzumab, T-DM1, lapatinib, neratinib, tucatinib, trastuzumab deruxtecan, and margetuximab, appear to be significantly lower as reported in the pivotal trials which led to their approval.

**Conclusions** Risk assessment for TIC should include cardiac imaging assessment and should incorporate prior anthracycline use, the strongest risk factor for TIC. Screening and prediction of cardiotoxicity, referral to a cardio-oncology specialist, and initiation of effective prophylactic therapy may all improve prognosis in patients receiving HER2-directed therapy. Beta blockers and ACE inhibitors appear to mitigate risk of TIC. Anthracycline-free regimens have been proven to be efficacious in early HER2-positive breast cancer and should now be considered the standard of care for early HER2-positive breast cancer. Newer HER2-directed therapies appear to have significantly lower cardiotoxicity compared to trastuzumab, but trials are needed in patients who have experienced TIC and patients with pre-existing cardiac dysfunction.

**Keywords** Cardiotoxicity · Trastuzumab · Herceptin · HER2 · Breast cancer · Chemotherapy · Trastuzumab-induced cardiotoxicity · TIC · Chemotherapy-related cardiac dysfunction · CRCD · Congestive heart failure · Left ventricular ejection fraction · LVEF · Anthracyclines · Taxanes · Echocardiography · Global longitudinal strain · Trastuzumab emtansine · T-DM1 · Kadcyla · Lapatinib · Tucatinib · Neratinib · Pertuzumab · Perjeta · Tucatinib · Trastuzumab deruxtecan · Margetuximab

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## Introduction

The gene encoding epidermal growth factor receptor-2 (HER2/ErbB2) is amplified in approximately 15–20% of breast cancers, conferring poor prognosis and low overall survival [1]. Development of the monoclonal antibody trastuzumab (Herceptin™) to inhibit signaling through HER2 has changed HER2-positive breast cancer from an aggressive disease to one with a relatively favorable outlook [2]. A joint analysis of the major adjuvant trastuzumab trials NCCTG N9831 and NSABP B-31 report a 37% relative improvement in overall survival with the addition of trastuzumab to standard anthracycline-containing chemotherapy, an unprecedented benefit for patients with early-stage HER2-positive breast cancer [3].

The benefits of trastuzumab are unfortunately accompanied by a significant risk of cardiac dysfunction, especially in patients receiving anthracyclines. In the landmark study by Slamon et al., 27% of patients treated with combinations of anthracyclines and trastuzumab developed cardiac dysfunction and 16% developed symptomatic heart failure, compared with 8% and 3%, respectively, of patients receiving an anthracycline without trastuzumab [4]. Modified regimens that avoid concurrent administration of trastuzumab and doxorubicin have reduced but not eliminated this risk. In the above referenced joint analysis of N9831 and B-31, 5% of patients planned to receive sequential trastuzumab after anthracycline were ultimately unable to receive trastuzumab due to anthracycline-related drops in EF [3].

Considerable progress has been made in identification of predisposing factors for cardiotoxicity caused by trastuzumab and other HER2-targeting agents. Methods for prevention using beta-adrenergic antagonists and ACE inhibitors show promise, but uncertainty remains surrounding patient selection and best management strategies for Trastuzumab-Induced Cardiotoxicity (TIC). This review will summarize strategies for preventing and detecting cardiotoxicity as well as the risks of cardiotoxicity associated with newer HER2-directed therapies.

### Assessing the risk of TIC

The cardiotoxicity of trastuzumab differs from that of anthracyclines: it is not dose-dependent, does not occur in all patients, and is usually reversible [5]. Unlike anthracyclines, which are directly cytotoxic [6, 7], trastuzumab reduces cardiomyocyte resistance to other stressors by interfering with survival signals downstream of HER2 [8–10]. Trastuzumab blocks the function of neuregulin, secreted by endothelial cells and required for normal cardiac growth and maintenance. Neuregulin binds to HER2-ErbB4 receptor dimers on the cardiac myocyte plasma membrane, activating downstream effectors critical for protection against oxidative stress-induced cell death [9], including phosphatidylinositol 3-kinase–AKT, mitogen-activated protein kinase and Janus kinase/STAT3 [11, 12]. As a consequence, trastuzumab promotes the damaging effects of oxidative stress, leading to DNA breakage and induction of the mitochondrial apoptotic pathway [13]. The attrition of myocytes over time is likely the most important mechanism leading to heart failure associated with trastuzumab [14].

Risk factors for development of HER2-targeted cardiomyopathy include age, previous anthracycline exposure, coronary artery disease, hypertension, diabetes, smoking, low-normal baseline EF, and obesity (Table 1) [5, 15–26]. Previous anthracycline exposure appears to be the most significant risk factor for TIC. Multiple studies comparing cardiotoxicity of trastuzumab-chemotherapy combinations with and without anthracyclines have shown that LVEF decline is significantly more common in patients receiving anthracyclines (Table 2) [27–33]. Ezaz et al. developed a model for stratifying patients into low, moderate, and high risk for TIC based on the presence or absence of diabetes, age, coronary artery disease, renal failure, atrial fibrillation/flutter, or prior exposure to any type of chemotherapy [20]. In a group of 143 Canadian breast cancer patients referred for pre-chemotherapy evaluation, a low score on this model had a negative predictive value of 94% for permanent cardiotoxicity, but a high score performed poorly, with a positive predictive value of only 0.17 [34]. Using similar clinical cardiac risk factors in a cohort of 90,104 women with early breast cancer, Abdel-Qadir et al. developed a point-based risk score that identified a more than 40-fold increase in ten-year risk for major cardiovascular events in women in the highest decile of the cohort compared to those in the lowest [35]. Despite such stratification, additional factors, including imaging data, may be required to improve the accuracy of future risk models.

### Cardiac imaging and biomarkers as predictors for cardiotoxicity

Cardiotoxicity can be recognized by the development of symptomatic heart failure, or through imaging studies that show deterioration of heart function in temporal relationship to treatment. Left ventricular ejection fraction (LVEF) is the most frequently used measure of cardiac contractile function in clinical practice, and can be determined by cardiac imaging with echocardiography, multiple-gated acquisition (MUGA), or cardiac magnetic resonance imaging (CMR). A frequently used definition of treatment-related cardiotoxicity in clinical trials is an absolute decrease in LVEF of 10% to a value of < 50%, although the American Society of Echocardiography suggest that the lower range of normal LVEF is likely 53% [36–39]. Current standard practice requires

**Table 1** Summary of studies evaluating clinical risk factors for development of trastuzumab-induced cardiomyopathy [5, 15–26]

| Trial | Number of patients | Population studied | Primary risk factor for TIC | Statistical significance of primary risk factor | Other risk factors for TIC |
|---|---|---|---|---|---|
| Previous anthracycline use | | | | | |
| Leung et al. [15] | 116,342 | Elderly patients receiving trastuzumab | Previous anthracycline use | $p < 0.00001$ | |
| Chen et al. [5] | 45,537 | Breast cancer patients receiving adjuvant therapy | Previous anthracycline use | Incidence rate ratio = 1.66 | |
| Jawa et al. [16] | 6,527 | Breast cancer patients receiving trastuzumab | Previous anthracycline use | OR = 2.14 | Older age, hypertension, diabetes |
| Naumann et al. [17] | 388 | Women who received trastuzumab | Older age among those who had received prior anthracycline | $p = 0.001$ | |
| Farolfi et al. [18] | 179 | Breast cancer patients receiving adjuvant trastuzumab | Cumulative dose of Doxorubicin > 240 mg/m$^2$ or Epirubicin > 500 mg/m$^2$ | OR = 3.07 | No other studied risk factors were statistically significant |
| Cardiac risk factors | | | | | |
| Chavez-MacGregor et al. [19] | 9,535 | Breast cancer patients over age 65 receiving chemotherapy | Coronary artery disease | HR 1.82 | Hypertension, age > 80 |
| Ezaz et al. [20] | 1,664 | Elderly women receiving adjuvant trastuzumab | Coronary artery disease | HR 2.16 | Anthracycline use, older age, renal failure, atrial fibrillation, diabetes, hypertension |
| Gunaldi et al. [21] | 111 | HER2 + breast cancer patients who received trastuzumab | Coronary artery disease, obesity | $p < 0.0001$ | Smoking, hypertension, post-menopausal |
| Guenancia et al. [22] | 8,745 | Breast cancer patients who received anthracycline or sequential anthracycline and trastuzumab | Obesity | OR = 1.47 | Obesity was the only factor studied |
| Tang et al. [23] | 160 | Breast cancer patients receiving adjuvant trastuzumab | History of myocardial infarction | $p < 0.001$ | Beta blocker use, mastectomy |
| Baron et al. [24] | 76 | Inner city breast cancer patients receiving trastuzumab | African American race | $p < 0.05$ | No other studied risk factors were statistically significant |
| Serrano et al. [25] | 45 | Breast cancer patients over age 70 receiving trastuzumab | Diabetes | $p = 0.01$ | Cardiac disease |

**Table 1** (continued)

| Trial | Number of patients | Population studied | | Primary risk factor for TIC | Statistical significance of primary risk factor | Other risk factors for TIC |
|---|---|---|---|---|---|---|
| Baseline borderline ejection fraction (EF) | | | | | | |
| Romond et al. [26] | 944 | Patients receiving trastuzumab | | Baseline EF 50–54% | $p < 0.001$ | Age |

*OR* odds ratio, *HR* hazard ratio

measurement of LVEF using one or more methods prior to initiation of anthracyclines or trastuzumab.

MUGA was the original mainstay for cardiac functional assessment, as it has high reproducibility and was readily available. Unlike echocardiography, MUGA cannot evaluate RV function, atrial size, or valvular and pericardial disease and compared with CMR, MUGA is less accurate in measuring LVEF at the critical thresholds of 50% and 55% used in most studies of cardiomyopathy [36, 40]. Echocardiography is presently the cornerstone of initial evaluation and surveillance of patients receiving cardiotoxic therapies because of its availability, reproducibility, cost, and safety [41]. Importantly, LVEF measurements from MUGA scans, echocardiograms and CMRs are not interchangeable, and measurements from different modalities should not be used in serial comparisons [37].

In addition to LVEF, echocardiographic measurement of longitudinal shortening of the heart during contraction, or global longitudinal strain (GLS), can identify early changes in left ventricular contractility before EF declines. Negishi et al. found that declines in GLS at 6 months of trastuzumab therapy predicted impaired LVEF at 12 months [42]. GLS may thus be helpful in the early identification of TIC prior to LVEF decline. In the SUCCOUR trial, Thavendiranathan et al. evaluated whether initiation of cardioprotective therapy (CPT) based on decline in GLS can improve long-term cardiac function compared to waiting for a drop in EF in patients receiving anthracycline. At the one year follow-up, although there was no significant difference in change in EF between the two arms, more patients in the GLS arm were on CPT. Among all patients receiving CPT, those in the GLS arm had a significantly lower reduction in EF [43].

Imaging by CMR is recommended as an alternative to echocardiography once LVEF falls, or when poor image quality prevents accurate measurements [36, 37, 44]. CMR is the gold standard for evaluation of ventricular function and volume, and has higher inter-operator reproducibility than echocardiography. CMR provides data on tissue viability, myocardial edema, fibrosis, and inflammation [44], and can detect subtle, early changes in LV mass, volumes, and function associated with myocardial injury [45]. CMR has been successfully utilized as a predictive tool for anthracycline-induced cardiotoxicity. Smith et al. showed that patients receiving anthracycline developed significant increases in LV mass on day 3, which predicted a drop in LVEF at 1 year [46]. Jordan et al. compared LV mass in patients receiving anthracycline vs those receiving non-anthracycline chemotherapy (mainly trastuzumab-based) and found that on average the anthracycline group lost 5 g in LV mass compared to no change in the non-anthracycline group [47]. One small study of CMR in 10 patients with TIC showed late gadolinium enhancement in the subepicardial lateral wall of the left ventricle which persisted after

**Table 2** Summary of studies evaluating cardiotoxicity in non-anthracycline-based regimens [27–33]

| Trial | Number of patients | Population studied | Comparator arms | Primary outcome | LVEF drop > 10% to ≤ 50% | Rate of heart failure |
|---|---|---|---|---|---|---|
| BCIRG006 Slamon et al. [27] | 3222 | Women with high-risk early-stage HER2-positive breast cancer receiving adjuvant chemotherapy | | 5-year DFS | | |
| | | | AC-T | 75% | 11.2% | 0.7% |
| | | | AC-T + Trastuzumab | 84% | 18.6% | 2.0% |
| | | | TCH | 81% | 9.4% | 0.4% |
| TRAIN-2 Ramshorst et al. [28] | 438 | Patients with untreated stage II–III HER2-positive breast cancer planned for neoadjuvant therapy | | pCR | | |
| | | | FEC-PH -> TCPH | 67% | 29% | 1% |
| | | | TCPH | 68% | 17% | 0 |
| TRYPHAENA Schneeweiss et al. [29] | 225 | Patients with operable locally advanced or inflammatory HER2-positive breast cancer planned to receive neoadjuvant therapy | | pCR | neoadjuvant/adjuvant | |
| | | | FEC-PH -> TPH | 61.6% | 5.6%/5.9% | 0 |
| | | | FEC -> TPH | 57.3% | 5.3%/12.3% | 2.7% |
| | | | TCHP | 66.2% | 3.9%/4.5% | 0 |
| TRIO-US B07 Hurvitz et al. [30] | 128 | Patients with early-stage HER2-positive breast cancer planned for neoadjuvant therapy | | pCR | | |
| | | | H + chemo | 47% | 2.9% | 0 |
| | | | L + chemo | 25% | 5.5% | 0 |
| | | | H + L + chemo | 52% | 1.7% | 0 |
| KRISTINE Hurvitz et al. [31] | 444 | Patients with stage II–III HER2-positive breast cancer planned for neoadjuvant therapy | | pCR | | |
| | | | T-DM1 + P | 44.4% | < 1% | 0 |
| | | | TCPH | 55.7% | 0% | < 1% |
| APT Tolaney et al. [32] | 406 | Patients with localized HER2-positive breast cancer < 3 cm with negative nodes | | 3-year DFS | | |
| | | | Paclitaxel and Trastuzumab | 98.7% | 3.2% | 0.5% |
| ATEMPT Tolaney et al. [33] Abstract only SABCS | 512 | Patients with stage 1 HER2-positive breast cancer planned for adjuvant therapy | | DFS/CRT | Not reported | Not reported |
| | | | T-DM1 | 97.7/25% | | |
| | | | Paclitaxel + Trastuzumab | 93.2/36% | | |

*LVEF* left ventricular ejection fraction; *AC-T* adriamycin, cyclophosphamide, docetaxel, *TCH* docetaxel, carboplatin, trastuzumab; *DFS* disease-free survival; *FEC-PH* 5-fluorouracil, epirubicin, cyclophosphamide, pertuzumab, trastuzumab; *TPH* docetaxel, pertuzumab, trastuzumab; *TCPH* docetaxel, carboplatin, pertuzumab, trastuzumab; *pCR* pathologic complete response; *SABCS* San Antonio Breast Cancer Symposium; *CRT* clinically relevant toxicity; *L* Lapatinib; *P* Pertuzumab; *H* trastuzumab

recovery of EF [48]. Disadvantages of CMR include its high cost and lower availability, as well as patient-related issues including claustrophobia, patient size limitations, and inability to safely accommodate many metal implants [44].

Serum biomarkers including troponins, NT-pro-BNP, and others have been proposed as predictors of future cardiac dysfunction among patients receiving chemotherapy. Table 3 provides a summary of these studies [49–57]. Troponin I (cTnI) may predict LVEF reduction and adverse cardiac events in patients treated with trastuzumab, particularly in those who have previously received anthracyclines [49, 58]. Cardinale et al. showed that elevated cTnI levels (≥ 0.08 ng/mL) identified individuals at risk for developing TIC (HR, 22.9) and for non-recovery (HR, 2.88) [50, 59, 60]. A recent, larger study by Demissei et al. found that elevated high sensitivity (hs)-cTnT levels of > 14 at the end of anthracycline treatment conferred a 2 × risk of subsequent TIC, suggesting that troponins reflect pre-existing or ongoing cardiac damage as a direct precursor of TIC, and thus may be valuable in identifying patients requiring closer scrutiny during

**Table 3** Summary of studies evaluating cardiac biomarkers as predictors for TIC [49–57]

| Trial | Number of patients | Population studied | Biomarker for development of TIC | Statistical significance of biomarker | Other findings or biomarkers studied |
|---|---|---|---|---|---|
| Troponin biomarkers | | | | | |
| Zardavas et al. [49] | 452 | Women from the HERA study: early HER2-positive breast cancer who received neoadjuvant or adjuvant chemotherapy being planned for trastuzumab | Troponin I (baseline)<br>Troponin T (baseline) | $p < 0.001$<br>$p < 0.001$ | Pro-BNP was measured but could not be standardized due to consistent lab normal |
| Cardinale et al. [50] | 251 | Cancer patients during and after trastuzumab therapy | Troponin I | $p < 0.001$ | Elevated Troponin I also predicted lack of EF recovery |
| Sawaya et al. [51] | 43 | Breast cancer patients who had received 3 months of trastuzumab and anthracycline | Troponin I | $p = 0.006$ | Non-significant biomarkers: Pro-BNP |
| Other biomarkers | | | | | |
| Sendur et al. [52] | 164 | Patients who completed trastuzumab treatment at least 6 months earlier | hsCRP<br>Pro-BNP | $p = 0.03$<br>$p = 0.008$ | Non-significant biomarkers: CK-MB, troponin I, troponin T, heart fatty acid binding protein |
| Putt et al. [53] | 78 | Breast cancer patients during and after doxorubicin and trastuzumab therapy | MPO<br>PlGF<br>GDF-15 | $p = 0.02$<br>$p = 0.047$<br>$p = 0.01$ | Non-significant biomarkers: hsCRP, Troponin I, NT-pro-BNP, Gal-3 |
| Not significant biomarkers | | | | | |
| Ponde et al. [54] | 345 | Anthracycline-naïve patients who were treated with trastuzumab, lapatinib, or a combination | None significant | | Non-significant biomarkers: Troponin T, Pro-BNP |
| Morris et al. [55] | 95 | Patients receiving anthracycline followed by trastuzumab and lapatinib | None significant | | Troponin I and CRP |
| Matos et al. [56] | 92 | Breast cancer patients who previously received anthracycline and were currently receiving trastuzumab | None significant | | NT-pro-BNP |
| Fallah-Rad et al. [57] | 42 | HER2-positive breast cancer patients treated with adjuvant trastuzumab | None significant | | Non-significant biomarkers: Troponin T, CRP, Pro-BNP |

*CRP* C-reactive protein, *GDF-15* growth differentiation factor 15, *MPO* myeloperoxidase, *P1GF* placental growth factor, *Gal-3* Galectin 3

**Table 4** Summary of studies evaluating strategies for prevention of TIC [66–71]

| Trial | Number of patients | Population studied | Strategy for prevention of TIC | Statistical significance of preventive strategy | Other findings or preventive strategies studied |
|---|---|---|---|---|---|
| Gujral et al. [66] | 1048 | Patients receiving anthracycline with or without trastuzumab | BB (significant in those who received trastuzumab) | $p=0.02$ | Not significant: ACEi |
| MANTICORE Pituskin et al. [67] | 94 | Patients with HER2-positive early breast cancer receiving trastuzumab | Bisoprolol (BB)<br>Perindopril (ACEi) | $p=0.001$ vs placebo<br>$p=0.03$ vs placebo | This study is also included in the Gujral et al. [66] meta-analysis |
| Guglin et al. [68] | 468 | Patients with early-stage HER2-positive breast cancer receiving adjuvant or neoadjuvant trastuzumab | Carvedilol (BB)<br>Lisinopril (ACEi) | $p=0.009$<br>$p=0.015$ | Findings only significant in the subset of patients who had previously received anthracycline |
| PRADA Gulati et al. [69] | 130 | Early-stage breast cancer planned to receive adjuvant anthracycline with or without trastuzumab | Candesartan (ARB) | $p=0.026$ | Not significant: metoprolol succinate (BB)<br>Only 22% of the patients on study received trastuzumab, but candesartan was favored among the subset |
| Calvillo-Arguelles et al. [70] | 129 | Women with HER2 + breast cancer who had received trastuzumab with or without anthracycline | Statins | $p=0.049$ | |
| Boekhout et al. [71] | 210 | Early-stage HER2-positive breast cancer planned to receive anthracycline followed by trastuzumab | Not significant | | Those receiving candesartan actually experienced more cardiac events |

*BB* beta blockers, *ACEi* ace inhibitors, *ARB* angiotensin II receptor blockers

trastuzumab therapy [61]. Importantly, most research on troponin evaluates trastuzumab in combination with, or after the use of anthracyclines and further study is needed in anthracycline-free regimens. NT-pro-BNP has demonstrated utility in predicting cardiotoxicity following anthracyclines [62–65], but data are less supportive of its predictive power during trastuzumab therapy [51, 53]. In the study by Demissei, pro-BNP levels correlated closely with changes in LVEF across the cohort but did not have significant predictive value for TIC [61].

## Prevention and treatment of trastuzumab-induced cardiotoxicity

Several drug classes have been proposed to prevent cardiac dysfunction caused by breast cancer treatment. (Table 4) [66–71]. In studies specifically looking at trastuzumab cardiotoxicity, the best-studied strategies include concurrent treatment with beta-adrenergic antagonists (beta blockers) and/or angiotensin converting enzyme inhibitors (ACEi). In a meta-analysis of 1,048 patients receiving anthracyclines with or without trastuzumab, Gujral et al. found that the subset of patients receiving both anthracycline and trastuzumab benefitted from prophylactic treatment with beta blockers, with a significantly smaller drop in LVEF ($p=0.02$) and fewer heart failure diagnoses (OR 0.33, $p=0.01$) [66]. Similar protective effects were not seen with ACEi alone. The MANTICORE study, included in the above analysis, studied prophylactic bisoprolol and perindopril in patients receiving trastuzumab, 77% of which were receiving an anthracycline-free regimen. Both of these interventions improved therapy-related change in EF, but they did not have a statistically significant effect on the primary endpoint of LV remodeling.

In a large multi-center randomized, placebo-controlled trial of 468 women with early HER2-positive breast cancer, Guglin et al. compared lisinopril, carvedilol and placebo in the incidence of TIC. There were no significant differences for the entire cohort, but significant differences in LVEF decline emerged in the subgroup who also received anthracyclines ($n=180$). The incidence of cardiotoxicity was 38% in this group vs. 25% in the rest of the cohort ($p=0.002$), and both carvedilol (HR = 0.49, $p=0.009$) and lisinopril (HR = 0.53, $p=0.015$) effectively doubled cardiotoxicity-free survival, indicating that both lisinopril and carvedilol

may be cardioprotective for patients at increased risk of TIC due to prior anthracycline exposure [68].

A retrospective study looked at patients who developed TIC following anthracycline-based chemotherapy and trastuzumab who were treated with ACEi and beta blockers ($n=31$) or observed ($n=6$). LVEF improved in all patients with symptomatic heart failure, regardless of ACEi and beta blocker treatment. Once symptoms and LVEF stabilized, trastuzumab was resumed in 25/38 patients with ACEi and beta blockers. Twenty-two of 25 patients maintained stable LVEF following re-initiation of trastuzumab [72]. A retrospective single-center study of 76 women (63% African American) treated with trastuzumab and sequentially imaged with MUGA identified TIC in 21 subjects. LVEF after trastuzumab discontinuation improved to > 50% in 8 of the 9 patients for whom follow-up data were available. Of 4 patients that were continued on trastuzumab, 3 recovered to > 55% LVEF [24]. These data suggest that once EF improves, trastuzumab may be safely resumed, although continuation of HF medication is advisable. In the SAFE-HEaRt study, 31 patients with HER2 + breast cancer and low baseline EF of 40–49% were prospectively given ACEi and beta blockers prior to therapy with trastuzumab (n = 15), ± pertuzumab (n = 14), or T-DM1. Encouragingly, 90% of the subjects were able to complete a full course of treatment, indicating that these agents may protect against TIC in patients with other pre-existing cardiomyopathies [73]. In the SCHOLAR study, 20 patients receiving trastuzumab who developed an LVEF between 40 and 54% or a ≥ 15% drop from baseline received beta blockers and ACEi and continued trastuzumab. 90% of patients were able to continue on trastuzumab uninterrupted, while the other 10% of patients discontinued trastuzumab due to an LVEF fall to ≤ 35% or other clinical cardiac event [74].

Once TIC has developed, treatment requires a multi-disciplinary approach with early referral to cardio-oncology for monitoring and titration of heart failure therapy. In patients with asymptomatic LVEF decline, HER2-directed therapy should be suspended, and beta blockers and ACEi initiated and up-titrated as blood pressure tolerates. All patients with any degree of TIC should be referred to a cardiologist with experience in the management of heart failure. Some patients may present with acute cardiac decompensation, with hypotension, cardiogenic shock, pulmonary edema and respiratory failure. These patients will typically require hospitalization and further diagnostic studies, and management should be guided by critical care and/or heart failure specialists following the updated 2017 ACC/AHA/HFSA treatment guidelines [75].

## Cardiotoxicity of other HER2-targeted cancer therapies

Another unresolved question is whether any other HER2-directed therapies can be safely administered in patients at risk for TIC. Five trastuzumab biosimilars have been approved, and they demonstrate similar rates of cardiotoxicity to the reference Herceptin. Other approved HER2-targeting breast cancer therapies, including pertuzumab, trastuzumab emtansine, lapatinib, and neratinib, appear to cause less cardiotoxicity than trastuzumab, and may be safer in patients with cardiac risk factors. It is worth noting these clinical trials may be selecting for patients previously exposed to trastuzumab ± anthracycline who did not develop ongoing cardiac toxicity at the time of trial enrollment. Despite this, newly FDA-approved agents tucatinib, trastuzumab deruxtecan, and margetuximab, have continued to yield hopeful results in metastatic HER2 + breast cancer, and other HER2-directed agents are moving into the early breast cancer space. Table 5 displays the rates of LVEF decline in the pivotal trials discussed below for the non-trastuzumab HER2-directed agents, and Fig. 1 shows their mechanisms of action [76–92].

### Antibodies

Pertuzumab is a monoclonal antibody that binds to a different HER2 epitope than trastuzumab and blocks the formation of HER2:HER3 heterodimers. It is approved for use with trastuzumab in the neoadjuvant, adjuvant, and metastatic settings [78]. In the APHiNITY trial, LVEF decline occurred in 0.7% of the trastuzumab/pertuzumab group and 0.3% in the trastuzumab/placebo group [76].The NeoSphere trial compared neoadjuvant taxol/trastuzumab, taxol/pertuzumab/trastuzumab, trastuzumab/pertuzumab, and pertuzumab/docetaxel. Significant LVEF decline occurred in 1, 3, 1, and 1%, respectively [77]. In the CLEOPATRA trial, LVEF decline occurred more frequently in the docetaxel/trastuzumab/placebo group than the taxol/trastuzumab/pertuzumab group (8.3 vs. 4.4%) [78]. Based on these results, pertuzumab adds little additional cardiac risk to trastuzumab, with which it is almost always paired.

Margetuximab is a novel anti-HER2 antibody which binds with increased affinity to CD16A, an Fc receptor which is important for antibody-dependent cell mediated cytotoxicity against tumor cells. In the phase 1 trial, no LVEF declines to < 50% or symptomatic heart failure were reported [90]. In the phase III SOPHIA trial, any grade LVEF declined occurred in 2.3% in the margetuximab arm vs 2.6% in the trastuzumab arm. Margetuximab received FDA approval in December 2020 for use in combination with chemotherapy for metastatic HER2 + breast cancer [91].

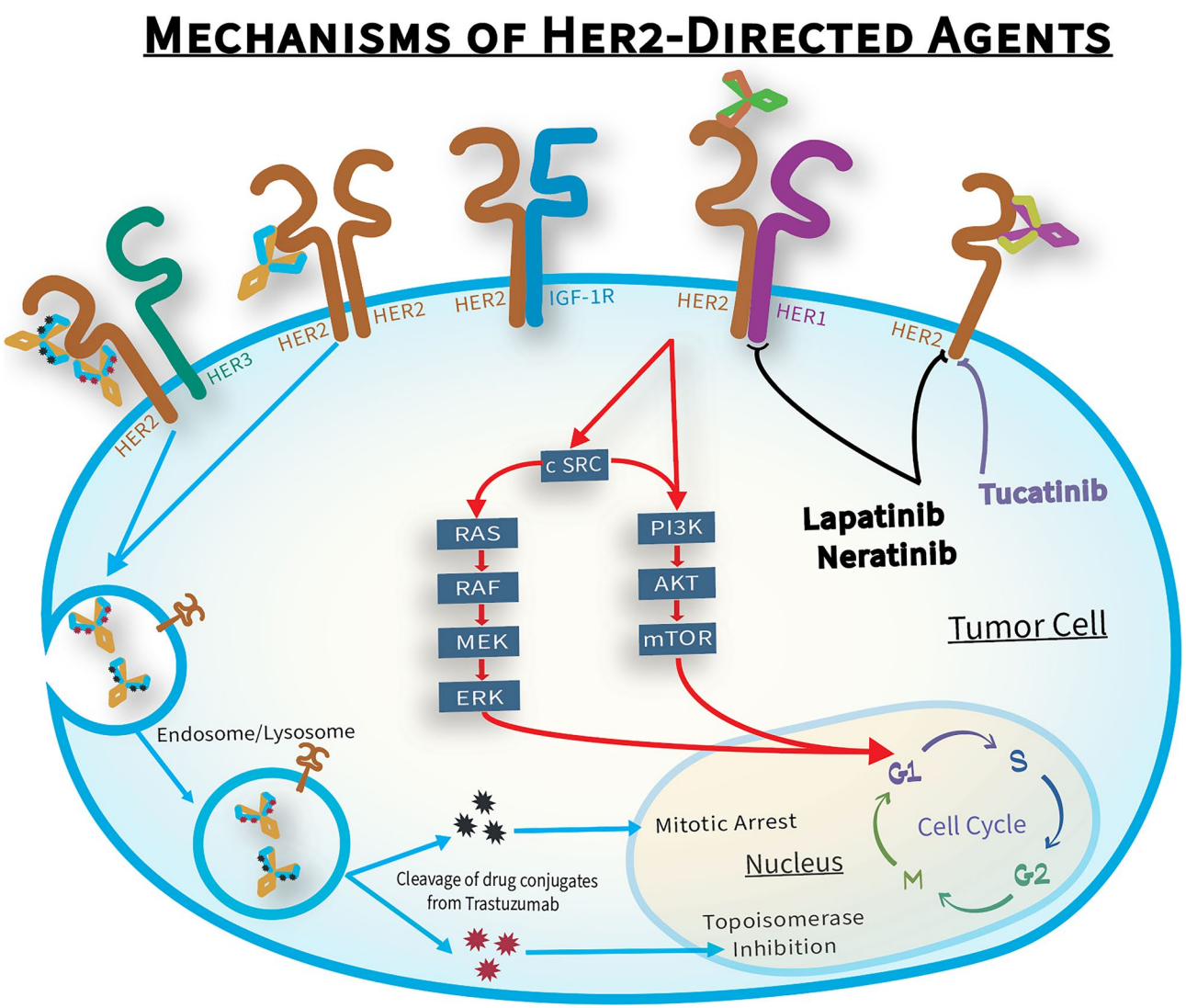
**Table 5** Summary of cardiotoxicity reported in pivotal trials of other HER2-directed agents (76–92)

| Trial | Number of patients | Population studied | Comparator arms | Rate of LVEF decline | Definition of EF drop |
|---|---|---|---|---|---|
| Pertuzumab | | | | | |
| APHINITY Von Minckwitz et al. [76] | 4805 | Patients with node-positive or high-risk node-negative HER2-positive breast cancer comparing 12 months adjuvant PH vs H + placebo | PH | 0.6% | NYHA Class III or IV heart failure and substantial decrease in LVEF |
| | | | Placebo + Trastuzumab | 0.2% | |
| NeoSphere Gianni et al. [77] | 417 | Patients with localized HER2-positive breast cancer comparing 4 different neoadjuvant regimens. All patients received adjuvant FEC and 1 year adjuvant trastuzumab | TH | 0.9% | EF < 50% and at least 10% < baseline |
| | | | TPH | 2.8% | |
| | | | PH | 0.9% | |
| | | | Docetaxel + Pertuzumab | 1.1% | |
| CLEOPATRA Baselga et al. [78] | 808 | Patients with metastatic HER2-positive breast cancer receiving first line TPH vs TH | TPH | 4.6% | EF < 50% and at least 10% < baseline |
| | | | TH + Placebo | 7.4% | |
| Trastuzumab Emtansine (T-DMI) | | | | | |
| TH3RESA Krop et al. [79] | 602 | Patients with metastatic HER2-positive breast cancer after 2 prior lines of therapy including trastuzumab, lapatinib, and taxane. Randomized to T-DM1 vs physician choice | T-DM1 | 1% | EF < 50% and at least 15% < baseline |
| | | | Physician's choice | 1% | |
| EMILIA Verma et al. [80] | 991 | Patients with metastatic HER2-positive breast cancer previously treated with trastuzumab and taxane, randomized to T-DM1 vs lapatinib and capecitabine | T-DM1 | 1.7% | EF < 50% and at least 15% < baseline |
| | | | Lapatinib + Capecitabine | 1.6% | |
| KRISTINE Hurvitz et al. [81] | 444 | Patients with stage II–III HER2-positive breast cancer randomized to neoadjuvant T-DM1 and pertuzumab vs TCPH | T-DM1 + Pertuzumab | 0.4% | Any grade EF decrease |
| | | | TCPH | 0% | |
| MARIANNE Perez et al. [82] | 1095 | Patients with metastatic HER2-positive breast cancer were randomized to first line therapy with trastuzumab + taxane, T-DM1, or T-DM1 + pertuzumab | Trastuzumab + taxane | 4.5% | EF < 50% and at least 15% < baseline |
| | | | T-DM1 | 0.8% | |
| | | | T-DM1 + Pertuzumab | 2.5% | |
| KATHERINE Von Minckwitz et al. [83] | 1486 | Patients with HER2-positive early breast cancer with residual disease after neoadjuvant treatment, randomized to adjuvant T-DM1 vs trastuzumab | T-DM1 | 0.1% | Cardiac events |
| | | | Trastuzumab | 0.6% | |
| Lapatinib | | | | | |
| Perez, et al. [84] | 3689 | Meta-analysis of patients receiving lapatinib, either alone or in combination | Lapatinib | 1.6% | EF < 50% and at least 20% < baseline or symptomatic CHF |
| Geyer et al. [85] | 324 | Patients with metastatic HER2-positive breast cancer who have progressed on anthracycline, taxane, and trastuzumab, randomized to lapatinib capecitabine vs capecitabine alone | Lapatinib + Capecitabine | 2.4% | EF < 50% and at least 20% < baseline or symptomatic CHF |
| | | | Capecitabine | 0.7% | |
| Neratinib | | | | | |
| NEfERT-T Awada et al. [86] | 479 | Patients with metastatic HER2-positive breast cancer randomized to neratinib paclitaxel vs trastuzumab paclitaxel | Neratinib + Paclitaxel | 1.3% | Cardiac events (Grade 3 or higher) |
| | | | Trastuzumab + Paclitaxel | 3.0% | |

**Table 5** (continued)

| Trial | Number of patients | Population studied | Comparator arms | Rate of LVEF decline | Definition of EF drop |
|---|---|---|---|---|---|
| ExteNET<br>Chan et al. [87]<br>2016 | 2840 | Patients with early HER2-positive breast cancer after adjuvant trastuzumab randomized to 1 year of neratinib vs placebo | Neratinib<br>Placebo | 0.1%.<br>0% | Cardiac failure |
| Tucatinib | | | | | |
| Murthy et al. [88] | 60 | Patients with advanced HER2-positive breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1, who received varying doses of tucatinib in combination with trastuzumab and capecitabine | Tucatinib + Trastuzumab + Capecitabine | 0% | |
| HER2CLIMB<br>Murthy et al. [89] | 612 | Patients with heavily pre-treated advanced HER2-positive breast cancer randomized to trastuzumab, capecitabine and tucatinib vs trastuzumab, capecitabine, and placebo | Tucatinib + Trastuzumab + Capecitabine<br>Placebo + Trastuzumab+ Capecitabine | < 1%<br>< 1% | |
| Margetuximab | | | | | |
| Bang et al. [90] | 66 | Patients with HER2-positive solid tumors (breast, gastric, or other carcinomas) with no available standard therapy, who received margetuximab of varying doses and schedules | Margetuximab | 0% | |
| SOPHIA<br>Rugo et al. [91] | 524 | Patients with HER2-positive advanced breast cancer with 1–3 lines of prior therapy, randomized to margetuximab + chemo vs trastuzumab + chemo | Margetuximab + chemo<br>Trastuzumab + chemo | 1.5%<br>2.3% | LV dysfunction leading to dose delay or discontinuation |
| Trastuzumab deruxtecan | | | | | |
| Modi et al. [92] | 184 | Patients with advanced heavily pre-treated HER2-positive breast cancer treated with trastuzumab deruxtecan | Trastuzumab deruxtecan | 1.6% | |

*PH* pertuzumab and trastuzumab, *TH* docetaxel and trastuzumab, *TPH* docetaxel, pertuzumab and trastuzumab, *TCPH* docetaxel, carboplatin, pertuzumab, trastuzumab




| Figure Legend | | |
|---|---|---|
| **Symbol** | **Molecule** | **Binding Domain of HER2** |
| | Trastuzumab | Domain IV (juxtamembrane) |
| | Pertuzumab | Domain II (dimerization) |
| | Trastuzuamb Emtansine (T-DM1) | Domain IV |
| | Emtansine (Cleaved Drug Conjugate) | N/A |
| | Trastuzumab Deruxtecan (DS-2801) | Domain IV |
| | Deruxtecan (Cleaved Drug Conjugate) | N/A |
| | Margetuximab | Domain IV |

**Fig. 1** Mechanism of action of HER2-directed agents

### Antibody–drug conjugates

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate in which trastuzumab is linked to the microtubule toxin DM1, a derivative of maytansine. The trastuzumab moiety allows targeted delivery of the cytotoxic complex to cells expressing the HER2 receptor via receptor-mediated endocytosis [93]. T-DM1 is approved for use as a single agent for metastatic HER2-positive breast cancer after progression on trastuzumab, and in the adjuvant setting when neoadjuvant trastuzumab does not provide a pathologic complete response. In the TH3RESA study, low rates of LVEF decline were observed (< 2%) that did not differ between T-DM1 vs physicians' choice of treatment including trastuzumab, lapatinib, and/or chemotherapy [79]. In the EMILIA trial, the incidence of LVEF decline was low and similar between T-DM1 (1.7%) or lapatinib + capecitabine (1.6%) arms [80, 94]. The phase III MARIANNE trial compared T-DM1 to T-DM1 + pertuzumab and trastuzumab + taxane, and the incidence of LVEF decline was lower in both T-DM1-containing regimens (0.8 and 2.5% respectively) than with trastuzumab (4.5%) [82]. In the KATHERINE trial, adverse cardiac events were very rare overall (0.3%), but occurred less frequently with T-DM1 (1/740) than with trastuzumab (4/720) [83].

Trastuzumab deruxtecan (DS-8201) is an antibody–drug conjugate with a topoisomerase I inhibitor as a cytotoxic payload. The phase II DESTINY-Breast01 study enrolled 184 patients with metastatic HER2-positive breast cancer who had previously received T-DM1. Overall response rate was 60.9%, and 6% achieved complete remission. Disease control rate was a stunning 97.3%. While cardiotoxicity of grade 3 or higher occurred in only 0.5% of patients, interstitial lung disease (ILD) was the main safety signal of concern leading to grade 5 events (death) in 4 patients (2.2%) [92]. Further investigation into screening, risk stratification, and management is required to improve ILD-related outcomes.

### Tyrosine kinase inhibitors

Lapatinib is a small molecule inhibitor of the HER1/ErbB1 and HER2/ErbB2 receptor tyrosine kinases and is approved in the metastatic setting. A 2008 meta-analysis of 3,689 patients in 44 ongoing clinical trials, including a large number of patients receiving lapatinib monotherapy, identified LVEF declines in 1.6% of lapatinib-treated patients vs. 0.7% of those receiving other therapies [84]. The majority of these were asymptomatic and most recovered whether or not lapatinib was discontinued. Sub-analysis of cardiac outcomes in the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial showed LVEF decline in 7.9% of patients in the trastuzumab/lapatinib arm, vs. 9.3% in the trastuzumab alone arm, which was not statistically significant (OR = 0.85 $p = 0.139$). This study also identified specific risk factors contributing to cardiotoxicity: pretreatment LVEF < 55% vs. > 64% (OR = 3.1; $p = 0.002$), diabetes (OR = 1.85; $p = 0.002$), obesity (BMI > 30 kg/m$^2$, OR = 2.21; $p < 0.001$), and prior anthracycline therapy (OR = 1.68, $p = 0.648$), while age ≥ 65 years ($p = 0.064$), hypercholesterolemia ($p = 0.629$), hypertension ($p = 0.402$), and prior chest radiotherapy did not confer additional risk. Although > 80% of patients recovered during a median of 3.5 months after treatment cessation, LVEF fell again in a significant percentage of patients after re-challenge (25.9% for trastuzumab alone, 37.5% for lapatinib + trastuzumab) [95]. The risk of cardiotoxicity with lapatinib thus appears to be substantially less than that of trastuzumab, and as with trastuzumab, is largely reversible and frequently asymptomatic.

Neratinib is an irreversible small molecule inhibitor of HER1, HER2 and HER4 tyrosine kinases, approved for the extended adjuvant treatment of women with early-stage and metastatic HER2 + breast cancer. Neratinib appears to have lower cardiotoxicity than trastuzumab, and diarrhea is the bigger concern. In the NEfERT-T study, Grade 3 or higher cardiotoxicity occurred in 1.3% of patients in the neratinib/paclitaxel arm versus 3.0% of patients on trastuzumab/paclitaxel [86]. In the ExteNET trial, only 1% of patients in either arm experienced LVEF decline, and no long-term cardiovascular toxicity was seen [87, 96].

Tucatinib is a third oral tyrosine kinase inhibitor, distinguished by high selectivity for HER2/ErbB2. This agent received FDA approval in 2020 in combination with capecitabine and trastuzumab for treatment of metastatic disease. The phase III HER2CLIMB trial randomized women with heavily pre-treated metastatic HER2-positive breast cancer to tucatinib or placebo in combination with capecitabine and trastuzumab. Tucatinib improved OS by 34% ($p = 0.005$), with particular benefits in patients with brain metastasis. Cardiotoxicity was reported in < 1% of study participants in either arm [89].

## Summary

Targeting HER2 has proven to be a highly successful and lifesaving strategy for patients with HER2-overexpressing breast cancer. However, the cardiotoxicity associated with trastuzumab poses a long-term threat to overall survival and quality of life in these patients. Strategies for preventing, monitoring, and detecting TIC in high-risk patients are needed. Although pre-existing risk factors can identify many of these patients, a significant number have no known risk factors. Following the TRAIN-2 trial, which showed similar pCR rates regardless of anthracycline use, the National Comprehensive Cancer Network (NCCN) adjusted its guidelines, removing anthracyclines from the preferred regimens

for localized HER2-positive breast cancer [28]. Because current and prior anthracycline use remains the most significant risk factor for TIC, we consider anthracycline-free regimens for localized HER2-positive breast cancer to be the new standard of care [4].

Based on data from the recent SAFE-HEaRt study, large observational studies, and consensus recommendations from the American Society of Clinical Oncology, it is reasonable to consider pre-treatment of patients at high risk with beta-adrenergic antagonists and/or ACE inhibitors prior to initiating trastuzumab [73, 97, 98]. Early referral to a cardio-oncologist is advisable in patients who develop asymptomatic LVEF decline and essential in those with symptomatic heart failure. New ESMO guidance recommends continuing trastuzumab and initiating ACEi/ARB/beta blocker if the patient develops an asymptomatic LVEF drop > 10% from baseline or to an LVEF 40–50% [99]. If trastuzumab therapy must be stopped, LVEF must be reexamined in 3–6 weeks and trastuzumab re-challenge may occur if EF exceeds 50%. Other HER2-directed therapies appear to have much less cardiotoxicity than trastuzumab and may be safely used in patients at higher risk of cardiac complications. Further study is needed with these agents in patients with TIC and in those with underlying cardiac dysfunction as HER2-directed therapy is vital to outcomes of patients with HER2-positive breast cancer.

## Declarations

**Conflict of interest** Marc Lippman as a possible COI as a director of Seattle Genetics, the manufacturer of Tucatinib.

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