Twenty years of anti-HER2 therapy-associated cardiotoxicity

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ABSTRACT

Over the past 20 years, the prognosis of HER2-positive breast cancer has been transformed by the development of anti-HER2 targeted therapies. In early clinical trials of trastuzumab (ie, the first anti-HER2 agent to be developed) cardiotoxicity became a major concern. In the first published phase 3 trial of trastuzumab, 27% of patients receiving anthracyclines and trastuzumab experienced cardiac events and 16% suffered from severe congestive heart failure. In subsequent trials conducted in advanced and early settings, the incidence of cardiac events was reduced through changes in chemotherapy regimens, more strict patient selection and close cardiac assessment. However, cardiotoxicity remains a significant problem in clinical practice that is likely to increase as new agents are approved and exposure times increase through improved patient survival. Though numerous trials have led to improved understanding of many aspects of anti-HER2 therapy-related cardiotoxicity, its underlying physiopathology mechanisms are not well understood. The purpose of this article is to provide an in-depth review on anti-HER2 therapy-related cardiotoxicity, including data on both trastuzumab and the recently developed anti-HER2 targeted agents.

INTRODUCTION

Breast cancer is the most common type of cancer among women as well as the first cause of cancer-specific mortality for women worldwide.1 It is, however, not a single disease but rather several distinct diseases that arise from the same organ.2 Among the currently identified subtypes, HER2-positive (HER2+) disease has been the focus of particularly intense and productive research in the past 20 years. Representing up to 20% of the total cases, HER2+ disease was traditionally considered a subtype with poor prognosis, a situation that has changed by the development of anti-HER2 targeted therapies (table 1).3 4 HER2 is part of the ErbB family of transmembrane growth factor receptor tyrosine kinases (that also includes HER3 and epidermal growth factor receptor (EGFR) among others). These proteins can be activated independently from ligands via homodimerisation or heterodimerisation (with HER3) or through neuregulin-1 (NRG-1), a panHER ligand that plays a significant role in multiple physiological and pathological processes.5 HER2+ tumour cells possess a highly proliferative phenotype, with increased capacity to invade, disseminate and stimulate angiogenesis.6 The success of trastuzumab in countering this aggressive behaviour has been, however, not total, with some patients either recurring after adjuvant trastuzumab in the early setting, or proving primary or secondary resistant to trastuzumab in the metastatic setting. This resistance can originate from multiple causes, such as alterations to the conformation of the extracellular domain, or autoactivation of intracellular downstream signalling pathways.7 8 To circumvent this, a new generation of anti-HER2 agents has been developed, each with unique mechanisms of action. Among these compounds several are already in clinical use or in phase 3 studies, while other agents still in earlier stages of development.9

Besides its usefulness during the process of neoplastic progression, just as any of the receptors and pathways that tumour cells exploit, HER2 plays physiological roles that are reflected in the toxicity profile of anti-HER2 agents. In mutated mice without HER2 expression, no embryos reached full development and all had cardiac malformations (such as lack of trabeculae in the myocardium) among other important lethal organic dysfunctions.10 In another murine model, genetically engineered mice lacking HER2 expression exclusively in the heart developed features of dilated cardiomyopathy, with left ventricular chamber dilation, wall thinning and reduced contractility.11 Additionally, these mice were more susceptible to anthracycline cardiotoxicity. In a similar study, mice had increased apoptosis of ventricular cells, and cardiac dysfunction was reversed through suppression of apoptosis.12 In models of cardiac lesions (ischaemia, viral and dilated cardiomyopathies),

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cardiac performance was improved and survival extended by the infusion of recombinant NRG-1 receptor-active peptide (rhNRG-1). Taken together, these data point towards a fundamental role for HER2 signalling in heart development during embryogenesis and in cardiomyocyte survival especially in situations of stress, through the promotion of survival pathways that inhibit apoptosis and maintain cardiac function. Thus, cardiotoxicity is the main concern during anti-HER2 therapy, as clinical trials with trastuzumab have pointed out.3

In this review, we will explore the state-of-the-art on anti-HER2 therapy-related cardiotoxicity, starting with trastuzumab and exploring the recently developed anti-HER2 targeted agents.

**MONOCLONAL ANTIBODIES**

**Trastuzumab**

Trastuzumab is a monoclonal antibody that binds to the extracellular domain of HER2. Its mechanisms of action include activation of antibody-dependent cytotoxicity, inhibition of signal transduction, inhibition of neoangiogenesis and inhibition of repair of DNA damage caused by the treatment.14 Trastuzumab is approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for HER2+ patients with breast cancer in the adjuvant, neoadjuvant and metastatic settings (table 1).

Cardiotoxicity is the only significant toxicity that trastuzumab treatment entails. From a clinical stand point, it manifests most often as an asymptomatic drop in left ventricular ejection fraction (LVEF) or, infrequently, as congestive heart failure (CHF).15 Remarkably, although a plethora of studies have revealed much about its clinical course, risk factors and incidence in different settings, much remains unknown regarding its pathophysiology.16 Available research suggests that trastuzumab affects the heart in multiple ways:

A. Blocking NRG-1-mediated activation of HER2 reduces fundamental intracellular mechanisms that allow cardiomyocytes to adequately carry out their highly specialised function (repetitive contraction). Affected mechanisms include the ability to maintain the structure and function of sarcomeres and scavenging of proapoptotic oxidative subproducts of ATP production in a cell that has high and constant ATP demands;17 18

B. Trastuzumab binding leads to the downregulation of the antiapoptotic protein BCL-XL and to the upregulation of the proapoptotic protein BCL-XS.19 The ratio between antiapoptotic and proapoptotic stimuli is also a key regulator of mitochondrial function;

C. Oxidative stress leads to the upregulation of angiotensin II. Angiotensin II is an inhibitor of NRG-1 that prevents its binding to other ErbB family receptors to compensate for HER2 blockade, leading to even more inhibition of the pathway, and thus to more oxidative stress forming a cytotoxic vicious cycle. It also activates NADPH oxidase leading to mitochondrial dysfunction and cell death. Furthermore, angiotensin II also induces apoptosis through the AT1 receptor.20 21

Twenty years of clinical experience, based on a set of pivotal phase 2 and 3 trials with trastuzumab have allowed the construction of a picture of the different aspects of trastuzumab-related cardiotoxicity. Table 2 summarises the incidence of trastuzumab-associated cardiotoxicity from the most relevant trials in the metastatic, neoadjuvant and adjuvant settings.1 22–37

### Metastatic setting

In the phase 3 trial that led to the approval of trastuzumab in the metastatic setting, patients with metastatic breast cancer received either a combination of doxorubicin and cyclophosphamide (AC) or paclitaxel monotherapy both with or without trastuzumab.4 Thirty-nine (27.2%) of 143 patients in the AC plus trastuzumab arm versus 11 (8.1%) of 135 in the AC alone arm and 12 (13.2%) of 91 in the paclitaxel plus trastuzumab arm versus 1 (1.1%) of 95 in the paclitaxel alone arm experienced CHF. Moreover, a proportionally higher number of patients who received concomitant anthracycline and trastuzumab had New York Heart Association (NYHA) class III and IV CHF when compared with paclitaxel and trastuzumab (16% vs 2%, respectively). These findings confirmed what has already been shown in smaller phase 1 and 2 trials that trastuzumab causes asymptomatic drops in LVEF or symptomatic and potentially deadly (one patient died) CHF.15 The large disparity between chemotherapy regimens suggests that the concomitant association of anthracycline and trastuzumab is potentially cardiotoxic. From a physiological point of view, their mechanisms of cardiotoxicity, though different, overlap significantly in the formation over oxidative

| Table 1 | Agents and approval status |
|---------|---------------------------|
| Agent   | Class                     | Status of approval |
| Trastuzumab | Monoclonal antibody      | Early and advanced disease |
| Pertuzumab    | Monoclonal antibody      | Early (neoadjuvant) and advanced disease |
| Trastuzumab-emtansine (T-DM1)| Drug–antibody conjugate | Advanced disease |
| Lapatinib    | Tyrosine kinase inhibitor | Advanced disease |
| Afatinib     | Tyrosine kinase inhibitor | Not approved |
| Neratinib    | Tyrosine kinase inhibitor | Not approved |
| Author (year) | Setting        | Study design | Treatment arms                          | Number of patients | Any LVEF drop Number (%) | Any CHF Number (%) |
|--------------|----------------|--------------|-----------------------------------------|--------------------|--------------------------|-------------------|
| Slamon et al (2001) | MBC first line | Phase 3      | AC+trastuzumab                           | 143                | Not reported             | 39 (27.2)         |
|               |                |              | AC                                       | 135                | 11 (8.1)                 |                   |
|               |                |              | Paclitaxel+trastuzumab                   | 91                 | 12 (13.2)                |                   |
|               |                |              | Paclitaxel                               | 95                 | 1 (1.1)                  |                   |
| Marty et al (2005) | MBC first line | Phase 2      | Docetaxel+trastuzumab                    | 86                 | 16 (18)                  | 2                 |
|               |                |              | Docetaxel                                | 76                 | 7 (8)                    | 0                 |
| Gasparini et al (2007) | MBC first line | Phase 2 | Paclitaxel+trastuzumab                   | 28                 | Not reported             | 0                 |
|               |                |              | Paclitaxel                               | 40                 | Not reported             | 0                 |
| Von Minckwitz et al (2011, 2009) | MBC beyond first line | Phase 3 | Paclitaxel                              | 78                 | 0                        | 0                 |
|               |                |              | Capicabine                               | 78                 | 1 (1.28)                 | 1 (1.28)          |
| Kaufman et al (2009) | MBC first line | Phase 3 | Anastrozole+trastuzumab                 | 103                | 1 (0.97)                 | 1 (0.97)          |
|               |                |              | Anastrozole                              | 104                | 0                        | 0                 |
| Buzdar et al (2007) | Neoadjuvant   | Phase 2      | FEC+paclitaxel+trastuzumab               | 45                 | Not reported             | 1                 |
|               |                |              | FEC+paclitaxel                           | 19                 | 1                        | 0                 |
| Gianni et al (2010) | Neoadjuvant   | Phase 3      | A+paclitaxel+CMF+trastuzumab             | 117                | 30 (27)                  | 2 (1.7)           |
|               |                |              | A+paclitaxel+CMF                         | 217                | 33 (15)                  | 0                 |
| Untch et al (2010) | Neoadjuvant   | Phase 3      | Chemotherapy+trastuzumab                 | 445                | 4 (0.89)                 | 1 (0.22)          |
|               |                |              | Chemotherapy                             | 1050               | 0                        | 2 (0.19)          |
| Buzdar et al (2013) | Neoadjuvant   | Phase 3      | FEC+paclitaxel+trastuzumab               | 142                | 35 (24.6)                | 1 (0.7)           |
|               |                |              | FEC+paclitaxel+trastuzumab               | 138                | 21 (15.2)                | 0                 |
| de Azambuja et al (2014) | Adjuvant | Phase 3 | Chemotherapy+trastuzumab 1 year         | 1682               | 120 (7.2)                | 19 (0.8)          |
|               |                |              | Chemotherapy+trastuzumab 2 years         | 1673               | 69 (4.1)                 | 14 (0.8)          |
|               |                |              | Chemotherapy                             | 1744               | 15 (0.9)                 | 0                 |
| Romond et al (2012) | Adjuvant      | Phase 3      | AC+paclitaxel                            | 743                | Not reported             | 9 (1.2)           |
|               |                |              | AC+paclitaxel+trastuzumab               | 947                | 114 (12)                 | 36 (3.8)          |
| Advani et al (2016) | Adjuvant      | Phase 3      | AC+paclitaxel                            | 664                | 64 (9.6)                 | 6 (0.9)           |
|               |                |              | AC+paclitaxel+trastuzumab               | 710                | 119 (16.7)               | 19 (2.6)          |
|               |                |              | AC+paclitaxel+trastuzumab               | 570                | 136 (23.8)               | 20 (3.5)          |
| Slamon et al (2011, 2015) | Adjuvant | Phase 3 | AC+docetaxel                           | 1073               | 114 (11.2)               | 8 (0.8)           |
|               |                |              | AC+docetaxel+trastuzumab               | 1074               | 206 (19.1)               | 21 (2.0)          |
|               |                |              | Docetaxel+carboplatin+trastuzumab      | 1075               | 97 (9.4)                 | 4 (0.4)           |
| Spielman et al (2009) | Adjuvant      | Phase 3      | FEC/ED                                 | 268                | 7 (2.6)                  | 1 (0.37)          |
|               |                |              | EC/ED+trastuzumab                       | 260                | 29 (11.1)                | 4 (1.5)           |
| Joensu et al (2006) | Adjuvant      | Phase 3      | Docetaxel+vinorelbine+FEC               | 116                | 0                        | 2 (1.72)          |
|               |                |              | Docetaxel+vinorelbine+trastuzumab+FEC   | 115                | 0                        | 1 (0.86)          |
| Pivot et al (2015) | Adjuvant      | Phase 3      | Chemotherapy+trastuzumab 6 months       | 1690               | 45 (2.7)                 | 9 (0.53)          |
|               |                |              | Chemotherapy+trastuzumab 1 year         | 1690               | 70 (4.1)                 | 11 (0.65)         |
| Tolane et al (2015) | Adjuvant      | Phase 2      | Paclitaxel+trastuzumab                  | 406                | 13 (3.2)                 | 2 (0.5)           |

A, doxorubicin; AC, doxorubicin, cyclophosphamide; CHF, cardiac heart failure; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; EC, epirubicin, cyclophosphamide; ED, epirubicin, docetaxel; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; HERA, hereceptin adjuvant; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer.
stress, making increased risk a reasonable hypothesis. Recent models of anthracycline toxicity also suggest that HER2 signalling is essential to protect cardiomyocytes from it. In the pivotal trial, patients who suffered from cardiac dysfunction mostly were treated with standard cardiac agents used for CHF, with 75% of patients experiencing cardiac recovery. In this study, older age was the only significant risk factor associated with cardiotoxicity. Other smaller trials also suggested that previous cardiovascular disease and hyperlipidaemia are risk factors for the development of cardiotoxicity.

Subsequent trials in the metastatic setting, with either chemotherapy or hormonotherapy showed significantly less cardiac events as shown in table 2. This reduction is explained by a different design of the trials and eligible population: trastuzumab was not given concomitantly with anthracyclines (though patients could in all cases have received previous adjuvant anthracyclines during adjuvant treatment), patients with an LVEF of <50% were excluded, and cardiovascular follow-up during study treatment included clinical examinations and serial cardiac assessment, mostly echocardiography. It is important to note that the initial results of trastuzumab impacted on the development of all anti-HER2 agents, the selected population in clinical trials does not always represent patients with HER2+ metastatic breast cancer treated in daily clinical practice. As shown in large cohort studies conducted in an unselected population, the risk of cardiotoxicity with the use of trastuzumab seems to be higher. Thus, it is likely that in daily clinical practice, the reported cardiotoxicity is higher than in trials as reported in some cohorts of patients.

In the meta-analysis of randomised trials versus cohort studies conducted by Mantonno et al, cohort studies consistently reported higher cardiotoxicity rates than randomised trials in the metastatic setting: 4.4% vs 2.8%, respectively.

**Neoadjuvant setting**

The neoadjuvant strategy has been explored extensively in HER2+ disease. The academic debate has been centred from an early point on the issue of associating anthracyclines and trastuzumab concomitantly versus sequentially and the need to balance potential benefits (ie, higher pathological complete response rate) with potential risks (ie, higher cardiotoxcity). In the seminal trial by Buzdar and colleagues, 45 women received fluorouracil, epirubicin, cyclophosphamide (FEC) and trastuzumab followed by paclitaxel and trastuzumab. A total of 19 women in the control group received only FEC followed by paclitaxel. The results of the trial suggested for the first time that concurrent administration of anthracycline and trastuzumab was safe (only one patient developed CHF) and yielded increased benefits (response rates were also significantly higher in the combination arm), putting into question the conclusions taken from the initial experience with metastatic disease.

Subsequently, the larger NeOAdjuvant Herceptin (NOAH) trial further investigated the safety of combining anthracyclines with trastuzumab concomitantly. Of the 117 patients who received combined therapy, 27% suffered LVEF drops (grades 2–3) and 1.7% had symptomatic CHF versus 15% and 0%, respectively, in the non-trastuzumab group (215 patients). Similarly, in the geparQUATTRO trial with 1495 patients, only 4 had LVEF drops and 2 CHF in the three groups that received combined therapy. Although a combined analysis of these three neoadjuvant trials showed that the trastuzumab regimens where more cardiotoxic than the non-trastuzumab (significant increase in the rate of cardiotoxicity (OR 1.95, 95% CI 1.16 to 3.29, p=0.36)), none of these trials had a design capable of resolving the critical question of the cardiac safety of concurrent treatment with anthracycline and trastuzumab.

The ACOSOG Z1401 was designed to answer this question with a total of 280 patients randomised between two trastuzumab containing regimens, one with concomitant anthracyline and one with trastuzumab after anthracyline. The dose of epirubicin in the FEC regimen was 75 mg/m². The combination arm had a non-significantly higher number of LVEF drops and CHF (24.6% and 0.7%, respectively) as compared with the sequential group (15.2% and 0%, respectively). The response rate was the same in the two treatment arms. Therefore, given the data presented above, it is generally recommended not to combine trastuzumab with anthracyclines in the curative setting, as well as in the metastatic setting, due to increased risk of cardiac events.

**Adjuvant setting**

The large adjuvant randomised phase 3 trials, with higher number of patients and predefined close cardiac follow-up, provided the most detailed and extensive information on trastuzumab-related cardiotoxicity (table 2). Specific cardiotoxicity analyses with long-term follow-up have been published for most of these trials.

In the herceptin adjuvant (HERA) trial, 5102 patients were randomised to observation or trastuzumab for 1 or 2 years. Cardiac assessment included LVEF assessment by either echocardiogram or multiple gated acquisition scintigraphy (MUGA) in predefined time points. After a median follow-up of 8 years, the study confirmed that the incidence of trastuzumab-associated toxicity remained low, that most cases of cardiac events occurred during trastuzumab use and that the majority were reversible after the interruption of trastuzumab. The incidence of LVEF decline was 0.9%, 4.1% and 7.2% in the observation, 1-year and 2-year trastuzumab arms, respectively. The observed incidence of CHF remained very low (0% in the observation arm and 0.8% in the 1-year and 2-year trastuzumab arms). It is important to note that the very low risk of cardiotoxicity is likely connected to patient selection and study design. The 2-year arm suffered more LVEF drops than the 1-year arm, suggesting that time of exposure plays a role in the risk of cardiotoxicity.
developing this side effect. Since there was no added clinical benefit for the 2-year arm, 1 year of trastuzumab remains the standard of care in the adjuvant setting. In the metastatic setting, however, considering the longer exposure times that are likely to issue from recently introduced regimens exposure times to trastuzumab may go beyond 2 years.49–51 Registries are currently in progress to better elucidate the safety of prolonged exposure to anti-HER2 targeted agents in the clinical practice setting.52 Other adjuvant trials showed a similar low number of cardiac events (table 2); however, selection criteria, cardiac follow-up and definitions of cardiac events varied across the studies, making direct comparisons difficult. Recently published long-term follow-up data (median follow-up 9.2 years) of the B31 trial showed that only 6 (0.9%) and 19 (2.6%) patients in the control arm and experimental arm, respectively, experienced CHF. An analysis for risk factors was conducted; 60 years or older, baseline LVEF between 50% and 54.9% (a group that was excluded from HERA by design) or 55% and 64.9%, use of antihypertensive medications proved to be significantly associated with increased risk of cardiotoxicity. Interestingly, the use of radiation therapy and BMI were not associated with significant increased risk in this trial, nor in the N9831 study.52 It is also important to note that the nature of cardiac vigilance during the study treatment varied widely between studies. For example, in the N9831 trial, LVEF assessment was maintained for 21 months at most, except in cases where there was a suspicion of cardiac toxicity, while in the HERA study cardiac assessment was mandated for 10 years.50 LVEF drops occurred in 15.4% of patients in the control arm (AC+paclitaxel), 31.1% in the sequential (AC+paclitaxel followed by trastuzumab) arm and 27.1% in the concomitant arm (AC+paclitaxel/trastuzumab; table 2). CHF grades 2–4 were respectively 0.3%, 2.8% and 3.3%.53 Long-term data of the same trial revealed a stably low 6-year incidence of cardiac events. In this trial, as in the HERA and B31 trials, most events happened during treatment and were reversed quickly when treatment was interrupted and cardiac intervention established.

Recently, the BCIRG 006 trial presented the 10-year results. This is the only trial testing a non-anthracycline regimen (TCH). Cardiac events were lower in the TCH arm compared with AC-TH (0.4% vs 2%, respectively). A recently published meta-analysis of all the adjuvant trials, with a total of 18111 patients concluded that adjuvant therapy with trastuzumab significantly increases the risk of grades 3 and 4 CHF (RR 3.04 (95% CI 1.12 to 7.85; p<0.00001)).54

**Pertuzumab**

Pertuzumab is a monoclonal antibody that acts by binding to domain II of HER2 receptor with consequent inhibition of HER2–HER3 heterodimerisation.55 It has been recently approved for clinical use (table 1) in combination with trastuzumab and chemotherapy as neoadjuvant therapy and first-line therapy in patients with HER2+ metastatic breast cancer.56 One early phase 2 study of the combination suggested increased cardiotoxicity, leading to early interruption of pertuzumab.57 Improved patient selection (exclusion of high-risk groups such as patient who had a history of trastuzumab-related cardiotoxicity) and cardiac assessment, led to a reduction in events during subsequent studies.58–61 In a large pooled analysis, Lenihan and colleagues evaluated the pertuzumab cardiac safety data. Overall, out of 598 patients included in the analysis, 35 (5.9%) developed asymptomatic left ventricular systolic dysfunction (LVSD), defined as a decrease from baseline in LVEF of ≥10 points to a value of <50% at any postbaseline LVEF assessment) and 4 (0.7%) patients developed symptomatic CHF.62

The main evidence supporting the cardiac safety of the trastuzumab–pertuzumab combination comes from the CLEOPATRA phase 3 trial in metastatic patients (table 3). The incidence of adverse cardiac events of any grade was 16.4% in the placebo arm and 14.5% in the pertuzumab arm.60 LVSD of any grade was the most frequently reported cardiac event (8.3% in the placebo arm vs 4.4% in the pertuzumab arm).63 Few cases of CHF were reported, 7 (1.8%) in the placebo arm and 4 (1.0%) in the pertuzumab arm.63 Prior exposure to anthracyclines and prior radiotherapy were identified as potentially important risk factors irrespective of treatment arm.63 Interestingly prior exposure to trastuzumab was not significantly associated with the development of LVSD,65 but only 10% of the study population was previously exposed in the early setting to anti-HER2 targeted therapy. Overall, the cardiotoxicity profile of the combination was favourable: adverse cardiac events were largely reversible and clinically manageable.65 Two studies of pertuzumab-based therapy in the neoadjuvant setting (ie, NeoSphere and TRYPHAENA) showed a similar low incidence of cardiac events.64,65 Hence, the available data coming from the neoadjuvant and metastatic settings do not suggest dual anti-HER2 blockade with trastuzumab and pertuzumab increases the incidence of cardiac events. This was also confirmed by a meta-analysis combining the cardiotoxicity data from the CLEOPATRA and NeoSphere studies; as compared with trastuzumab alone, the addition of pertuzumab was not associated with an increased risk of LVEF drops (OR 0.66, p=0.19).66 No published data are available so far on the use of pertuzumab in the adjuvant setting; the results of the APHINITY trial (NCT01358877) will give further insight into the cardiac safety of combining two anti-HER2 monoclonal antibodies.

**ANTIBODY DRUG CONJUGATE**

**Trastuzumab-emtansine**

Trastuzumab-emtansine (T-DM1) is an antibody drug conjugate composed of a monoclonal antibody (ie, trastuzumab) connected to a potent cytotoxic antimicrotubule
This formulation has been recently approved for the treatment of patients with HER2+ metastatic breast cancer previously exposed to taxane and trastuzumab (table 1).

All the published phase 2 studies available showed a favourable cardiotoxicity profile with the use of T-DM1. Most of these studies were conducted in patients with metastatic breast cancer beyond first-line therapy: hence, the majority of them had prior exposure to trastuzumab. Nevertheless, the risk of developing a cardiac event with the use of this compound is low, as also confirmed by the available phase 3 studies (table 3).

In the EMILIA trial, T-DM1 was compared with lapatinib plus capecitabine in 991 patients with HER2+ metastatic breast cancer. Only three patients in each arm had a decrease in LVEF from baseline to <40%. A total of eight patients (1.7%) in the T-DM1 arm and 7 (1.6%) in the lapatinib plus capecitabine arm had a LVEF reduction ≥15 points below the baseline value and to <50%. Only one patient in the T-DM1 arm developed grade 3 LVSD. The TH3RESA trial in a heavily pretreated population showed similar results.

In the early setting, two studies with the use of neoadjuvant T-DM1-based therapy have reported results, but no cardiotoxicity data were reported. In the adjuvant setting, the single-arm phase 2 TDM4874g (BO22857) trial investigated the cardiac safety and overall feasibility of T-DM1 for ∼1 year after prior exposure to anthracycline-based chemotherapy in the (neo)adjuvant setting. Patients received 4 cycles of (neo)adjuvant AC or 3–4 cycles of FEC followed by 4 cycles of T-DM1; then, patients could have received an optional 3–4 cycles of docetaxel with or without trastuzumab, and finally all patients continued T-DM1 for a planned 17

**Table 3** Cardiotoxicity in the main phase 3 clinical trials with the use of anti-HER2 targeted agents other than trastuzumab

| Author | Setting | Treatment arms | Number of patients | LVEF drop (≥10 points and <50%) N (%) | CHF N (%) |
|--------|---------|----------------|-------------------|--------------------------------------|-----------|
| Swain et al | MBC, first-line | Docetaxel+trastuzumab + placebo | 396 | 27 (6.6) | 13 (3.3) |
| Verma et al | MBC, first-line and beyond first-line | Lapatinib+capecitabine | 496 | 7 (1.6) | 0 (0.0) |
| Krop et al | MBC, beyond first-line | Treatment of physician’s choice | 404 | 6 (1.0) | 0 (0.0) |
| Geyer et al | MBC, beyond first-line | Lapatinib+capecitabine | 163 | 4 (2.5) | 0 (0.0) |
| Cameron et al | MBC, beyond first-line | Lapatinib+paclitaxel | 161 | 4 (2.5) | 0 (0.0) |
| da Azambuja et al | Neoadjuvant setting | Trastuzumab+paclitaxel | 154 | 2 (1.3) | 1 (0.6) |
| Piccart-Gebhart et al | Adjuvant setting | CT+trastuzumab | 2097 | 97 (4.6) | 53 (2.5) |
| | | CT+lapatinib | 2100 | 63 (3.0) | 37 (1.8) |
| | | CT+trastuzumab → lapatinib | 2091 | 57 (2.7) | 37 (1.8) |
| Harbeck et al | MBC, first-line and beyond first-line | Afatinib+vinorelbine | 332 | 1 (0.3) | 0 (0.0) |
| Awada et al | MBC, first-line | Trastuzumab+vinorelbine | 168 | 3 (1.8) | 2 (1.2) |
| | | Neratinib+paclitaxel | 242 | Not reported | Not reported |
| | | Trastuzumab+paclitaxel | 237 | Not reported | Not reported |
| Chan et al | Adjuvant setting | Neratinib | 1420 | 4 (0.3) | 1 (0.1) |
| | | Placebo | 1420 | 2 (0.1) | 0 (0.0) |

*Defined as CHF, decreased LVEF, LVSD and peripheral oedema.

CHF, cardiac heart failure; CT, chemotherapy; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MBC, metastatic breast cancer; T-DM1, trastuzumab-emtansine.

agent (ie, emtansine or DM1). This formulation has been recently approved for the treatment of patients with HER2+ metastatic breast cancer previously exposed to taxane and trastuzumab (table 1).

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cycles of HER2-directed therapy. A total of 153 patients were randomised: no symptomatic CHF were reported and mean LVEF was stable throughout T-DM1 treatment. A total of four patients (2.6%) experienced a LVEF decline ≥10 points below the baseline value and to <50%, and one of these women discontinued T-DM1 with an LVEF of 45%. Two of four LVEF declines occurred during treatment with optional docetaxel plus trastuzumab. Ongoing studies in this setting (eg, the KATHERINE (NCT01772472), the KAITLIN (NCT01966471) and the ATEMPT (NCT01853748) trials) are awaited to better define the safety profile of long-term exposure to T-DM1.

TIROSINE KINASE INHIBITORS

Lapatinib

Lapatinib is a FDA and EMA approved dual tyrosine kinase inhibitor (TKI) of EGFR and HER2 available for patients with advanced disease (table 1). Lapatinib activates the AMP-kinase pathway which increases ATP reserves and induces a metabolic stress response in human cardiomyocytes that may protect against TNF-α-induced cell death. Hence, preclinical evidence suggested that lapatinib may ultimately protect the heart against the cardiotoxicity induced by anti-HER2 targeted agents. Table 3 show the most relevant phase 3 studies for lapatinib.

In the registration phase 3 study, 324 patients with HER2+ metastatic breast cancer progressing after anthracycline, taxane and trastuzumab were randomly allocated to receive lapatinib combined with capecitabine or capecitabine alone. In the study, lapatinib showed a favourable cardiotoxicity profile. Overall, 11 patients developed 12 events. A total of 11 patients experienced 12 events of LVEF drop; 4 patients in each arm, developed grade ≥3 LVSD or ≥20 points absolute decrease in LVEF from the baseline value, but all these episodes were reported as asymptomatic. The patients with LVEF drop were previously exposed to cardiotoxic agents (anthracyclines and trastuzumab) and/or had other cardiac risk factors (ie, hypertension, left chest radiation and cardiopulmonary diseases).

Following the results of this study, several other phase 3 randomised trials evaluated the efficacy and safety of lapatinib as single-agent or combined with chemotherapy, endocrine therapy or trastuzumab in the treatment of patients with HER2+ metastatic breast cancer. Overall, these studies confirmed the low risk of cardiotoxicity with lapatinib; however, the definition of cardiac events used in these studies was not homogeneous and thus a clear comparison with other results becomes more difficult.

A large combined analysis conducted by Perez et al investigated the cardiotoxicity profile of lapatinib in 3689 patients treated with the TKI as monotherapy (54%) or in combination (41% with chemotherapy or endocrine therapy, and 5% with trastuzumab). This large analysis confirmed the low incidence of cardiac events (1.6%) with a high rate of demonstrated reversibility of LVEF (88%) with the use of lapatinib. It is, however, important to note that only a small part of the patient population (14.9%) had previously received anthracyclines.

In the neoadjuvant and adjuvant settings, all phase 3 trials confirmed the safety of the combined treatment of lapatinib–trastuzumab and of lapatinib alone. In the NeoALTTO study there were three arms: trastuzumab alone, lapatinib alone and the combination of trastuzumab and lapatinib were compared in the neoadjuvant setting; a low incidence of primary cardiac events was observed in all treatment arms (<1%) although there were more primary and secondary cardiac events in the combined arm (7, 5%) than in either the lapatinib arm (2, 1%) or the trastuzumab arm (2, 1%). No significant difference for primary or secondary cardiac events was observed between the three treatment arms.

Afatinib and neratinib

Neratinib and afatinib are novel next-generation TKIs targeting EGFR, HER2 and HER4. They are not yet approved for use in breast cancer (table 1). In the metastatic setting, several phase 2 trials evaluated the activity of neratinib and afatinib either as monotherapy or in combination with chemotherapy (neratinib in combination with paclitaxel or capecitabine, afatinib in combination with vinorelbine) or endocrine therapy (afatinib in combination with letrozole). Overall, the cardiotoxicity profile of these compounds showed to be favourable as demonstrated in the phase 3 studies (NEERI-T and LUX-Breast 1) in the metastatic and early (ExteNET) settings (table 3). The only phase 3 trial exploring the use of neratinib in the adjuvant setting reported a low rate of cardiac events (table 3).

ELDERLY POPULATIONS

Elderly patients (more than 70 years old) benefit from adjuvant treatment, although to a lesser extent than...
younger patients due to issues of comorbidity, function-
ality and life expectancy.97 However, it is clear that wel-
selected patients can safely receive and benefit from adjuvant therapy.98 99 Data for use of trastuzumab in the
elderly populations are limited, since most studies
placed age limitations for inclusion.100 The available
data from phase 3 trials suggested higher risk of cardio-
toxicity (both in B31 and N9831) in patients above
60 years of age.31 32 101 Although there are few trials spe-
cifically studying the use of trastuzumab in the elderly
populations, observational studies suggest high treat-
ment completion rates.102 103 In the APT phase 2 study
of weekly paclitaxel and trastuzumab, 10.1% of patients
were older than 70. The study showed no signifi-
cance of weekly paclitaxel and trastuzumab, 10.1% of patients
were TnI-negative (35% vs100%, HR 2.88, 95% CI 1.78
to 4.65; p<0.001). Thus, the results of this study suggest
that TnI predicts which patients will not recover. It is,
however, significant to note that 7 of the 36 patients with
elevated TnI had elevated level already at baseline, sug-
gest that possibly they already had otherwise
undetectable cardiac injuries (from anthracyclines or
other causes). Furthermore, these results are not corro-
bated by other smaller studies (77). A recently pub-
lished study where 214 women were receiving adjuvant
EC followed by docetaxel with or without trastuzumab
(depending on HER2 status) showed no correlation
between trastuzumab and elevated TnI levels (4.2% in
trastuzumab group and 5% in trastuzumab-free group).108

TnT, CRP and BNP have less evidence in favour of
their usefulness as biomarkers. In one study, 54 women
with early-stage HER2+ breast cancer, elevated CRP pre-
dicted decreased LVEF, but no association was found
between LVEF and BNP or TnI.109 Another study testing
eight biomarkers in 78 patients receiving adjuvant trastu-
 zumab, found no positive correlation between CRP and
BNP and the risk of cardiotoxicity.110 An exploratory
cardiac substudy within the phase 2 study of first-line
weekly paclitaxel in combination with trastuzumab and
pertuzumab,61 investigated cardiac biomarkers (TnI and
BNP) and speckle-tracking echocardiography (to measure
global longitudinal strain) as adjuncts to LVEF
monitoring for the early detection of treatment-related
 cardiotoxicity.111 No changes in global longitudinal
strain were observed during the study. TnI was detect-
able in 3 (4.3%) patients and BNP in 2 (3.0%) but they
were not associated with LVEF decline.111 Looking spe-
cifically at TnT, a small study with only 19 patients sug-
gests that TnT increase predicts LVEF decrease at
15 months.112 Another, larger study (42 patients),
however, found no correlation.113

Another possible strategy in risk stratification is the
use of variations in single nucleotide polymorphisms
(SNPs). Evidence has associated SNPs with enhanced tox-
icity or efficacy in cancer treatments. Small studies suggest
that SNPs in the HER2 gene, namely Pro1170Ala and
Il655Val, can predict the occurrence of trastuzumab-
associated cardiotoxicity.114 115 However, this deserves
further confirmation before being used in clinical practice.
Currently, there is not enough evidence to recom-
mand routine use of any biomarker, including TnI in
daily practice.116

BIOMARKERS
The search and clinical testing of biomarkers for cardio-
toxicity has been a central area for research in
cardio-oncology. An ideal biomarker could help stratify
patients between different risks, thus allowing for more
personalised follow-up regimens during treatment, as
well as early interruption before functional alteration
LVEF is established.106 Several different potential bio-
markers have been studied, including troponins I and T
(TnI and TnT, both markers of myocardial injury),
B-natriuretic peptide (BNP a marker of wall stress), and
C reactive protein (CRP; a marker of inflammation).

Multiple studies dealt with the role of TnI in predict-
ing trastuzumab cardiotoxicity, with discordant results.
The largest study conducted so far investigated the role
of TnI in 251 women receiving trastuzumab therapy. TnI
levels were measured before and after each dose of tras-
tuzumab.107 A total of 42 (17%) patients suffered
cardiotoxicity (LVEF drop or CHF) and the cardiac
events were positively correlated to TnI elevation.
Approximately 60% of these patients recovered, but a
significantly lower number of those who were
TnI-positive recovered as compared with women who
were TnI-negative (35% vs100%, HR 2.88, 95% CI 1.78
to 4.65; p<0.001). Thus, the results of this study suggest

FUNCTIONAL IMAGING
Functional imaging has a crucial role in identifying
patients at risk of developing adverse cardiac events
when treated with anti-HER2 agents and those experi-
cencing cardiac vents while on treatment. The serial meas-
urement of LVEF is the mainstay of cardiac surveillance
in patients under treatment with anti-HER2 agents.

Echocardiography is the most well-established and
widely used technique in the monitoring of cardiac
diseases while on treatment. Major advantages of this tech-
nique include widely availability, no use of radiation, no
side effects and the relative low cost.\textsuperscript{117} Echocardiography allows volumetric measures, ejection fraction evaluation and assessment of diastolic heart function. Recent data suggest that newer echocardiography-derived measures of myocardial mechanics (ie, strain indices and ventricular–arterial coupling) can provide additional insights into cardiac function during cancer treatments and may serve as a sensitive marker of early myocardial dysfunction.\textsuperscript{118}

MUGA is more accurate than echocardiography in determining ejection fraction and has an important role in the surveillance of cardiotoxicity associated with cancer treatments.\textsuperscript{119} Nevertheless, MUGA requires the injection of a radiotracer, which is very expensive and is not available in all cancer centers.\textsuperscript{117}

Cardiac MR (CMR) is an extremely accurate technique in determining cardiac volumes and ejection fraction with a potential role in identifying small regions of scarring and inflammation.\textsuperscript{117} Recently, CMRI with myocardial strain showed to be a potential useful mean of detecting trastuzumab-related cardiotoxicity.\textsuperscript{120} However, the high cost and lack of availability are likely to limit the clinical use of this technique.\textsuperscript{119}

**CARDIOPROTECTIVE STRATEGIES**

A number of pharmacological agents are currently in use to treat CHF with high-quality evidence of improvements in outcomes (including β-blockers and ACE inhibitors).\textsuperscript{121 122} As we have seen these standard CHF treatment agents have been used in patients experiencing cardiac events due to trastuzumab-associated cardiotoxicity, and most patients experience cardiac recovery with these treatments. This has led to interest in investigating such agents as cardioprotective strategies during anthracycline and/or trastuzumab treatments. In the case of anthracycline-associated cardiotoxicity, few small studies suggest that this strategy may be useful.\textsuperscript{123 124} This has led to the design of randomised trials exploring this pharmacological strategy, including two recently reported trials—MANTICORE and PRADA.

MANTICORE is a randomised trial of perindopril (ACE inhibitor) in comparison to bisoprolol (β-blocker) and placebo in patients who are to start adjuvant trastuzumab. The planning accrual was 153 patients, but this trial was interrupted early (99 patients) due to the evident superiority of one of the strategies. In this trial, bisoprolol significantly prevented reduction in LVEF and trastuzumab treatment interruptions when compared with perindopril or placebo (p value of <0.001). No significant change was detected in left ventricular remodelling (a possible early marker of trastuzumab cardiotoxicity).\textsuperscript{125}

In the PRADA study candesartan (an angiotensin receptor blocker) and metoprolol were compared in combination or alone against placebo in 150 early breast cancer treated patients with adjuvant anthracyclines and trastuzumab. Study treatment was started before chemotherapy with FEC and only 22.2% of patients received trastuzumab. The overall decline of LVEF in the placebo group was 2.6% (95% CI 1.5% to 3.8%) and 0.8% (95% CI 20.4% to 1.9%) in the candesartan group (p=0.026). Combination or metoprolol alone did not show significant benefit. This result suggests that candesartan may reduce the incidence of LVEF drops.\textsuperscript{126}

Though the results of MANTICORE and PRADA are interesting, it is very important to bear in mind that both studies are small in size and exclude patients with cardiac comorbidities, and therefore their results are not at the moment a solid basis for clinical decision-making and should be further explored in larger studies.

**CONCLUSIONS**

Cardiotoxicity remains a clinically significant toxicity of anti-HER2 therapies. Novel agents seem to have a reduced potential for cardiotoxicity. However, the findings from clinical trials should be considered in the context of the patient selection criteria: the eligible population in these studies (ie, younger age, higher LVEF at baseline and less cardiovascular comorbidities) do not always fit with average patients in clinical practice. Further analysis of data is also made more difficult by the myriad of different criteria used to define cardiac events in each study, as well as the different follow-up plans during and after study treatments. Therefore, a common definition on cardiac events should be applied in future clinical trials.

In practice, longer periods of combined treatment, more lines of therapies and longer survival is likely to increase the relevance of cardiotoxicity in the context of metastatic disease. The data available to be applied in clinical practice are almost exclusively derived from trastuzumab trials, and can provide some guidance on some risk factors that can help in deciding the chemotherapy choice and cardiac assessment during treatment. Importantly, at the first suspicion of cardiac toxicity, patients should have a cardiac assessment because of its high proportion of reversibility with anti-HER2 interruption and proper cardiac intervention. Unfortunately, at this moment, there is no validated biomarker or any other means of selecting patients who need less exhaustive cardiac follow-up or less cardiotoxic chemotherapy regimens, with the exception of clinical cardiac risks (eg, hypertension, obesity, etc).

Guidelines and position papers by the European Society for Medical Oncology (ESMO), the European Society of Cardiology (ESC) and the American Society of Clinical Oncology (ASCO) address the issue of trastuzumab-associated cardiotoxicity.\textsuperscript{127–129} These guidelines highlight the importance of patient selection, treatment of potential risk factors for increased cardiotoxicity and of adequate cardiac assessment during treatment. It is important to note, however, that no studies showed that such methods may change cardiac outcomes.\textsuperscript{130} The recently published ASCO guidelines on treatment of HER2+ early disease suggests the use of trastuzumab, carboplatin and docetaxel in patients considered to be at
high risk for cardiotoxicity as a reasonable approach. As more data from new studies with pertuzumab and T-DM1 become available, further insights into this phenomenon will probably be available.

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Cardiotoxicity associated with trastuzumab (herceptin) therapy in the treatment of metastatic breast cancer. *Breathe* 2004;13:73–83.

40. Mantarro S, Rossi M, Bonifazi M, et al. Risk of severe cardiotoxicity following treatment with trastuzumab: a meta-analysis of randomized and cohort studies of 29,000 women with breast cancer. *Intern Emerg Med* 2016;11:123–40.

41. Rossi M, Caroli G, Bonifazi M, et al. Trastuzumab for HER2+ metastatic breast cancer in clinical practice: cardioxicity and overall survival. *Eur J Cancer* 2015;52:41–9.

42. Zardavas D, Piccart M. Neoadjuvant therapy for breast cancer. *Ann Rev Med* 2015;66:31–48.

43. Pegram M, Hsu S, Lewis G, et al. Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers. *Oncogene* 1999;18:2241–51.

44. Bozovic-Spasojevic I, Azim HA, Paesmans M, et al. Neoadjuvant anthracycline and trastuzumab for breast cancer: is concurrent treatment safe? *Lancet Oncol* 2011;12:239–11.

45. Piccart-Gebhart MJ, Procter M, Llombart-Cussac A, et al. Pertuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659–72.

46. Swain SM, Baselga J, Kim S-B, et al. Pertuzumab plus docetaxel in HER2-positive metastatic breast cancer: results from the randomized phase III trial. *J Clin Oncol* 2015;33:1136–42.

47. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:2733–43.

48. Cameron D, Casey M, Oliva C, et al. Lapatinib plus capecitabine in women with HER2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. *Oncologist* 2010;15:924–34.

49. de Azambuja E, Holmen AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol* 2014;15:1137–46.

50. Piccart-Gebhart M, Holmes E, Baselga J, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive early-stage breast cancer. *J Clin Oncol* 2015;33:1136–42.

51. Awada A, Colomer R, Inoue K, et al. Neratinib plus paclitaxel versus trastuzumab plus paclitaxel in previously untreated metastatic ERBB2-positive breast cancer: the NERIERT-T randomized clinical trial. *JAMA Oncol* 2016;2:1063–6.

52. Krop IE, Lutrbova P, Miller KD, et al. Phase I study of switch therapy with trastuzumab-DM1 in patients with HER2-positive advanced breast cancer after prior HER2-directed therapy. *J Clin Oncol* 2011;29:398–405.

53. Bunnis HA, Rugo HS, Vukelja SJ, et al. Phase II study of the antibody drug conjugate trastuzumab-DX1 in the management of women with breast cancer. *Future Oncol* 2015;11:923–31.

54. Portera CC, Walshe JM, Rosing DR, et al. Cardiac toxicity and efficacy of trastuzumab combined with pertuzumab in patients with [corrected] human epidermal growth factor receptor 2-positive metastatic breast cancer. *Clin Cancer Res* 2008;14:2710–16.

55. Cortés J, Fumoleau P, Bianchi G, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2012;30:1594–600.

56. Gianni L, Liedtke C, Bianchi G, et al. Open-label, phase II, multicenter, randomized study of the efficacy and safety of two dose levels of pertuzumab, a human epidermal growth factor receptor 2 dimerization inhibitor, in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 2010;28:1131–7.

57. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. *J Clin Oncol* 2010;28:1138–44.

58. Jung C, Iyengar N, Datko F, et al. Phase II study of pacitaxel given once per week along with pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 2015;33:442–7.

59. Lenihan D, Suter T, Brummer M, et al. Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab. *Ann Oncol* 2012;23:791–800.

60. Swain SM, Ewer MS, Cortés J, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. *Oncologist* 2013;18:257–64.

61. Gianni L, Pienkowski T, Im Y-H, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012;13:35–32.

62. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2012;24:2278–84.

63. Portera CC, Walshe JM, Barton C. Cardiotoxicity associated with trastuzumab (herceptin) and docetaxel in HER2-positive metastatic breast cancer. *Ann Gen Med* 2005;5:372–74.

64. Valachis A, Ntouma A, Polyzos NP, et al. Cardiac toxicity in breast cancer patients treated with dual HER2 blockade. *Int J Cancer* 2013;133:2245–52.

65. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012;367:1783–91.

66. Bozovic-Spasojevic I, Azim HA, Paesmans M, et al. Anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive advanced breast cancer. *Ann Oncol* 2015;26:880–07.

67. Ewertz M, Dirix L, Kocsis J, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer patients treated with dual HER2 blockade. *Eur J Cancer Oxf Engl* 2015;20:880–8.
T-D1M in patients with previously treated human epidermal growth factor receptor 2–positive metastatic breast cancer. *Clin Pharmacol Drug Dev* 2013;2:11–24.

81. Miller KD, Diéras V, Miller KD, Diéras V, et al. Phase IIa trial of trastuzumab emtansine with or without lapatinib for HER2-positive advanced breast cancer: a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:689–99.

82. Krop IE, Kim S-B, González-Martín A, et al. Trastuzumab emtansine versus treatment of physician’s choice for pretreated HER2-positive advanced breast cancer: the EGF65081 study. *J Clin Oncol* 2014;32:1437–44.

83. Harbeck N, Gluz O, Christgen M, et al. Final analysis of WSG-ADAPT HER2+R+ phase II trial: efficacy, safety, and predictive markers for 12-weeks of neoadjuvant TDM1 with or without endocrine therapy in trastuzumab-endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer. San Antonio Breast Cancer Symposium 2015;Abstract: S5–03.

84. Martin KD, Fumoleau P, Dewar JA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol* 2013;31:422–32.

85. Miles D, Baselga J, Amadori D, et al. Treatment of older patients with HER2-positive metastatic breast cancer with pertuzumab, trastuzumab, and docetaxel: subgroup analyses from a randomized, double-blind, placebo-controlled phase III trial (CLEOPATRA). *Breast Cancer Res Treat* 2013;142:89–99.

86. Spector NL, Yarden Y, Smith B, et al. Activation of AMP-activated kinase by human EGF receptor 2/EGF receptor tyrosine kinase inhibitor protects cardiac cells. *Proc Natl Acad Sci USA* 2007;104:10666–71.

87. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:2733–43.

88. Johnston S, Pippen J, Pivot X, et al. Lapatinib combined with letrozole versus letrozole plus placebo as first-line therapy for postmenopausal hormone-receptor-positive metastatic breast cancer. *J Clin Oncol* 2009;27:5358–46.

89. Di Leo A, Gomez HL, Aziz Z, et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. *J Clin Oncol* 2008;26:5644–52.

90. Blackwell KL, Burstein HJ, Stormiolio AM, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol* 2010;28:1124–30.

91. Guan Z, Xu B, DeSilvio ML, et al. Randomized trial of lapatinib versus placebo added to paclitaxel in the treatment of human epidermal growth factor receptor 2-overexpressing metastatic breast cancer. *Clin Cancer Res* 2010;16:1234–9.

92. Burstein HJ, Cirrincione CT, Barry WT, et al. Endocrine therapy with or without inhibition of epidermal growth factor receptor and human epidermal growth factor receptor 2: a randomized, double-blind, placebo-controlled phase III trial of fulvestrant with or without lapatinib for postmenopausal women with HR+/HER2+ receptor-positive advanced breast cancer-CALGB 40302 (Alliance). *J Clin Oncol* 2014;32:3959–66.

93. Perez EA, Koehler M, Byrne J, et al. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc* 2008;83:879–86.

94. Untch M, Lobit S, Bischoff J, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GepaQuintin, GBG 44): a randomised phase 3 trial. *Lancet Oncol* 2012;13:135–44.

95. Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013;14:1183–92.

96. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALLTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet Lond Engl* 2013;379:633–40.

97. Pondé N, Dai Lago L, Azim HA. Adjuvant chemotherapy in elderly patients with breast cancer: key challenges. *Expert Rev Anticancer Ther* 2016;16:661–71.

98. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014;32:2595–603.

99. Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012;13:e148–60.

100. Hurria A, Mohile SG, Dale W. Research priorities in geriatric oncology: addressing the needs of an aging population. *J Natl Comp Canc Netw* 2012;10:286–8.

101. Albalami J, Ciruelos EM, Luch A, et al. Trastuzumab in small tumours and in elderly women. *Eur J Cancer* 2014;40:41–7.

102. Freedman RA, Vaz-Luis I, Barry WT, et al. Patterns of chemotherapy, toxicity, and short-term outcomes for older women receiving adjuvant trastuzumab-based therapy. *Breast Cancer Res Treat* 2014;145:491–501.

103. Vaz-Luis I, Keating NL, Lin NJ, et al. Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. *J Clin Oncol* 2014;32:927–34.

104. Chavez-MacGregor M, Zhang N, Buchholz TA, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol* 2013;31:422–32.

105. Christenson ES, James T, Agrawal V, et al. Use of biomarkers for the assessment of chemotherapy-induced cardiac toxicity. *Clin Biochem* 2015;48:223–35.

106. Cardinale O, Carrabba N, Cilia R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *J Clin Oncol* 2010;28:3910–16.

107. Mokuyasu S, Suzuki Y, Kawahara E, et al. High-sensitivity troponin I detection for 2 types of drug-induced cardiotoxicity in patients with breast cancer: *Breast Caner Res Treat* 2012;129:563–9.

108. Oniloo AA, Engel JM, Stankowski RV, et al. High-sensitivity C-reactive protein (hs-CRP) as a biomarker for trastuzumab-induced cardiotoxicity in HER2-positive early-stage breast cancer: a pilot study. *Breast Cancer Res Treat* 2012;134:291–9.

109. Ky B, Putt M, Sawaya H, et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. *J Am Coll Cardiol* 2012;60:2115–21.

110. Yang AF, Manrique C, Pun S, et al. Cardiac safety of paclitaxel plus trastuzumab and pertuzumab in patients with HER2-positive metastatic breast cancer. *Oncologist* 2016;21:418–24.

111. Katsurada K, Ichida M, Sakuragi M, et al. Activation of AMP-activated kinase by human EGF receptor 2/EGF receptor tyrosine kinase inhibitor protects cardiac cells. *Proc Natl Acad Sci USA* 2007;104:10666–71.

112. Onitilo AA, Engel JM, Stankowski RV, et al. High-sensitivity troponin I as a marker to predict cardiotoxicity in breast cancer patients with adjuvant trastuzumab therapy. *Cardiovasc Drugs Ther* 2014;28:63–70.

113. Fellé C, Massard C, Cohen A, et al. Trastuzumab-induced cardiotoxicity: is it time for troponin for all patients? *Am J Clin Oncol* 2012;35:183–4.

114. Akes F, Zardavas D, Pinto AC, et al. Cardiotoxicity of systemic agents used in breast cancer. *Breast Edif Scot* 2014;23:317–28.

115. Narayan HK, French B, Khan AM, et al. Noninvasive measures of ventricular-arterial coupling and circumferential strain predict cancer therapeutics-related cardiac dysfunction. *JACC Cardiovasc Imaging* 2015;8:261–71.

116. Cardinale O, Carrabba N, Cilia R, et al. Targeted therapies in breast cancer: are heart and vessels also being targeted? *Breast Cancer Res Treat* 2012;14:209.

117. Nakano S, Takahashi M, Kimura F, et al. Cardiac magnetic resonance imaging-based strain study for evaluation of cardiotoxicity in breast cancer patients treated with trastuzumab: a pilot study to evaluate the feasibility of the method. *Cardiol J* 2016;23:270–80.

118. Lee VC, Rhew DC, Dylan M, et al. Meta-analysis: angiotensin receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Intern Med* 2004;141:693–704.

119. Schocken DD, Benjamin EJ, Fonarow GC, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical
Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation* 2008;117:2544–65.

123. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol* 2006;48:2258–62.

124. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation* 2006;114:2474–81.

125. Pituskin E, Mackey JR, Koshman S, et al. Prophylactic beta blockade preserves left ventricular ejection fraction in HER2-overexpressing breast cancer patients receiving trastuzumab: Primary results of the MANTICORE randomized controlled trial. SABCS 2015.

126. Gulati G, Heck SL, Ree AH, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Eur Heart J* 2016;37:1671–80.

127. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol* 2012;23:vii155–66.

128. Eschenhagen T, Force T, Ewer MS, et al. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2011;13:1–10.

129. Denduluri N, Somerfield MR, Eisen A, et al. Selection of optimal adjuvant chemotherapy regimens for early breast cancer and adjuvant targeted therapy for human epidermal growth factor receptor 2-positive breast cancers: an American society of clinical oncology guideline adaptation of the cancer care Ontario clinical practice guideline. *J Clin Oncol* 2016;34:2416–27.

130. Dang CT, Yu AF, Jones LW, et al. Cardiac surveillance guidelines for trastuzumab-containing therapy in early-stage breast cancer: getting to the heart of the matter. *J Clin Oncol* 2016;34:1030–3.