## Title
Cardiovascular Safety Reporting in Contemporary Breast Cancer Clinical Trials



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ORIGINAL RESEARCH

# Cardiovascular Safety Reporting in Contemporary Breast Cancer Clinical Trials

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**BACKGROUND:** Several cancer therapies have been associated with cardiovascular harm in early-phase clinical trials. However, some cardiovascular harms do not manifest until later-phase trials. To limit interdisease variability, we focused on breast cancer. Thus, we assessed the reporting of cardiovascular safety monitoring and outcomes in phase 2 and 3 contemporary breast cancer clinical trials.

**METHODS AND RESULTS:** We searched Embase and Medline records for phase 2 and 3 breast cancer pharmacotherapy trials. We examined exclusion criterion as a result of cardiovascular conditions, adverse cardiovascular event reporting, and cardiovascular safety assessment through cardiovascular imaging, ECG, troponin, or natriuretic peptides. Fisher's exact test was utilized to compare reporting. Fifty clinical trials were included in our study. Patients were excluded because of cardiovascular conditions in 42 (84%) trials. Heart failure was a frequent exclusion criterion (n=31; 62% trials). Adverse cardiovascular events were reported in 43 (86%) trials. Cardiovascular safety assessments were not reported in 23 (46%) trials, whereas natriuretic peptide and troponin assessments were not reported in any trial. Cardiovascular safety assessments were more frequently reported in industry-funded trials (69.2% versus 0.0%; $P<0.001$), and in trials administering targeted/immunotherapy agents compared with only hormonal/conventional chemotherapy (78.6% versus 22.7%, $P<0.001$).

**CONCLUSIONS:** Our findings demonstrate significant under-representation of patients with cardiovascular conditions or prevalent cardiovascular disease in contemporary later-phase breast cancer trials. Additionally, cardiovascular safety is not routinely monitored in these trials. Therefore, contemporary breast cancer clinical trials may possibly underestimate the cardiovascular risks of cancer pharmacotherapy agents for use in clinical practice.

**Key Words:** cancer therapy ■ cardio-oncology ■ cardiovascular disease ■ pharmacotherapy ■ safety

Breast cancer contributes to one quarter of all incident cancers in women and is the most common cause of female cancer-related mortality.[1] Furthermore, breast cancer shares a number of common risk factors with cardiovascular disease (CVD) such as age, obesity, tobacco use, alcohol intake, and hormone replacement therapy.[2] One third of patients with breast cancer have CVD.[3] With greater efficacy and introduction of improved breast cancer therapies, the 5-year survival of breast cancer patients has risen from 75% to 91%.[4] Given the increased survival rate, cancer therapy–induced cardiovascular toxicity is a growing cause of morbidity and mortality in patients with breast cancer.[5] Breast cancer pharmacotherapy agents including conventional chemotherapies (alkylating agents, antimetabolites, and antimicrotubule agents),[6,7] targeted therapies,[7] and immunotherapy[8] are associated with varying degrees of adverse

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## CLINICAL PERSPECTIVE

### What Is New?

- We highlight that breast cancer pharmacotherapy trials under-represent patients with cardiovascular conditions.
- Cardiovascular safety assessments frequently are not reported in breast cancer pharmacotherapy trials.
- Although patients with cardiovascular disease were often excluded from breast cancer pharmacotherapy trials, included participants commonly experienced adverse cardiovascular events during these trials.

### What Are the Clinical Implications?

- Breast cancer trials may underestimate the cardiovascular risks of cancer pharmacotherapy agents for the general population.
- Later-phase breast cancer pharmacotherapy trials may not be able to uncover cardiovascular risks that have not been identified in smaller-scale trials and as a result, subclinical cardiotoxicity may remain undetected in these trials.
- Judiciously conducted cardiovascular safety assessments may allow inclusion of patients with cardiovascular conditions, early identification of adverse cardiovascular events, and demonstrate subclinical cardiovascular harm of pharmacotherapy.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **FDA** | US Food and Drug Administration |

cardiovascular effects. Oncologic pharmacotherapy-induced cardiovascular effects can be serious and possibly fatal, including events such as myocardial infarction, arrhythmias, myocarditis, cardiomyopathy, pericardial disease, stroke, and heart failure.[7] Recent advances in the field of oncology have led to the rapid introduction of novel therapies, resulting in a rise in the number of agents gaining US Food and Drug Administration (FDA) approval every year.[9] Rigorous safety and efficacy testing in multiphase clinical trials must be performed before FDA approval. Given the high prevalence of CVD in women with breast cancer, it is important to understand potential cardiovascular harm from novel agents in this population. However, it is unclear whether large contemporary phase 2 and 3 clinical trials adequately assess cardiovascular safety and are able to uncover cardiovascular risks that were not identified in early-phase trials. Therefore, we assessed reporting of cardiovascular safety in breast cancer trials administering cancer pharmacotherapy through the evaluation of 3 key domains: inclusion/exclusion of patients with cardiovascular conditions, cardiovascular safety assessments (cardiovascular laboratories or imaging assessments), and adverse cardiovascular events.

## METHODS

### Study Identification

We searched Embase and Medline records before January 4, 2019 for clinical trial articles assessing efficacy of cancer pharmacotherapy in breast cancer until 50 articles that fit inclusion criteria were acquired. The search strategy used was: "Breast" AND "Cancer" with trial filters activated (Figure). The inclusion criteria of studies were as follows: (1) phase 2 and 3 trials; (2) enrolled >50 participants; (3) assessed the use of cancer pharmacotherapy as primary intervention on primary or secondary end points of survival, response, or safety in patients with active breast cancer; and (4) were registered with the national clinical trials registry or other international trial registries (this permits acquisition of further eligibility criteria and adverse event data). Studies were excluded if they were (1) quality of life or cost-analysis studies, (2) expanded access programs, or (3) involved treatment of other (nonbreast) types of cancer (to limit interdisease variability). Using the above criteria, our search was conducted with an all-inclusive approach to any stage of cancer, pharmacotherapy administered, or length of follow-up for articles published in any journal. This was done to maintain generalizability of our results. Two independent reviewers screened selected studies and abstracted data; in the event of disagreement, a third reviewer resolved discordant assessments. Furthermore, corresponding authors of articles were contacted for queries if needed. If corresponding authors failed to respond, then best judgment and consensus of reviewers was implemented. We acquired 50 published trials (Table S1) after review of 1775 records (Figure). Institutional Review Board approval was waived for this article because it is a review of publicly available data. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Data Abstraction

Data from primary articles, trial databases, protocols, and supplementary files were reviewed as a pooled analysis of trial data (Figure S1). The following data were abstracted from articles, registries, protocols, or supplements: (1) publication year, (2) number of participants, (3) age, (4) race (if specified), (5) median survival duration (if reached/available), (6) trial phase, (7) funding/sponsor, (8) cancer pharmacotherapy intervention, (9) trial end point,

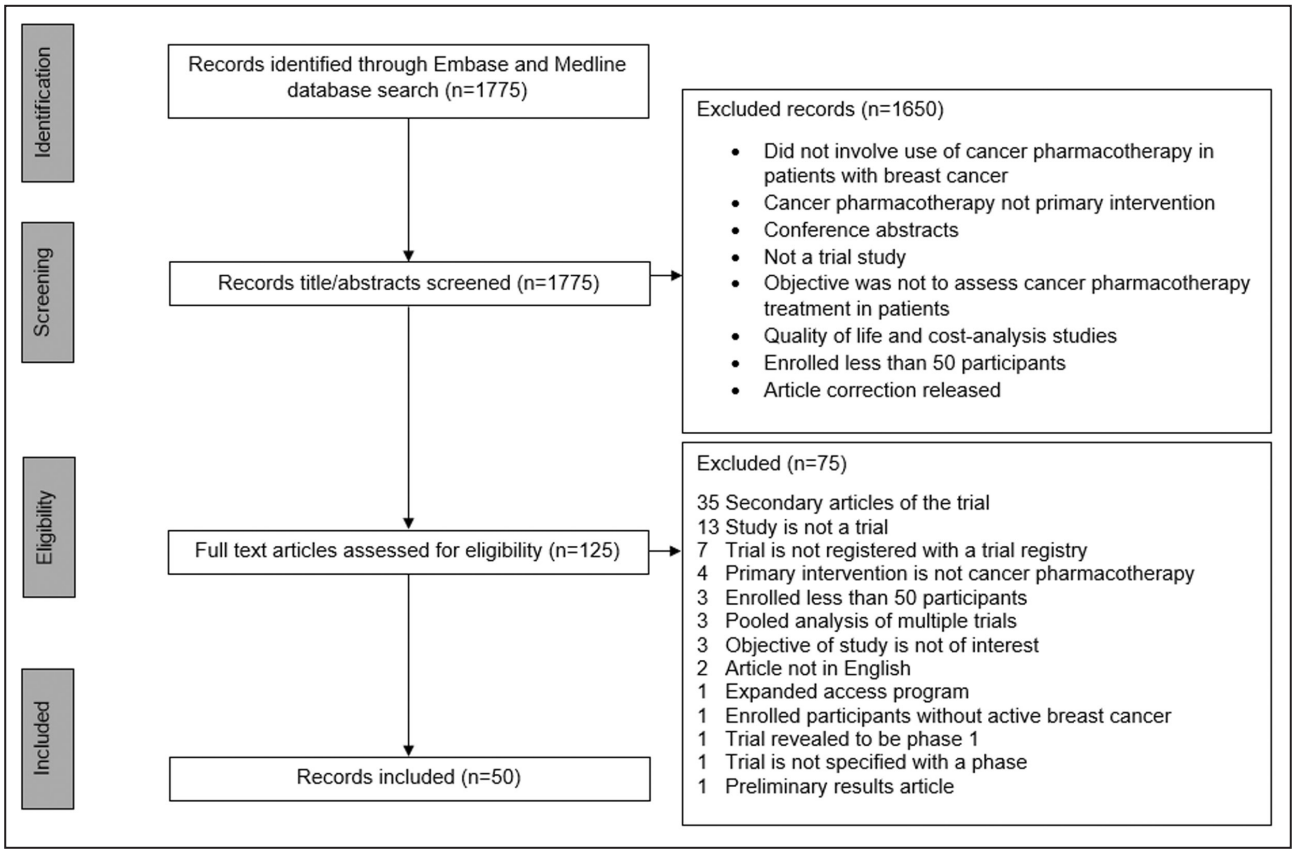


**Figure. Trial search.**

(10) inclusion/exclusion criteria, (11) safety assessments, and (12) adverse events. Registry data for demographics were utilized when articles did not present clear data. Data were last updated April 25, 2020.

## Definition of Reporting Variables

Cardiovascular conditions were defined as any CVD, cardiovascular symptoms (for example, dyspnea, peripheral edema, or chest pain), or any abnormal cardiovascular examination/laboratory parameters (for example, ejection fraction [EF], blood pressure, or heart rate). CVD was classified as heart failure (reported as history of heart failure, symptomatic heart failure, cardiopulmonary failure, or New York Heart Association class >1), angina, ischemic heart disease/coronary artery disease, myocardial infarction (reported as history of myocardial infarction or a recent myocardial infarction), hypertension (reported as history of hypertension or with blood pressure cutoffs), arrhythmia (reported as history of arrhythmias that were uncontrolled, unstable, clinically significant, or other unspecified ECG abnormalities), QT interval prolongation, stroke (ischemic or hemorrhagic), cardiomyopathy, pericardial disease (pericarditis or pericardial effusion), pulmonary hypertension/cor pulmonale, aortic aneurysm, acute coronary syndrome, cardiac tamponade, hypercholesterolemia/hypertriglyceridemia, cardiac/cardiorespiratory arrest, cardiac infection, structural heart disease, thrombosis (deep venous thrombosis, pulmonary embolism, or thromboembolic disease) or peripheral artery disease/carotid artery disease. Hypertension was divided into a history of hypertension and hypertension. When hypertension was listed without a blood pressure cutoff, this was considered a history of hypertension. Alternatively, hypertension with a blood pressure cutoff (eg, uncontrolled/poorly controlled hypertension [>140/90 mm Hg under treatment with 2 antihypertensive drugs]) was abstracted as hypertension, because this could possibly indicate hypertension identified upon screening (however, timeline of blood pressure assessment was mostly not specified in trials). Myocardial infarctions were also subdivided into a history of myocardial infarction if the timeline was not specified or a recent myocardial infarction if timeline was specified to have been at most in the past 1 year of study enrollment, entry, randomization, or first dose of therapy.

Cardiovascular safety assessments were defined as planned evaluations at baseline or pre/post therapy administration at any time in the trial. Cardiovascular

safety assessments included ECG, cardiac imaging (echocardiography, multigated acquisition scan, or cardiac magnetic resonance imaging [CMR]), natriuretic peptides (brain natriuretic peptide and N-terminal pro–brain natriuretic peptide), troponins, lipid profile, or creatine phosphokinase. Adverse cardiovascular events were defined as any reported adverse cardiovascular symptom, disease, or condition encountered at any point during the study or that may have resulted in death.

## Statistical Analysis

Continuous variables were abstracted as medians or absolute counts and summarized as means and SDs. Categorical variables were summarized as frequencies and percentages. Where demographic data in trials were presented in multiple groups (interventional group or control group), demographic data for the trial overall were summarized as mean of all groups. Where demographic data were available for only 1 study group, it was extrapolated to the entire study population. Fisher's exact test was applied for comparisons of reporting by various trial characteristics (funding, type of agent, and phase of trial). A 2-sided $P$ value of <0.05 was considered significant. All statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 23.0 (IBM, Armonk, New York, USA).

# RESULTS

## General Characteristics

In total, 1775 records were screened and 50 clinical trials that cumulatively enrolled 26 893 participants were included in our study (Figure and Table S1). The majority of these trials were published in 2018 (n=39; 78% trials) (Table 1). On average, trials had a population of 538 participants, median age of 55.7 years, median follow-up time of 31.3 months, median progression-free survival of 8.5 months, median overall survival of 24.0 months, and 81.1% of participants were White race (Table 1).

Included trials were most often phase 3 (n=27; 54% trials), industry sponsored (n=39; 78% trials), and reported a primary end point of therapy response (n=23; 46% trials). The most common therapy administration regimen was a combination of targeted therapy with conventional chemotherapy (n=20; 40% trials) (Table 1).

**Table 1. Trial and Participant Characteristics**

| Characteristic | Trials |
|---|---|
| Mean number of participants per trial | 537.9±880.9 |
| Mean of trial median follow-up, mo | 31.3±21.4 |
| Mean of participants median age, y | 55.7±7.4 |
| Mean of participants racial distribution, % | |
| White | 81.1±12.9 |
| Black | 5.1±8.1 |
| Asian | 9.5±11.4 |
| Other* | 4.3±3.3 |
| Trials published in year, n (%) | |
| 2019 | 11 (22.0) |
| 2018 | 39 (78.0) |
| Mean of participants median progression-free survival, mo | 8.5±4.2 |
| Mean of participants median overall survival, mo | 24.0±11.4 |
| Trial phase, n (%) | |
| 2 | 23 (46.0) |
| 3 | 27 (54.0) |
| Trial sponsor/funding, n (%) | |
| Industry (entirely or partially) | 39 (78.0) |
| University/Research organization/Government | 11 (22.0) |
| Type of agent administered, n (%) | |
| Targeted+Chemotherapy† | 20 (40.0) |
| Targeted+Hormonal | 4 (8.0) |
| Targeted+Chemotherapy†+Hormonal | 3 (6.0) |
| Immuno+Chemotherapy† | 1 (2.0) |
| Chemotherapy† monotherapy | 8 (16.0) |
| Hormonal monotherapy | 2 (4.0) |
| Chemotherapy†+Hormonal therapy | 12 (24.0) |
| Primary reported trial end point, n (%) | |
| Survival (progression free and overall) | 20 (40.0) |
| Response | 23 (46.0) |
| Safety/adverse events | 2 (4.0) |
| Other‡ | 5 (10.0) |
| Available trial data sources, n (%) | |
| Included articles | 50 (100.0) |
| Supplementary files | 29 (58.0) |
| Protocols | 18 (36.0) |

Certain demographic data were not available in trials, including: 25 (50%) trials missing median follow-up duration, 7 (14%) trials missing median age of participants, 30 (60%) trials missing racial distribution of participants, 32 (64%) trials missing median overall survival of participants, and 26 (52%) trials missing median progression-free survival of participants.

*Other includes Native Americans, Alaskans, unknown race, or unspecified as "other race."

†Chemotherapy here includes cytotoxic chemotherapy agents, antimetabolites, alkylating agents, platinum agents, and microtubule-inhibiting agents.

‡Other includes clinical benefit rate, time to treatment failure, time to progression, resumption of menstruation, and disease control rate.

## Reporting of Cardiovascular Exclusion

The majority of trials (n=42; 84% trials) listed at least 1 cardiovascular condition as an exclusion criterion, and 34 (68%) trials listed at least 1 CVD as an exclusion criterion (Table 2). The most frequently reported cause for exclusion was heart failure (n=31; 62% trials). Reported exclusion by nonspecific cardiac causes was encountered in 26 (52%) trials (for example, listed as "uncontrolled heart disease" or "history of cardiac disease"). Other common causes of exclusion were

**Table 2. Reporting of Cardiovascular Exclusion Criteria**

| Exclusion criteria | Number of trials reported exclusion, n (%) |
|---|---|
| Any cardiovascular condition | 42 (84) |
| Any CVD | 34 (68) |
| Heart failure | 31 (62) |
| Arrythmia* | 29 (58) |
| Low ejection fraction | 27 (54) |
| Angina | 26 (52) |
| Nonspecific cardiac cause† | 26 (52) |
| Recent myocardial infarction‡ | 25 (50) |
| Hypertension§ | 11 (22) |
| History of hypertension | 10 (20) |
| Structural disease | 8 (16) |
| Ischemic/Coronary heart disease | 8 (16) |
| History of myocardial infarction | 6 (12) |
| QT interval prolongation | 6 (12) |
| Pericardial disorders (effusion or pericarditis) | 5 (10) |
| Stroke (ischemic or hemorrhagic) | 4 (8) |
| Dyspnea | 4 (8) |
| Pro-arrhythmic medication use | 4 (8) |
| Cardiomyopathy | 3 (6) |
| Thrombosis/thromboembolism | 2 (4) |
| Hypotension | 2 (4) |
| Hypercholesterolemia/ hypertriglyceridemia | 2 (4) |
| Aortic aneurysm | 1 (2) |
| Peripheral artery disease | 1 (2) |
| Elevated creatine phosphokinase levels | 1 (2) |

CVD indicates cardiovascular disease.

*Includes arrhythmia, atrioventricular block, atrial fibrillation, bradycardia, high-risk arrhythmia, brugada, torsades, and tachycardia. These arrhythmias were largely labeled as unstable or uncontrolled.

†Nonspecific reporting such as "Uncontrolled cardiac/cardiovascular/heart disease, history of heart/cardiac disease or dysfunction, significant or clinically significant cardiac disorders/disease, clinically significant cardiac disease, cardiac/cardiovascular disease precluding study, nonmalignant systemic disease (cardiac), major cardiovascular comorbidity, severe heart disease with life expectancy from disease <2 years, active cardiac disease, other cardiac disease, serious cardiac disease/illness; inclusion of participants with normal cardiopulmonary/cardiac function as assessed by echocardiography, normal/adequate cardiac function, or functionally preserved heart". The nonspecificity terms were summarized in the interest of brevity.

‡Recent myocardial infarction includes myocardial infarctions before specific timeline of study entry, randomization, enrollment, or first dose therapy (8 studies did not specify baseline from which recent myocardial infarctions will be excluded). Different trials listed exclusions at different timelines, 18 trials excluded patients with myocardial infarctions within 6 months, 5 trials excluded patients with myocardial infarctions within 12 months, and 2 trials excluded patients with myocardial infarctions within the past 3 months.

§Hypertension as classified as an elevated blood pressure cutoff. Blood pressure cutoffs varied, eg, >140/90 (while on 2 antihypertensive medication) or if systolic blood pressure was >150, >160, >180, <90 mm Hg or if diastolic blood pressures were>90 or >100 mm Hg.

arrhythmias in 29 (58%) trials, low EF in 27 (54%) trials, and a recent myocardial infarction in 25 (50%) trials (Table 2). Exclusion criteria set for EF varied from trial to trial, ranging from EF <40% to EF <55%.

Of note, 10 (20%) trials excluded patients with a history of hypertension and 11 (22%) trials excluded patients with hypertension with various blood pressure cutoffs (Table 2). Altogether, 20 (40%) trials excluded patients with a history of hypertension or hypertension (with listed blood pressure cutoffs).

## Reporting of mCardiovascular Safety Assessments

Cardiovascular safety assessments were rarely reported by the included trials. Nearly half of these trials (n=23; 46% trials) did not report any cardiovascular safety assessments either at baseline or throughout treatment cycles (Table 3). The most frequently reported cardiovascular safety assessments were ECGs (n=23; 46% trials) and cardiac imaging (n=20; 40% trials) (Table 3). The 20 (40%) trials that conducted cardiac imaging assessments all utilized echocardiograms and/or multigated acquisition scans, while only 1 (2%) trial conducted some cardiac imaging assessments with CMR. Cardiac biomarker measurements were rarely reported. Assessment of creatine kinase or creatine phosphokinase levels was reported in only 2 (4.3%) trials, and no trial reported assessment of natriuretic peptides or troponins (Table 3).

Although 27 (54%) trials reported exclusion of patients based on low EF, only 20 (40%) trials reported cardiac imaging as a safety assessment (Tables 2 and 3). Further assessment of this discordance demonstrated that one quarter (n=7; 26% trials) of these 27 trials, which reported exclusion of patients with low EF, did not report any cardiac imaging (by echocardiography or myocardial gated uptake assessment) as a safety assessment performed during the trial.

## Reporting of Adverse Cardiovascular Events

Adverse cardiovascular events were commonly encountered, as 43 (86%) trials reported at least 1 cardiovascular adverse event and 36 (72%) trials reported at least 1 CVD event (Table 4). The most frequently reported adverse events were hypertension (n=23; 46% trials), thrombosis/thromboembolisms (n=23; 46% trials), dyspnea (n=22; 44% trials), edema (n=22; 44%), heart failure (n=19; 38% trials), and arrhythmia (n=19; 38% trials) (Table 4). The majority of trials (n=46; 92% trials) reported adverse events via a standardized grading system (ie, the National Cancer Institute common terminology criteria for adverse events/common toxicity criteria). Death caused by CVD was reported in one third of these trials (n=18; 36% trials). Common causes of death were heart failure, stroke, myocardial infarctions, thromboembolic events, arrhythmias, and cardiac arrest.

**Table 3. Reporting of Cardiovascular Safety Assessments**

| Safety assessment | Number of trials reported assessment, n (%) |
|---|---|
| Any cardiovascular assessment | 27 (54) |
| ECG | 23 (46) |
| Cardiac imaging* | 20 (40) |
| Lipid profile | 5 (10) |
| Creatine kinase/creatine phosphokinase | 2 (4) |
| Troponin | 0 (0) |
| BNP/NT-proBNP | 0 (0) |

BNP indicates brain natriuretic peptide; and NT-proBNP, N-terminal pro–brain natriuretic peptide.

*Cardiac imaging was conducted in trials through echocardiograms, multigated acquisition scan, or cardiac magnetic resonance imaging (CMR). Only 1 (2%) trial reported use of CMR, while 20 (40%) trials reported use of echocardiograms and/or multigated acquisition scans as cardiac imaging modalities.

Symptoms such as dyspnea (n=22; 44% trials), peripheral edema (n=22; 44% trials), and chest pain (n=6; 12% trials) were commonly reported; however, they were primarily reported with no specified cause (Table 4). Only 1 trial reported chest pain specifically as cardiac chest pain. Furthermore, reporting of cardiovascular events in a nonspecific manner was encountered in 4 (8%) trials, with events reported as a "cardiac/cardiovascular adverse event" (Table 4).

## Association of Trial Factors With Reporting

Industry-funded trials more frequently reported cardiovascular safety assessments, compared with non–industry-funded trials (69.2% versus 0.0%, respectively, $P<0.001$). Furthermore, industry-funded trials more frequently reported cardiovascular adverse events, compared with non–industry-funded trials (97.4% versus 45.5%, respectively; $P<0.001$) (Table 5).

Trials administering targeted/immunotherapy agents more frequently reported cardiovascular safety assessments, compared with trials administering conventional chemotherapy or hormonal therapy (78.6% versus 22.7%, respectively, $P<0.001$). We also observed more frequent exclusion of participants with cardiovascular conditions in trials administering targeted/immunotherapy agents, compared with trials administering conventional chemotherapy or hormonal therapy (96.4% versus 68.2%, respectively; $P=0.015$) (Table 5).

# DISCUSSION

This study provides unique insight as the first report assessing cardiovascular safety reporting within contemporary later-phase breast cancer pharmacotherapy clinical trials by 3 major criteria: eligibility, cardiovascular safety assessment monitoring, and adverse event reporting.

**Table 4. Reporting of Adverse Cardiovascular Events**

| Adverse cardiovascular event reporting | Number of trials reported adverse events, n (%) |
|---|---|
| Reported any cardiovascular adverse event | 43 (86) |
| Reported any CVD adverse event | 36 (72) |
| Hypertension | 23 (46) |
| Thrombosis/thromboembolism | 23 (46) |
| Dyspnea | 22 (44) |
| Edema | 22 (44) |
| Heart failure | 19 (38) |
| Arrhythmia* | 19 (38) |
| Stroke | 14 (28) |
| Low/decreased ejection fraction | 12 (24) |
| Pericardial disease (effusion or pericarditis) | 9 (18) |
| Myocardial infarction | 8 (16) |
| Hypotension | 8 (16) |
| Hypercholesterolemia/hypertriglyceridemia | 7 (14) |
| Cardiac/cardiopulmonary arrest | 7 (14) |
| LV dysfunction/failure | 7 (14) |
| Chest pain | 6 (12) |
| Ischemic heart/coronary artery disease/coronary artery stenosis | 5 (10) |
| Cardiomyopathy | 4 (8) |
| Nonspecific cardiac event† | 4 (8) |
| QT interval prolongation | 3 (6) |
| Cardiac decompensation/insufficiency/circulatory collapse | 3 (6) |
| Acute coronary syndrome | 3 (6) |
| Creatine phosphokinase/troponin elevation | 3 (6) |
| Cardiac tamponade | 2 (4) |
| Palpitations | 2 (4) |
| Pulmonary hypertension/cor pulmonale | 2 (4) |
| Cardiac infection | 2 (4) |
| Angina | 1 (2) |
| Structural heart disease | 1 (2) |
| Vasovagal episode | 1 (2) |
| Peripheral artery disease | 1 (2) |

CVD indicates cardiovascular disease; and LV, left ventricle.

*Includes atrial fibrillation, atrial flutter, bradycardia, heart block, premature ventricular contraction, sinus arrhythmia, supraventricular tachycardia, tachycardia, torsades, ventricular tachycardia, ventricular arrhythmia, ventricular extrasystole, or ECG abnormality.

†Nonspecific reporting such as "cardiac/cardiovascular adverse events, cardiac disorder, other cardiovascular adverse events, cardiac complications, any cardiovascular disease, cardiac events not otherwise specified, cardiac other". Reporting terms were summarized in the interest of brevity.

Our findings demonstrate significant underrepresentation of patients with CVD (by exclusion of cardiovascular conditions or prevalent CVD) in these clinical trials. Although patients with CVD were often excluded from

**Table 5. Association of Cardiovascular Safety Reporting and Trial Characteristics**

| Trial characteristics | Trials reported, n (%)* | | | | | |
|---|---|---|---|---|---|---|
| | Reported any cardiovascular exclusion | | Reported any cardiovascular safety assessment | | Reported any cardiovascular event | |
| | Reporting | *P* value | Reporting | *P* value | Reporting | *P* value |
| Funding | | 0.174 | | <0.001 | | <0.001 |
| Industry | 31 (79.5) | | 27 (69.2) | | 38 (97.4) | |
| University/Research organization/ Government | 11 (100.0) | | 0 (0.0) | | 5 (45.5) | |
| Use of targeted/immunotherapy | | 0.015 | | <0.001 | | 1.000 |
| Included in regimen | 27 (96.4) | | 22 (78.6) | | 24 (85.7) | |
| Not included in regimen | 15 (68.2) | | 5 (22.7) | | 19 (86.4) | |
| Use of anthracyclines | | 0.087 | | 1.000 | | 1.000 |
| Included in regimen | 14 (100.0) | | 8 (57.1) | | 12 (85.7) | |
| Not included in regimen | 28 (77.8) | | 19 (52.8) | | 31 (86.1) | |
| Phase | | 1.000 | | 0.087 | | 0.225 |
| 2 | 19 (82.6) | | 9 (39.1) | | 18 (78.3) | |
| 3 | 23 (85.2) | | 18 (66.7) | | 25 (92.6) | |

*Percentage is reported as fraction of trial characteristic group (for example, 79.5% of industry-funded trials reported any cardiovascular exclusion).

breast cancer pharmacotherapy clinical trials, included participants commonly experienced adverse cardiovascular events during these trials. Furthermore, our findings highlight that cardiovascular safety may not be routinely monitored in all breast cancer pharmacotherapy studies. Therefore, potential cardiovascular harm from these cancer pharmacotherapy agents might be underestimated and subclinical cardiotoxicity may remain undetected in later-phase breast cancer clinical trials. Lastly, other factors such as trial funding source and type of pharmacotherapy agent were associated with discrepant cardiovascular safety monitoring.

The underrepresentation of patients with CVD in cancer pharmacotherapy trials linked to FDA drug approval has previously been described by Bonsu et al. They observed that 34% of pharmacotherapy trials for any cancer type and ≈50% for breast cancer exclude patients with CVD.[10] This was lower compared with our observation that 68% of breast cancer trials exclude patients with CVD and was far lower compared with our finding that 84% of trials exclude patients with cardiovascular conditions. Therefore, we highlight that in addition to direct exclusion of patients with CVD, breast cancer pharmacotherapy trials may further exclude patients with CVD by using cardiovascular symptoms (dyspnea) or cardiovascular parameters (left ventricular EF) as cardiovascular exclusion criterion. As a result, patients with cardiovascular conditions are excluded in the majority of these trials.

Similar to our observations, Bonsu et al also encountered nonspecific reported exclusion of patients with CVD in more than one third of trials compared with approximately half of trials in our study.[10] The use of nonspecific/ill-defined terminology (eg, "history of cardiac disease" or "uncontrolled heart disease") possibly indicates the use of subjective exclusion criteria, resulting in the possibility of either the inclusion of patients with real risk factors for cardiovascular toxicity or exclusion of patients with minimal to no added risk of toxicity.

An evaluation of cancer trials by Bonsu et al suggested that cancer pharmacotherapy trials linked with FDA drug approval underreport adverse CVD events in comparison to population-based estimates.[11] Furthermore, they demonstrated that 45% of breast cancer trials do not report adverse CVD events, compared with 28% in our observation.[11] Our study demonstrates that cancer trials sometimes report events as symptoms (dyspnea) or abnormal parameters (decreased left ventricular ejection fraction), rather than diagnosed CVD; this may also have reflected on the findings of Bonsu et al on the underreporting of CVD. Furthermore, our study highlights a possibility that this observation of adverse event underreporting may be because of underdetection as a result of poor conduct of cardiovascular safety assessments, because nearly half of trials in our observation did not report any form of cardiovascular safety assessment. Therefore, improved conduct of cardiovascular safety assessments may possibly permit better adverse cardiovascular event detection and identification at earlier stages.

Preclinical studies offer an opportunity to study cardiovascular risks of cancer pharmacotherapy before introduction in human models. These are largely conducted in animal models, based on studied cardiovascular pharmacology and physiology. However, preclinical studies on their own are not sufficient to uncover cardiovascular risks of cancer pharmacotherapy in humans because of several limitations including

size of the model (smaller animals usually utilized) and species-dependent sensitivity to myocardial injury.[12] This highlights the importance of clinical trials in uncovering cardiovascular toxicity in humans that otherwise cannot be observed in preclinical models.

Large, later-phase clinical trials present an opportunity to uncover cardiovascular risks (particularly subclinical cardiovascular risks) not previously demonstrated in smaller trials, and ultimately these later-phase trials are the primary drivers of decision making in clinical practice. Currently, guidelines on the management of patients with high cardiovascular risk receiving cancer pharmacotherapy are nonexistent. However, studies suggest the use of less cardiotoxic agents (or at minimal dose), risk class allocation based on risk scores from initial evaluation, then appropriate monitoring (with periodic echocardiography, ECG, troponin, natriuretic peptides), and management.[13] Patients with cardiovascular risks still receive cancer pharmacotherapy but the criteria for their inclusion are not standardized. Therefore, exclusion of patients who otherwise could be candidates to receive therapy in clinical practice may impact the generalizability of results garnered from trials.

Cancer trials are not the only type of trials that exclude patients with comorbidities/multimorbidity. Patients included in clinical trials have half as many medical comorbidities as compared with the general population.[14] The percentage of included patients with comorbidities varies depending on the patient condition under treatment.[14] While a more inclusive approach to clinical trials may generate more generalizable data, this raises several issues with primary trial outcomes. Clinical trials are often created with narrowly defined populations (for example, by excluding patients with CVD), with the intention of generating results specific to the primary outcome.[15] Factors such as regimen compliance[16] and patient survival[17,18] are directly impacted by the presence of comorbidities (such as CVD) in patients with cancer. These factors are therefore likely to affect trial success and may alter results, particularly with respect to cancer trials where more than one third of all trials in our observation used survival end points to determine therapy efficacy. Because of these reasons, breast cancer trials may opt to include healthier populations when assessing pharmacotherapy in the interest of primary outcomes.

Rather than exclude patients with CVD, cancer trials may possibly consider improvement in protocol-driven safety assessments (baseline, pretreatment, and posttreatment), and identification of high-risk participants who require more frequent assessment or dose adjustments. Early changes in left ventricular strain and effective arterial elastance in patients with breast cancer receiving pharmacotherapy have been indicative of future heart failure symptoms.[19] Furthermore, brain natriuretic peptide[20] and troponin[21] are proven predictors of cancer pharmacotherapy-related cardiotoxicity and cardiac events. However, reporting of cardiac imaging as a safety assessment was observed in less than half of trials, and no trials we studied reported using troponin, brain natriuretic peptide, or N-terminal pro–brain natriuretic peptide for screening or safety assessments.

The European Society of Cardiology supports the use of natriuretic peptides and cardiac troponins in patients receiving cancer pharmacotherapy.[22] Biomarkers can help risk stratify patients at baseline and uncover early cardiac injury or strain. Elevations in cardiac biomarkers can indicate patients requiring closer monitoring, initiation of cardioprotective therapy, and do not necessarily mean cessation of therapy.[22] However, baseline troponin levels at times may not always correlate with increased risks of cancer pharmacotherapy–related cardiotoxicity.[23,24] As a result, their consistent use may not be widely adopted as yet. The European Society of Cardiology recommendations on cardiac biomarkers have evolved to more clearly defined timelines of collection from the 2016 to 2020 position statements.[22,25] Therefore, in the evolving field of cardio-oncology, the consensus on their use in routine surveillance in pharmacotherapy-induced cardiotoxicity is also evolving. While biomarker assessments offer better surveillance of cardiotoxicity in patients receiving cancer pharmacotherapy, there are still no established standards with respect to assay selection, cut-off values for clinically significant changes, and the ideal timing of sampling.[22] This may suggest why biomarker analyses were not conducted in any of the contemporary breast cancer trials assessed in our study. Cardiac biomarkers offer an opportunity for cancer pharmacotherapy trials in the future to identify and prevent cancer pharmacotherapy-induced cardiotoxicity.

While 20 (40%) trials reported use of cardiac imaging modalities, we observed only 1 (2%) trial that reported use of CMR. CMR as a modality offers the benefit of early identification of cancer pharmacotherapy-induced cardiotoxicity compared with echocardiograms or multigated acquisition scans with the utility of T1/T2 mapping, the ability to detect subtle decreases in left ventricular ejection fraction, myocardial edema (in T2 images), early inflammation, and early fibrosis.[26] In the future, we suggest that cancer pharmacotherapy trials may utilize CMR in higher-risk populations to allow inclusion of participants with cardiovascular conditions because of the comfort of identification of early cardiotoxicity, before the development of overt cardiotoxicity. However, because of cost constraints, CMR is largely used when echocardiograms and multigated acquisition scans are indeterminate,[26] which may explain why we observed its negligible use in cancer pharmacotherapy trials. Lack of use of cardiac biomarkers as well as cardiac imaging (particularly CMR) may result

in a missed opportunity for the identification of newly uncovered cancer pharmacotherapy-induced cardiotoxicity. Improved conduct in cardiovascular safety assessments may permit better detection of incident early CVD, patients requiring dose adjustments, and may uncover subclinical risks of therapy. This would permit safer inclusion of participants with comorbidities and would generate data that could lead to better-informed decision making in clinical practice.

Trials frequently reported adverse cardiovascular events despite most of them excluding patients with prevalent CVD. Hypertension was the most commonly reported adverse event among trials and can be caused by a variety of agents.[27] Specifically, it is one of the most common adverse effects of targeted therapies.[25,28] Targeted therapies are relatively new and were evaluated in a majority of trial regimens in our study. An analysis of clinical trials with patients receiving targeted therapy reported cardiotoxic adverse events more often than any other type of adverse event.[29] In our study, clinical trials excluded patients with CVD more frequently and took greater caution in the conduct and reporting of cardiovascular safety assessments when targeted therapy or immunotherapy were administered (as the sole therapy or in combination with other agents). This may be because targeted therapies are relatively newer agents and exhibit a large variety of cardiotoxic effects, ranging from cardiac pump dysfunction (HER2 monoclonal antibodies/HER2 inhibitors) to prolonged QT interval (tyrosine kinase inhibitors), which is why more stringent monitoring is required.[7] In contrast, while anthracyclines are known to cause cardiovascular dysfunction, we observed no significant difference in reporting irrespective of anthracycline use.[25]

Industry funding/sponsorship may play a role in the presentation of positive results and outcomes; however, for the most part, this has no effect on study quality.[30,31] Our study similarly demonstrated better study practices in industry-funded trials with greater reporting of safety assessments and adverse cardiovascular events. Industry-funded studies are often thoroughly scrutinized; thus, they may take further precautions to maintain safety and transparency in trials.[31]

Our study has some limitations that must be taken into consideration. Detailed safety assessments are often reported in study protocols, and protocols were unavailable for two thirds of trials (Table 1). We thoroughly searched for protocols of all trials, but many trials do not upload trial protocols. Hence, throughout our study we can only comment on what trials opted to report (in terms of safety assessments and eligibility criteria). Furthermore, this study retrieved trials conducted in patients with breast cancer; therefore, results cannot be generalized to other cancer types.

## CONCLUSIONS

The study populations of contemporary later-phase breast cancer trials administering pharmacotherapy are underrepresentative of patients with CVD. This possibly results in a lack of generalizability of generated data. Before the initiation of pharmacotherapy and during its course, cardiovascular safety assessments are rarely reported, suggesting room for improvement in the conduct and reporting of cardiovascular safety assessments. Reporting of cardiovascular safety assessment data may depend on the source of trial funding and the type of agent administered. Judiciously conducted cardiovascular safety assessments may allow inclusion of patients with CVD, early identification of adverse cardiovascular events, and demonstrate subclinical cardiovascular harm of pharmacotherapy. Thus, later-phase breast cancer clinical trials may not be able to uncover cardiovascular risks that have not been identified in smaller-scale trials. These findings suggest that contemporary later-phase breast cancer clinical trials may underestimate the cardiovascular risks of cancer pharmacotherapy. Trials conducted in populations more inclusive of CVD, with increased scrutiny in monitoring of cardiovascular harm related to novel cancer therapies, could possibly lead to more informed clinical decision making for oncology patients with CVD in clinical practice.

## ARTICLE INFORMATION

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## Supplemental Material

Table S1
Figure S1

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# SUPPLEMENTAL MATERIAL

**Table S1. List of all included studies.**

| Serial Number | Title | Citation |
|---|---|---|
| 1 | Sorafenib in combination with docetaxel as first-line therapy for HER2-negative metastatic breast cancer: Final results of the randomized, double-blind, placebo-controlled phase II MADONNA study | Mavratzas A, Baek S, Gerber B, Schmidt M, Moebus V, Foerster F, Grischke EM, Fasching P, Strumberg D, Solomayer E, et al. Sorafenib in combination with docetaxel as first-line therapy for HER2-negative metastatic breast cancer: Final results of the randomized, double-blind, placebo-controlled phase II MADONNA study. *Breast*. 2019;45:22-28 |
| 2 | Randomized phase II study evaluating weekly oral vinorelbine versus weekly paclitaxel in estrogen receptor-positive, HER2-negative patients with advanced breast cancer (NorBreast-231 trial) | Aapro M, Ruiz-Borrego M, Hegg R, Kukielka-Budny B, Morales S, Cinieri S, Freitas-Junior R, Garcia-Estevez L, Szombara E, Borges GS, et al. Randomized phase ii study evaluating weekly oral vinorelbine versus weekly paclitaxel in estrogen receptor-positive, HER2-negative patients with advanced breast cancer (NorBreast-231 trial). *Breast*. 2019;45:7-14 |

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| 3 | Concurrent neoadjuvant chemotherapy and estrogen deprivation in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (CBCSG-036): A randomized, controlled, multicenter trial | Yu KD, Wu SY, Liu GY, Wu J, Di GH, Hu Z, Hou YF, Chen CM, Fan L, Tang LC, et al. Concurrent neoadjuvant chemotherapy and estrogen deprivation in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (CBCSG-036): A randomized, controlled, multicenter trial. *Cancer*. 2019;125:2185-2193 |
| 4 | A multi-national, randomised, open-label, parallel, phase III non-inferiority study comparing NK105 and paclitaxel in metastatic or recurrent breast cancer patients | Fujiwara Y, Mukai H, Saeki T, Ro J, Lin YC, Nagai SE, Lee KS, Watanabe J, Ohtani S, Kim SB, et al. A multi-national, randomised, open-label, parallel, phase III non-inferiority study comparing NK105 and paclitaxel in metastatic or recurrent breast cancer patients. *Br J Cancer*. 2019;120:475-480 |
| 5 | Efficacy and safety of everolimus plus exemestane in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2- | Tesch H, Stoetzer O, Decker T, Kurbacher CM, Marme F, Schneeweiss A, Mundhenke C, Distelrath A, Fasching PA, Lux MP, et al. Efficacy and safety of everolimus plus exemestane in postmenopausal women with hormone |

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| | negative locally advanced or metastatic breast cancer: Results of the single-arm, phase IIIB 4EVER trial | receptor-positive, human epidermal growth factor receptor 2-negative locally advanced or metastatic breast cancer: Results of the single-arm, phase IIIB 4EVER trial. *Int J Cancer*. 2019;144:877-885 |
| 6 | PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: a randomised, double-blind study | Pegram MD, Bondarenko I, Zorzetto MMC, Hingmire S, Iwase H, Krivorotko PV, Lee KS, Li RK, Pikiel J, Aggarwal R, et al. PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: A randomised, double-blind study. *Br J Cancer*. 2019;120:172-182 |
| 7 | Randomized Phase II Study Evaluating Palbociclib in Addition to Letrozole as Neoadjuvant Therapy in Estrogen Receptor–Positive Early Breast Cancer: PALLET Trial | Johnston S, Puhalla S, Wheatley D, Ring A, Barry P, Holcombe C, Boileau JF, Provencher L, Robidoux A, Rimawi M, et al. Randomized phase II study evaluating palbociclib in addition to letrozole as neoadjuvant therapy in estrogen receptor-positive early breast cancer: PALLET Trial. *J Clin Oncol*. 2019;37:178-189 |

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| 8 | Safety, activity, and molecular heterogeneity following neoadjuvant non-pegylated liposomal doxorubicin, paclitaxel, trastuzumab, and pertuzumab in HER2-positive breast cancer (Opti-HER HEART): an open-label, single-group, multicenter, phase 2 trial | Gavila J, Oliveira M, Pascual T, Perez-Garcia J, Gonzalez X, Canes J, Pare L, Calvo I, Ciruelos E, Munoz M, et al. Safety, activity, and molecular heterogeneity following neoadjuvant non-pegylated liposomal doxorubicin, paclitaxel, trastuzumab, and pertuzumab in HER2-positive breast cancer (Opti-HER HEART): An open-label, single-group, multicenter, phase 2 trial. *BMC Med*. 2019;17:8 |
| 9 | Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto—GBG 84): A randomised phase III trial | Schneeweiss A, Mobus V, Tesch H, Hanusch C, Denkert C, Lubbe K, Huober J, Klare P, Kummel S, Untch M, et al. Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto—GBG 84): A randomised phase III trial. *Eur J Cancer*. 2019;106:181-192 |

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| 10 | A randomized and open-label phase II trial reports the efficacy of neoadjuvant lobaplatin in breast cancer | Wu X, Tang P, Li S, Wang S, Liang Y, Zhong L, Ren L, Zhang T, Zhang Y. A randomized and open-label phase ii trial reports the efficacy of neoadjuvant lobaplatin in breast cancer. *Nat Commun*. 2018;9:832 |
| 11 | Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial | van Ramshorst MS, van der Voort A, van Werkhoven ED, Mandjes IA, Kemper I, Dezentje VO, Oving IM, Honkoop AH, Tick LW, van de Wouw AJ, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual her2 blockade for HER2-positive breast cancer (TRAIN-2): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19:1630-1640 |
| 12 | A Randomized Phase II Study of Eribulin/Cyclophosphamide or Docetaxel/Cyclophosphamide as Neoadjuvant Therapy in | Yardley DA, Shipley D, Zubkus J, Wright GL, Ward PJ, Mani A, Shastry M, Finney L, DeBusk L, Hainsworth JD. A randomized phase ii study of eribulin/cyclophosphamide or docetaxel/cyclophosphamide as neoadjuvant therapy in operable HER2- |

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| | Operable HER2-negative Breast Cancer | negative breast cancer. *Clin Breast Cancer*. 2019;19:1-9 |
| 13 | Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer | Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Dieras V, Hegg R, Im SA, Shaw Wright G, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379:2108-2121 |
| 14 | Combination versus sequential paclitaxel plus gemcitabine as first-line chemotherapy for women with metastatic breast cancer: a prospective randomized phase II study. | Shao B, Song G, Li H, Dil L, Jiang H, Liang X, Yan Y, Zhang R, Ran R, Wang J, el al. Combination versus sequential paclitaxel plus gemcitabine as first-line chemotherapy for women with metastatic breast cancer: A prospective randomized phase II study. *J BUON*. 2018;23:1583-1590 |
| 15 | Fulvestrant plus goserelin versus anastrozole plus goserelin versus goserelin alone for hormone receptor-positive, HER2-negative tamoxifen-pretreated premenopausal women with | Kim JY, Im SA, Jung KH, Ro J, Sohn J, Kim JH, Park YH, Kim TY, Kim SB, Lee KS, et al. Fulvestrant plus goserelin versus anastrozole plus goserelin versus goserelin alone for hormone receptor-positive, her2-negative tamoxifen-pretreated premenopausal women with |

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| 16 | Intermittent versus continuous first-line treatment for HER2-negative metastatic breast cancer: the Stop & Go study of the Dutch Breast Cancer Research Group (BOOG) | Claessens AKM, Bos M, Lopez-Yurda M, Bouma JM, Rademaker-Lakhai JM, Honkoop AH, de Graaf H, van Druten E, van Warmerdam LJC, van der Sangen MJC, et al. Intermittent versus continuous first-line treatment for her2-negative metastatic breast cancer: The stop & go study of the dutch breast cancer research group (BOOG). *Breast Cancer Res Treat*. 2018;172:413-423 |
| 17 | Paclitaxel With Inhibitor of Apoptosis Antagonist, LCL161, for Localized Triple-Negative Breast Cancer, Prospectively Stratified by Gene Signature in a Biomarker-Driven Neoadjuvant Trial | Bardia A, Parton M, Kummel S, Estevez LG, Huang CS, Cortes J, Ruiz-Borrego M, Telli ML, Martin-Martorell P, Lopez R, et al. Paclitaxel with inhibitor of apoptosis antagonist, LCL161, for localized triple-negative breast cancer, prospectively stratified by gene signature in a biomarker- |

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| | | driven neoadjuvant trial. *J Clin Oncol*. 2018:JCO2017748392 |
| 18 | Multicenter Phase II Study of Lurbinectedin in BRCA-Mutated and Unselected Metastatic Advanced Breast Cancer and Biomarker Assessment Substudy | Cruz C, Llop-Guevara A, Garber JE, Arun BK, Perez Fidalgo JA, Lluch A, Telli ML, Fernandez C, Kahatt C, Galmarini CM, et al. Multicenter phase II study of lurbinectedin in BRCA -mutated and unselected metastatic advanced breast cancer and biomarker assessment substudy. *J Clin Oncol*. 2018;36:3134-3143 |
| 19 | Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor–Positive, HER2-Negative Advanced Breast CancerThe BOLERO-6 Randomized Clinical Trial | Jerusalem G, de Boer RH, Hurvitz S, Yardley DA, Kovalenko E, Ejlertsen B, Blau S, Ozguroglu M, Landherr L, Ewertz M, et al. Everolimus plus exemestane vs everolimus or capecitabine monotherapy for estrogen receptor-positive, HER2-negative advanced breast cancer: The BOLERO-6 randomized clinical trial. *JAMA Oncol*. 2018;4:1367-1374 |
| 20 | UCBG 2-08: 5-year efficacy results from the UNICANCER-PACS08 | Campone M, Lacroix-Triki M, Roca L, Spielmann M, Wildiers H, Cottu P, Kerbrat P, Levy C, Desmoulins I, Bachelot T, et al. |

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| | randomised phase III trial of adjuvant treatment with FEC100 and then either docetaxel or ixabepilone in patients with early-stage, poor prognosis breast cancer | UCBG 2-08: 5-year efficacy results from the UNICANCER-PACS08 randomised phase iii trial of adjuvant treatment with FEC100 and then either docetaxel or ixabepilone in patients with early-stage, poor prognosis breast cancer. *Eur J Cancer*. 2018;103:184-194 |
| 21 | Adjuvant dose-dense doxorubicin-cyclophosphamide versus docetaxel-doxorubicin-cyclophosphamide for high-risk breast cancer: First results of the randomised MATADOR trial (BOOG 2004-04) | van Rossum AGJ, Kok M, van Werkhoven E, Opdam M, Mandjes IAM, van Leeuwen-Stok AE, van Tinteren H, Imholz ALT, Portielje JEA, et al. Adjuvant dose-dense doxorubicin-cyclophosphamide versus docetaxel-doxorubicin-cyclophosphamide for high-risk breast cancer: First results of the randomised MATADOR trial (BOOG 2004-04). *Eur J Cancer*. 2018;102:40-48 |
| 22 | Results From the First Multicenter, Open-label, Phase IIIb Study Investigating the Combination of Pertuzumab With Subcutaneous Trastuzumab and a Taxane in Patients | Woodward N, De Boer RH, Redfern A, White M, Young J, Truman M, Beith J. Results from the first multicenter, open-label, phase IIIb study investigating the combination of pertuzumab with subcutaneous trastuzumab and a taxane in patients with HER2-positive metastatic |

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| 37 | Randomized phase II trial of fulvestrant plus everolimus or placebo in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer resistant to aromatase | Kornblum N, Zhao F, Manola J, Klein P, Ramaswamy B, Brufsky A, Stella PJ, Burnette B, Telli M, Makower DF, et al. Randomized phase ii trial of fulvestrant plus everolimus or placebo in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer resistant to aromatase |

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| | (trastuzumab biosimilar) and reference trastuzumab in patients treated with neoadjuvant therapy for human epidermal growth factor receptor 2-positive early breast cancer | the efficacy, safety, and immunogenicity of SB3 (trastuzumab biosimilar) and reference trastuzumab in patients treated with neoadjuvant therapy for human epidermal growth factor receptor 2-positive early breast cancer. *J Clin Oncol*. 2018;36:968-974 |
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| 45 | Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial | Loibl S, O'Shaughnessy J, Untch M, Sikov WM, Rugo HS, McKee MD, Huober J, Golshan M, von Minckwitz G, Maag D, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer |

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| 46 | Phase III, Randomized study of dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with HER2-positive, hormone receptor-positive metastatic breast cancer: ALTERNATIVE | Johnston SRD, Hegg R, Im SA, Park IH, Burdaeva O, Kurteva G, Press MF, Tjulandin S, Iwata H, Simon SD, et al. Phase III, randomized study of dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with her2-positive, hormone receptor-positive metastatic breast cancer: ALTERNATIVE. *J Clin Oncol.* 2018;36:741-748 |
| 47 | Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly | Wildiers H, Tryfonidis K, Dal Lago L, Vuylsteke P, Curigliano G, Waters S, Brouwers B, Altintas S, Touati N, Cardoso F, et al. Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): An open-label, randomised, phase 2 trial from the Elderly Task Force/Breast |

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| 48 | Comparing neoadjuvant nab-paclitaxel vs paclitaxel both followed by anthracycline regimens in women with ERBB2/ HER2-negative breast cancer-the evaluating treatment with neoadjuvant abraxane (ETNA) trial a randomized phase 3 clinical trial | Gianni L, Mansutti M, Anton A, Calvo L, Bisagni G, Bermejo B, Semiglazov V, Thill M, Chacon JI, Chan A, et al. Comparing neoadjuvant nab-paclitaxel vs paclitaxel both followed by anthracycline regimens in women with ERBB2/ HER2-negative breast cancer-the evaluating treatment with neoadjuvant abraxane (ETNA) trial: A randomized phase 3 clinical trial. *JAMA Oncol*. 2018;4:302-308 |
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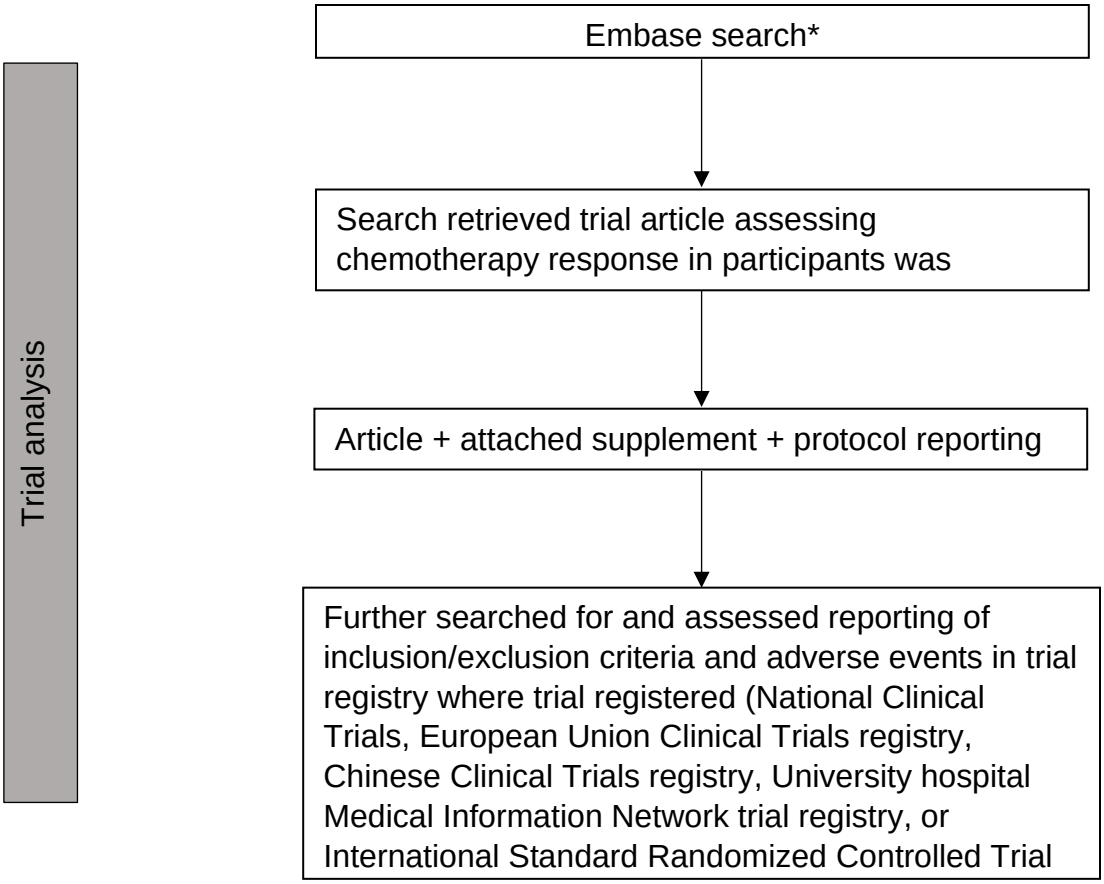
**Figure S1. Data collection strategy.**




*The search string applied was “breast:ti,ab,kw AND cancer:ti,ab,kw AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)”.