Published in final edited form as:

Breast Cancer Res Treat. 2020 January ; 179(1): 161–171. doi:10.1007/s10549-019-05453-z.

A Pooled Analysis of the Cardiac Events in the Trastuzumab Adjuvant Trials

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Abstract

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Compliance with Ethical Standards

Conflict of Interest

Evandro de Azambuja has received honoraria and advisory board from Roche/GNE and Seattle Genetics; travel grants from Roche/GNE and GSK/Novartis and research grants to his Institute: Roche/GNE; Astra-Zeneca, GSK/Novartis, Servier

Noam Ponde has received honoraria from AZ and Eli Lilly and travel grants Eli Lilly and Novartis.

Marion Procter has declared that her institution received funding from Roche in respect to the APHINITY trial.

Matteo Lambertini has received honoraria Therame and consulting fee from TEVA

Priya Rastogi has received travel and accommodations supported by Lilly, AZ, and GNE/Roche

Martine Piccart has declared board Member (Scientific Board) : Oncolytics, Radius; consultant (honoraria) : AstraZeneca, Camel-IDS, Crescendo Biologics, Debiopharm, G1 Therapeutics, Genentech, Huya, Immunomedics, Lilly, Menarini, MSD, Novartis, Odonate, Periphen, Pfizer, Roche, Seattle Genetics; research grants to her Institute: AstraZeneca, Lilly, MSD, Novartis, Pfizer, Radius, Roche-Genentech, Servier, Synthon

Thomas Suter has declared research Support from Novartis and Amgen; consultant from Pfizer and advisory Board from Alnylam

Richard D Gelber declares that his institution receives support for his salary from Roche, AstraZeneca, Merck, Novartis, Ipsen, Celgene, Pfizer, and Ferring.

Dimitrios Zardavas has declared employment from BMS

Karla V. Ballman has declared consulting or Advisory Role from ARIAD; Medtronic; Takeda; Agenus; Patents, Royalties, Other Intellectual Property: Prostate cancer signature patent (Inst); Expert Testimony - Janssen Oncology; **Lilly**

Lise Roca, Alvaro Moreno Aspitia and Reena Cecchini have no conflict of interest to declare

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in each of the studies (HERA, NSABP B-31 (NRG Oncology) and NCCTG N9831 (Alliance)).

Background: Trastuzumab-associated cardiotoxicity remains an issue for patients with HER2-positive breast cancer. This pooled analysis of 3 adjuvant trials investigated the incidence, timing, impact on treatment completion and risk factors for trastuzumab-associated cardiotoxicity.

Methods: This is an individual patient data level pooled analysis of HERA, NSBAP B-31, and NCCTG 9831 (Alliance Trials). Definitions of cardiac events were as per each individual study.

Results: A total of 7,445 patients enrolled in the 3 trials were included in the analysis, of which 4,017 were in the trastuzumab and 3,428 in the control (observation) arms, respectively. Median follow-up exceeded 10 years (119.2 – 137.2 months). Nearly all patients (97.4%) in the trastuzumab arms received anthracycline-based chemotherapy. In total, 452 patients in the trastuzumab arms experienced a cardiac event (11.3%), with most being mildly symptomatic or asymptomatic left ventricular ejection fraction (LVEF) decrease (351 patients, 8.7%). Severe congestive heart failure was more common in the trastuzumab arm (2.3%) than in the control arm (0.8%). Most cardiac events occurred during trastuzumab treatment (78.1%) and cardiac events were the main cause of discontinuation across the sample (10.0%); nevertheless, a large majority of patients completed trastuzumab treatment (76.2%). Baseline risk factors that were significantly associated with development of cardiac events were baseline LVEF <60%, hypertension, body mass index >25, age ≥ 60 and non-Caucasian ethnicity.

Conclusion: One year of trastuzumab increases the risk of cardiac events, though most consist of asymptomatic or mildly symptomatic LVEF drops. Adjuvant trastuzumab should be considered a safe treatment from a cardiac standpoint for most patients. Trastuzumab-associated cardiotoxicity is the main cause of discontinuation and further research is needed to individualize prevention and management.

Keywords

trastuzumab; LVEF; cardiotoxicity; breast cancer

Introduction

The treatment of patients with human epidermal growth factor receptor 2 (HER2) positive early breast cancer (BC) is based on combining adjuvant chemotherapy to 1 year of the monoclonal antibody trastuzumab [1]. Despite multiple attempts at changing this long-standing standard, either via dual HER2 blockade (lapatinib, pertuzumab), extended treatment (neratinib) or via reduction of the length of trastuzumab treatment (to 9 weeks, 3 months or 6 months), many patients continue to receive trastuzumab alone for 1 year [1]. The trastuzumab standard is based on a series of pivotal phase III trials of women with HER2-positive early breast cancer, including Herceptin Adjuvant (HERA; BIG1-01), National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCTG) 9831 (Alliance Trials) and Breast Cancer International Research Group (BCIRG) 006 [2, 3].

These trials have shown that, similarly to what was seen in the advanced setting, trastuzumab use entails a significantly increased risk of cardiotoxicity, which most often manifests either as an asymptomatic decrease in left ventricular ejection fraction (LVEF) or, less frequently, as symptomatic congestive heart failure (CHF) [4–7]. Existing results,

originated by cardiac-safety focused analysis of data from the individual trials, suggest that trastuzumab-associated cardiotoxicity is mostly clinically manageable, that it occurs typically during treatment and is frequently reversible with interruption of trastuzumab and adequate cardiac treatment and, moreover, that it can be predicted by a number of risk factors, which have varied across trials [8].

Nevertheless, the relatively low overall number of cardiac events in the individual trials has precluded a complete understanding of the occurrence and clinical course of trastuzumab-associated cardiotoxicity. The purpose of pooling the individual patient data from the three trials was to investigate potential risk factors for a cardiac event in patients treated with trastuzumab and the impact of risk factors being present based on a larger dataset with a larger number of patients with a cardiac event. These are exploratory analyses to be considered in addition to the published literature from individual trials.

Patients and Methods

Study Design

HERA, NSABP B-31 (NRG Oncology) and NCCTG N9831 (Alliance) were randomized phase III trials which assessed 1 year of trastuzumab vs observation in patients with HER2-positive early breast cancer, sequentially to or concomitantly with chemotherapy (anthracycline/taxane based) [2, 3, 9]. The 2-year trastuzumab arm of HERA was not included in this analysis considering that it's not standard of care based on the lack of survival benefit shown with trastuzumab prolongation beyond 1 year [10]. The design, eligibility criteria and endpoints of each trial were described in detail in previous publications [2, 3]. Appendix 1 describes the essential aspects of the design of each of the 3 trials and Appendix 2 shows the consort diagram. Of note in NSABP B-31 and N9831, patients were randomized prior to the start of adjuvant therapy, with those experiencing cardiac events or LVEF reductions being prevented from starting trastuzumab use; on the contrary, in HERA, patients were randomized only after the completion of (neo)adjuvant chemotherapy plus radiotherapy (if indicated), and thus trastuzumab treatment was sequential. In HERA, furthermore, patients had to have a LVEF of $\geq 55\%$ function after the completion of chemotherapy to be eligible for randomization. In NSABP B-31 and NCCTG N9831, LVEF on echocardiography (ECHO)/ Multigated Acquisition (MUGA) scan had to be above the lower limit of the institutional normal.

Definitions of Cardiac Events and Acute Recovery

Each of the 3 trials used different definitions for cardiac events (Appendix 3). Briefly, in HERA, cardiac events could be primary (cardiac death or New York Heart Association class III or IV CHF) or secondary (LVEF decrease that is either asymptomatic or mildly symptomatic). In NSABP B-31 cardiac events were defined as cardiac death or symptomatic CHF with an LVEF drop. In N9831, cardiac events were defined as symptomatic CHF or cardiac death. Acute cardiac recovery was likewise defined differently in each trial (Appendix 4).

Treatment Interruption

In order to safeguard patients from cardiotoxicity, each trial had recommendations for interruption of trastuzumab treatment in case of cardiac events. Briefly, in HERA patients with severe CHF or confirmed LVEF decreases had to interrupt treatment. In NSABP B-31 patients with confirmed symptomatic CHF discontinued treatment and patients with asymptomatic LVEF decrease followed guidelines in the protocol for treatment interruption.. In N9831 patients with substantial LVEF decrease lasting beyond four weeks had to interrupt treatment. Appendix 4 details these rules further.

Cardiac Monitoring

Each study followed a different schedule for cardiac monitoring, particularly for long-term cardiac follow-up after the end of study treatment (Appendix 5). HERA required cardiac monitoring with an ECHO or MUGA to be performed annually between years 5 through 10 [4]. NSABP B-31 required cardiac history forms to be submitted yearly after 5 years [7]. Any indications of possible late cardiac events were followed up with specific queries. In NCCTG N9831, a subset (approximately 33.4%) of patients who went on to trastuzumab (arms B and C) or observation (arm A) had an LVEF evaluation at 6 years [5, 6].

Identifying cardiac events

For NSABP B-31 and N9831, the definition of a cardiac event in the protocol could be considered as cardiac death or severe CHF (NYHA class III/IV). For the pooled analysis, patients in the trastuzumab arm of NSABP B-31 who discontinued trastuzumab as a result of asymptomatic declines in LVEF were considered as having asymptomatic CHF. Patients in trastuzumab arms of N9831 who discontinued trastuzumab as a result of asymptomatic declines in LVEF were considered as having asymptomatic CHF during the trastuzumab treatment period. Further details are described in Appendix 6.

Statistical Analysis

The NSABP B-31 and N9831 datasets consider the intention to treat (ITT) population. It is important to note that for NSABP B-31, the ITT population differs from the primary cardiac safety analysis population, which excluded those who did not initiate trastuzumab based on an unacceptable post-AC cardiac evaluation. The trastuzumab arm from the HERA trial considers patients who received at least one dose of trastuzumab. The HERA patients who were randomized to observation and selectively crossed over to trastuzumab after the release of the trial results were censored at the time of selective crossover for the purpose of this analysis.

Baseline patient and tumor characteristics were described by trial and in the combined arms. Reasons for trastuzumab discontinuation and the incidence of cardiac events were summarized by trial and for the combined trastuzumab arm. The time period of the occurrence of cardiac events in the combined trastuzumab arm was summarized. Cardiac events described as occurring during trastuzumab treatment included those taking place up to 28 days after last administration of trastuzumab. The incidence of any cardiac event was summarized in the combined trastuzumab arm by potential risk factor. The 95% confidence interval (CI) for the incidence of cardiac events was calculated as an exact 95% CI for one

sample binomial using the Pearson-Clopper method. The 95% CI for the difference in incidence of cardiac events was calculated using the Hauck-Anderson correction. Baseline factors selected for analysis were chosen based on previously published literature on the subject as well as the current understanding of the underlying physiopathology of cardiotoxicity. The impact of having multiple concurrent risk factors was investigated in the combined trastuzumab arm by calculating the cumulative incidence of any cardiac event. The mean LVEF value was displayed for the combined trastuzumab arm at visits up to month 18 and for the trastuzumab arms by trial up to month 36. The statistical analysis was performed in SAS 9.4, and further details on programming algorithms are in Appendix 6.

Results

Patient Characteristics

The 3 trials randomized a total of 7,445 patients, with 4,017 in the pooled 1-year trastuzumab arm and 3,428 in the pooled observation arm. The median follow-up in the combined trastuzumab arm was 132.0 months (IQR 119.9–142.6 months) (Appendix 7). Table 1 summarizes patient characteristics for both the trastuzumab and observation arms for all patients included in this analysis, as well as for the individual trials (with further detail given in Appendix 8). While in NSABP B-31 all patients received concomitant trastuzumab with taxanes, in N9831 some patients received trastuzumab only after the end of therapy – sequential therapy (67.3%); in HERA all patients were treated sequentially.

Discontinuation of Trastuzumab Treatment

As per all study protocols, trastuzumab dose reductions were not allowed during treatment. Table 2 summarizes the occurrence, as well as the causes of trastuzumab treatment discontinuation in total and by study. Cardiac safety was the most common reason for treatment discontinuation in the combined study population (10.0%). In HERA, disease recurrence was the most common cause of trastuzumab discontinuations (5.4%) followed by cardiac safety (5.2%).

Incidence of Cardiac Events

Out of 4,017 patients in the trastuzumab arms, 452 (11.3%) experienced a cardiac event (Table 3). Seven cardiac deaths occurred in the combined trastuzumab arms of the trials (0.2%) as compared to 5 in the combined control arms (0.1%). Severe CHF (NYHA III/IV) was more common in the trastuzumab arms with 94 (2.3%) patients with a reported event as compared to 28 (0.8%) in the control arms (Appendix 9). Three hundred and fifty one (8.7%) of the reported events in the trastuzumab arms was asymptomatic or mildly symptomatic (mild heart failure {NYHA II} or asymptomatic drops in LVEF {NYHA I}). In terms of timing of occurrence in relation to trastuzumab, 78.1% of reported cardiac events occurred during trastuzumab use and only 10.6% after anti-HER2 treatment completion. The remaining 11.3% of cardiac events occurred in patients who did not start trastuzumab (i.e. during chemotherapy). Appendix 10 summarizes the timing of events in relation to trastuzumab use. The incidence of cardiac events was numerically higher in the concurrent trastuzumab arms as compared to the sequential arms (Appendix 11).

Acute Recovery from Cardiac Events

Unfortunately, the heterogeneity existing among the definitions of acute recovery among trials did not allow for a pooled analysis of this particular study endpoint.

Risk Factors for Cardiac Events

Nearly all patients in this study received anthracycline-based chemotherapy (97.5%), precluding analysis of the influence of anthracycline as a risk factor for cardiac events. Identified risk factors for the development of cardiac events in the combined sample were LVEF at baseline <60%; history of hypertension, high body mass index (BMI) (>25), age 60 and being ethnically non-Caucasian (Table 4). There were too few patients with a history of diabetes to draw conclusions, despite the numerical risk increase. Having 2 or more risk factors increases the risk of experiencing a cardiac event over time, as compared to 0 or 1 risk factor (Figure 1). By 12 months, the cumulative incidence of having a cardiac event in patients with two or more risk factors is approximately twice the cumulative incidence in patients with zero risk factors (Figure 1). Further details on programming algorithms for Figure 1 are described in Appendix 6.

LVEF Value Over time

Figure 2A depicts mean LVEF value over time for patients in the trastuzumab arms. Figure 2B depicts mean LVEF value over time by trial. The graph shows that mean LVEF falls progressively during trastuzumab treatment but recovers to near pre-treatment levels approximately 6 months after the end of trastuzumab treatment. Further details on programming algorithm for Figure 2 are in Appendix 6.

Discussion

To our knowledge, this study, including individual data originating from 3 well conducted randomized clinical trials with long term follow-up is the largest study investigating trastuzumab-associated cardiotoxicity in the adjuvant setting. Patients in the combined trastuzumab arms had a numerically increased incidence of cardiac events, as compared to patients in the combined observation arms, though these cardiac events in most cases were asymptomatic or mildly symptomatic and occurred during trastuzumab treatment.

The pathophysiology of anti-HER2 treatment associated cardiac dysfunction is not yet completely understood [8]. HER2 seems to play an important role in cardiac homeostasis, particularly when the myocardium suffers physiological stress [11]. This explains why anti-HER2 treatment is particularly cardiotoxic in situations in which myocardial oxidative stress is heightened, i.e. during or immediately after the use of anthracyclines, in patients with arterial hypertension or pre-existing cardiac diseases [12–14]. In contrast to anthracyclines, which have the potential to induce myocyte cell death, inhibition of HER2 signaling leads to cardiac dysfunction either by affecting the cardiomyocyte contraction or by interfering with mitochondrial metabolism [15, 16].

This framework for comprehending trastuzumab-associated cardiotoxicity is further strengthened by currently available data on cardiac damage biomarkers, which suggest that

troponins are elevated early in trastuzumab treatment and almost exclusively in patients who are pre-treated with anthracycline-based chemotherapy [17, 18]. In our study, this is well reflected in the progressive yet slight (mean still above 60%) reduction in mean LVEF for the combined population, followed by the recovery approximately 6 months after the end of treatment.

Clinically, trastuzumab-associated cardiotoxicity manifests most often as asymptomatic LVEF drops and mildly symptomatic CHF, with cardiac death being an exceedingly rare occurrence [8]. Additionally, most cardiac events occur during the trastuzumab treatment phase and are reversible. Heterogeneity in the definition of acute recovery among trials, as well as the differences in long-term cardiac follow-up has precluded combined analysis of the recovery data. Results from the individual trials suggest a high chance of recovery with interruption of treatment and adequate cardiac treatment [4, 5, 7]. For example, 81.2% of patients in HERA who experienced a cardiac event eventually recovered (median time to recovery was 7.2 months).

Ten percent of patients in the combined trastuzumab arms discontinued trastuzumab treatment due to cardiac events. Discontinuation, particularly if it occurs early in treatment (before completing 6 months), can compromise outcomes. Therefore, in our view, discontinuation of anti-HER2 treatment due to cardiotoxicity is not always necessary. For many patients, especially those with asymptomatic LVEF drops, maintaining trastuzumab use while conducting closer follow-up with a cardiologist and adequate cardiac treatment may be the appropriate first management option. Short interruptions with resumption after intervention (with ACE inhibitors and/or beta-blockers) and LVEF recovery is also a valid option [19]. The results of the PERSEPHONE trial, which suggest the non-inferiority of 6 months of adjuvant trastuzumab vs 1 year with a substantial reduction in cardiac events (12% to 9%) and non-inferior survival outcomes also points towards the possibility of halting treatment after 6 months, though this remains a hotly debated topic [20, 21].

Heterogeneity in the definition for cardiac events (Appendix 3), in the point of patient inclusion and in the follow up schedule used in the different studies are among the challenges facing the field of cardiac-oncology and the authors of guidelines today (Appendix 4) and are therefore major limitations of our study. Although the European Society of Cardiology (ESC) has proposed definitions for cardiac events to be used in clinical trials, including those testing anti-HER2 agents, these have thus far not been extensively used [19].

Several unanswered research questions remain, including: (1) what is the long term risk of cardiac dysfunction for patients receiving trastuzumab (and/or newer anti-HER agents); notably when patients suffer from pre-existing cardiac illness; (2) what is the long term clinical course of patients who experienced dysfunction during treatment, notably when they eventually develop other cardiac diseases (such as coronary insufficiency). It is hoped that trials such as APHINITY, in which pertuzumab plus trastuzumab vs trastuzumab was tested, will provide further cardiac data in the future [22]. Additionally, registry studies such as SystHERs () should help evaluating the cardiotoxicity associated with anti-HER2 agents in “real life” populations. Currently available “real life” retrospective cohorts suggest that

trastuzumab-associated cardiotoxicity is more common phenomena than data coming from clinical trials results suggest, notably in older patients [8]. A recent study, including over 16.000 patients with early breast cancer from the Truven health MarketScan database detected 692 patients who developed CHF during or after cancer treatment (4.2% of the entire sample). For patients who received trastuzumab, the incidence was 8.3% (vs 2.7% for those who did not use trastuzumab, $p<0.001$), with nearly all events being identified within the first year [23].

The possibility of trastuzumab-associated cardiotoxicity should be taken into consideration when making decisions regarding adjuvant trastuzumab use despite the low overall incidence of cardiac events in our study. Our study identified a few risk factors, including LVEF at baseline $<60\%$, history of hypertension, high BMI (>25), and age ≥ 60 . Though the eligibility criteria of HERA precluded a combined analysis of patients with LVEF between 50% and 54%, it is relevant to mention that these lower LVEF levels were significantly associated with cardiac events in a cardiac-specific analysis of NSABP B-31 [7]. Considering the outstanding long-term benefit of adjuvant trastuzumab, excluding patients from treatment based solely on one of these risk factors should not be a standard approach. As our results show, multiple risk factors substantially increase the risk of a cardiac event. Hence, when multiple factors (3 or more) are present a non-anthracycline regimen should be preferred, such as the taxane, carboplatin and trastuzumab regimen tested in BCIRG-006 (with the possibility of adding pertuzumab or taxane and trastuzumab tested in the APT trial (for lower risk patients) as well as closer follow-up and pro-active measures to control risk factors [24, 25]. In addition, cardioprotective pharmacological interventions, as per the results of the PRADA, MANTICORE or the carvedilol and lisinopril trials, cannot be considered as standard at this point, but should be the focus of further studies [26–28]. Additionally, based on the results of PERSEPHONE, a shorter (6 months) adjuvant trastuzumab regimen may be considered for a certain number of patients in some countries where trastuzumab is not broadly available.

In conclusion, the results of our study, which is the largest individual patient level combined analysis concerning trastuzumab-associated cardiotoxicity performed to date shows an increase in the incidence of cardiac events, though most cases are asymptomatic or mildly symptomatic nature and occurring during trastuzumab treatment. One-year of adjuvant trastuzumab should be considered as a safe treatment from a cardiac stand-point for most patients. Collaboration between cardiologists and oncologists is necessary to advance the field and reduce the risk of cardiotoxicity during cancer treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to acknowledge the teams of HERA, NSABP B –31, NCCTCG N9831 and PACS004 for their help in making this project possible.

Financial Disclosures

The NSABP B-31 Trial was supported by NCI grants: U10CA180868, –180822, UG1–189867, and U24–196067.

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Figure 1:
cumulative incidence plot of any cardiac events in the Trastuzumab combined arm based on competing risks

Figure 2A:
plot of mean LVEF value over time up to month 18

Figure 2B:
plot of mean LVEF value over time up to month 36

Table 1:

Patient Baseline Characteristics

	Trials Combined		HERA		NSABP B-31		N9831	
	Trastuzumab N=4017	Control N=3428	Trastuzumab N=1682	Control N=1717	Trastuzumab N=1055	Control N=1047	Trastuzumab N=1280	Control N=664
NODAL STATUS								
Not assessed *	191 (4.8%)	181 (5.3%)	191 (11.4%)	181 (10.5%)	0	0	0	0
0 positive nodes	610 (15.2%)	601 (17.5%)	538 (32.0%)	560 (32.6%)	0	0	72 (5.6%)	41 (6.2%)
1–3 positive nodes	1737 (43.2%)	1434 (41.8%)	477 (28.4%)	499 (29.1%)	611 (57.9%)	600 (57.3%)	649 (50.7%)	335 (50.5%)
4 positive nodes	1479 (36.8%)	1211 (35.3%)	476 (28.3%)	476 (27.7%)	444 (42.1%)	447 (42.7%)	559 (43.7%)	288 (43.4%)
Unknown	0	1 (0.0%)	0	1 (0.1%)	0	0	0	0
ADJUVANT CHEMOTHERAPY REGIMEN								
No anthracyclines	101 (2.5%)	102 (3.0%)	99 (5.9%)	101 (5.9%)	0	0	2 (0.2%)	1 (0.2%)
Anthracycline but no taxane	1167 (29.1%)	1216 (35.5%)	1138 (67.7%)	1173 (68.3%)	29 (2.7%)	43 (4.1%)	0	0
Anthracycline and taxane	2747 (68.4%)	2094 (61.1%)	445 (26.5%)	443 (25.8%)	1024 (97.1%)	988 (94.4%)	1278 (99.8%)	663 (99.8%)
None/unknown	2 (0.0%)	16 (0.5%)	0	0	2 (0.2%)	16 (1.5%)	0	0
AGE (years)								
< 35	285 (7.1%)	239 (7.0%)	124 (7.4%)	130 (7.6%)	69 (6.5%)	62 (5.9%)	92 (7.2%)	47 (7.1%)
35–39	417 (10.4%)	361 (10.5%)	183 (10.9%)	176 (10.3%)	103 (9.8%)	108 (10.3%)	131 (10.2%)	77 (11.6%)
40–49	1381 (34.4%)	1165 (34.0%)	566 (33.7%)	583 (34.0%)	367 (34.8%)	352 (33.6%)	448 (35.0%)	230 (34.6%)
50–64	1634 (40.7%)	1437 (41.9%)	688 (40.9%)	713 (41.5%)	436 (41.3%)	451 (43.1%)	510 (39.8%)	273 (41.1%)
65	300 (7.5%)	226 (6.6%)	121 (7.2%)	115 (6.7%)	80 (7.6%)	74 (7.1%)	99 (7.7%)	37 (5.6%)
PATHOLOGICAL TUMOR SIZE (cm)								
Not assessed *	191 (4.8%)	181 (5.3%)	191 (11.4%)	181 (10.5%)	0	0	0	0
0- <2	1273 (31.7%)	1134 (33.1%)	536 (31.9%)	536 (31.2%)	319 (30.2%)	358 (34.2%)	418 (32.7%)	240 (36.1%)
2-<5	2150 (53.5%)	1772 (51.7%)	843 (50.1%)	845 (49.2%)	595 (56.4%)	574 (54.8%)	712 (55.6%)	353 (53.2%)
5	391 (9.7%)	321 (9.4%)	103 (6.1%)	139 (8.1%)	138 (13.1%)	111 (10.6%)	150 (11.7%)	71 (10.7%)
Unknown	12 (0.3%)	20 (0.6%)	9 (0.5%)	16 (0.9%)	3 (0.3%)	4 (0.4%)	0	0

	Trials Combined		HERA		NSABP B-31		N9831	
	Trastuzumab N=4017	Control N=3428	Trastuzumab N=1682	Control N=1717	Trastuzumab N=1055	Control N=1047	Trastuzumab N=1280	Control N=664
HISTOLOGICAL GRADE OF TUMOR								
3	1750 (43.6%)	1718 (50.1%)	1020 (60.6%)	1025 (59.7%)	730 (69.2%)	693 (66.2%)	Not available	Not available
2	835 (20.8%)	884 (25.8%)	543 (32.3%)	568 (33.1%)	292 (27.7%)	316 (30.2%)	Not available	Not available
1	60 (1.5%)	67 (2.0%)	37 (2.2%)	38 (2.2%)	23 (2.2%)	29 (2.8%)	Not available	Not available
Not assessed	71 (1.8%)	78 (2.3%)	71 (4.2%)	78 (4.5%)	0	0	Not available	Not available
Unknown	21 (0.5%)	17 (0.5%)	11 (0.7%)	8 (0.5%)	10 (0.9%)	9 (0.9%)	Not available	Not available

* Neo-adjuvant chemotherapy

Table 2:

Causes of trastuzumab treatment discontinuation

	Trastuzumab Arms Combined N=4017	HERA N=1682	NSABP B-31 N=1055	N9831 N=1280
Completed trastuzumab	3059 (76.2%)	1416 (84.2%)	720 (68.2%)	923 (72.1%)
Discontinued trastuzumab	954 (23.7%)	266 (15.8%)	331 (31.4%)	357 (27.9%)
Safety reasons	524 (13.0%)	123 (7.3%)	218 (20.7%)	183 (14.3%)
Cardiac safety *	401 (10.0%)	88 (5.2%)	200 (19.0%)	113 (8.8%)
Other safety	123 (3.1%)	35 (2.1%)	18 (1.7%)	70 (5.5%)
Recurrence of disease	144 (3.6%)	90 (5.4%)	23 (2.2%)	31 (2.4%)
Other reason	286 (7.1%)	53 (3.2%)	90 (8.5%)	143 (11.2%)

NOTE: The NSABP B-31 dataset and N9831 dataset considers an ITT population

* As the NSABP B-31 dataset considers an ITT population, this number includes patients who did not initiate trastuzumab based on an unacceptable post-chemotherapy cardiac evaluation

Table 3:

Incidence of cardiac events in the trastuzumab arms

	Trastuzumab Arms Combined N=4017	HERA N=1682	NSABP B-31 N=1055	N9831 N=1280
Any cardiac event *	452 (11.3%)	92 (5.5%)	205 (19.4%)	155 (12.1%)
Did not start trastuzumab	51 (1.3%)	-	49 (4.6%)	2 (0.2%)
During trastuzumab treatment **	353 (8.8%)	67 (4.0%)	144 (13.6%)	142 (11.1%)
After trastuzumab treatment	48 (1.2%)	25 (1.5%)	12 (1.1%)	11 (0.9%)
Cardiac death	7 (0.2%)	3 (0.2%)	2 (0.2%)	2 (0.2%)
Severe CHF (NYHA class III/IV)	94 (2.3%)	15 (0.9%)	41 (3.9%)	38 (3.0%)
Did not start trastuzumab	3 (0.1%)	-	2 (0.2%)	1 (0.1%)
During trastuzumab treatment **	71 (1.8%)	12 (0.7%)	28 (2.7%)	31 (2.4%)
After trastuzumab treatment	20 (0.5%)	3 (0.2%)	11 (1.0%)	6 (0.5%)
Asymptomatic or mildly symptomatic (NYHA class II)	351 (8.7%)	74 (4.4%)	162 (15.4%)	115 (9.0%)
Did not start trastuzumab	46 (1.1%)	-	46 (4.4%)	0
During trastuzumab treatment **	281 (7.0%)	55 (3.3%)	116 (11.0%)	110 (8.6%)
After trastuzumab treatment	24 (0.6%)	19 (1.1%)	0	5 (0.4%)

* The precise definition of the types of cardiac event was not consistent across the trials

** During trastuzumab treatment includes up to 28 days after last administration of trastuzumab

In NSABP B31, the timing of the asymptomatic or mildly symptomatic CHF from randomization is set as the timing of last administration of trastuzumab or, for patients who did not start trastuzumab, as the last administration of chemotherapy.

The precise date of asymptomatic or mildly symptomatic CHF in N9831 could not be determined. The timing can be approximated from trastuzumab treatment discontinuation.

Table 4:

Risk Factors for cardiac event - Trastuzumab Arms Combined

Variable	n	Incidence of Cardiac Event [*]	95% CI for Incidence ^{**}	Difference in Incidence (%)	95% CI for the Difference ^{***}
SCREENING LVEF ^{****}					
Lower limit LVEF < 60%	1026	157 (15.30)	(13.15, 17.65)	5.41	(2.91, 7.91)
60%	2973	294 (9.89)	(8.84, 11.02)		
60% LVEF < 65%	1181	128 (10.84)	(9.12, 12.75)	1.57	(-0.69, 3.84)
65%	1792	166 (9.26)	(7.96, 10.70)		
PREVIOUS RADIOTHERAPY					
Left sided	1537	163 (10.61)	(9.11, 12.25)	-0.74	(-3.35, 1.86)
None	934	106 (11.35)	(9.39, 13.56)		
HYPERTENSION					
Yes	729	112 (15.36)	(12.82, 18.19)	5.03	(2.15, 7.92)
No	3282	339 (10.33)	(9.31, 11.42)		
HIGH BODY MASS INDEX					
>25	2338	311 (13.30)	(11.95, 14.75)	4.87	(2.84, 6.91)
20 BMI 25	1412	119 (8.43)	(7.03, 10.00)		
SMOKING STATUS					
Yes	349	40 (11.46)	(8.32, 15.28)	0.71	(-3.01, 4.42)
No	2380	256 (10.76)	(9.54, 12.07)		
DIABETES					
Yes	80	17 (21.25)	(12.89, 31.83)	10.73	(1.00, 20.45)
No	2651	279 (10.52)	(9.38, 11.76)		
AGE (years)					
50 to 59	1280	144 (11.25)	(9.57, 13.11)	1.50	(-0.68, 3.69)
< 50	2083	203 (9.75)	(8.51, 11.10)		
60	654	105 (16.06)	(13.32, 19.10)	5.74	(2.66, 8.81)
< 60	3363	347 (10.32)	(9.31, 11.40)		
RACE					
Caucasian	3374	360 (10.67)	(9.65, 11.76)	-3.57	(-6.55, -0.59)
Non-Caucasian	639	91 (14.24)	(11.62, 17.19)		

^{*} The precise definition of the types of cardiac event was not consistent across the trials

^{**} Exact 95% CI for one sample binomial using Pearson-Clopper method

^{***} Approximate 95% CI for difference of two rates using Hauck-Anderson correction

^{****} The LVEF eligibility criteria was not consistent across the trials

LVEF = left ventricular ejection fraction