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Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab

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Background: Pertuzumab, a human epidermal growth factor receptor (HER) 2 dimerization inhibitor, has demonstrated promising efficacy in combination with trastuzumab in patients with metastatic breast cancer. As HER signaling pathways are not only involved in oncogenesis, but also in myocardial homeostasis, an analysis of cardiac safety data was undertaken in a large group of patients treated with pertuzumab.
Patients and methods: A complete database of patients treated with full-dose pertuzumab was used to describe the incidence of asymptomatic left ventricular systolic dysfunction (LVSD) and symptomatic heart failure (HF).
Results: Information for 598 unique patients was available for the current analysis. Of the patients treated with pertuzumab alone ($n = 331$) or pertuzumab in combination with a non-anthracycline-containing cytotoxic ($n = 175$) or trastuzumab ($n = 93$), 23 (6.9%), 6 (3.4%), and 6 (6.5%), respectively, developed asymptomatic LVSD and 1 (0.3%), 2 (1.1%), and 1 (1.1%), respectively, displayed symptomatic HF. None of the 15 patients receiving both pertuzumab and erlotinib demonstrated LVSD.
Conclusions: Patients treated with pertuzumab experienced relatively low levels of asymptomatic LVSD or symptomatic HF. There was no notable increase in cardiac side-effects when pertuzumab was given in combination with other anticancer agents.
Key words: cardiac, combination, HER, pertuzumab, safety

introduction

Pertuzumab, the first in a new class of targeted anticancer agents known as human epidermal growth factor receptor (HER) 2 dimerization inhibitors, inhibits the ability of HER2 to pair with other HER family members [1]. Dimerization is essential for HER signaling and is required for cell growth and survival in many tumor types (Figure 1A). In addition to blocking cell signaling, pertuzumab is capable of inducing antibody-dependent cell-mediated cytotoxicity [10].

Besides their essential role in cell growth and survival, HER2 and HER4 receptors are also important for homeostatic mechanisms in the cardiac myocyte [11]. HER2 and HER4 are crucial for mouse embryonic heart development [12, 13], and it has been demonstrated in rodents that HER2 expression is required for the development of ventricular muscles and valves, while activation of HER2 promotes cardiomyocyte survival [5, 14]. Moreover, in adult rat myocardium, neuregulin signaling through HER2:HER4 heterodimers mediates synthesis and stabilization of myocardial structural proteins and attenuates myocyte death [5]. Although mice with a cardiac-restricted deletion of HER2 survive into adulthood and initially show no phenotypic abnormalities, they develop progressive cardiomyopathy with left ventricular dysfunction and dilation and are more susceptible to cardiac stress [15]. HER signaling is also thought to play an important role in the sympathovagal control systems of the heart [16, 17]. Therefore, despite the anticancer benefits offered by HER2-targeted agents, there is justified concern regarding the potential for undesirable effects on the heart.

An asymptomatic decline in left ventricular ejection fraction (LVEF), known as left ventricular systolic dysfunction (LVSD), is recognized as a potential side-effect of therapy with the HER2-targeted monoclonal antibody trastuzumab [8, 18], although symptomatic heart failure (HF) is relatively uncommon [17]. In a meta-analysis of randomized trials employing adjuvant trastuzumab in patients with HER2-positive early breast cancer, the likelihood of cardiac toxicity was 2.45-fold higher in patients receiving trastuzumab compared with those not receiving trastuzumab [19]. Most cases of LVSD are asymptomatic and normalize on withdrawal of therapy [20]. Myocardial dysfunction with anti-HER2

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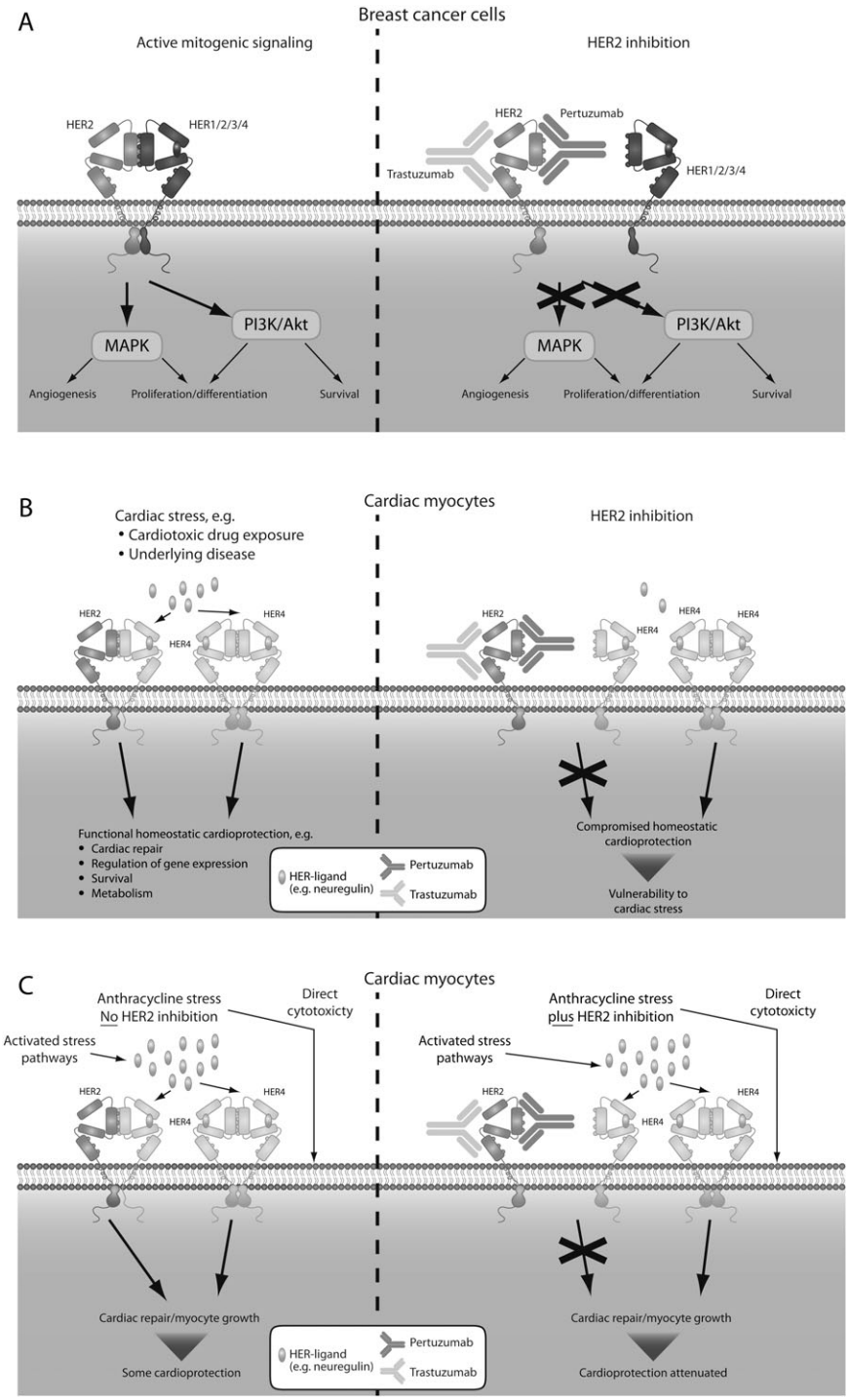

Figure 1. Human epidermal growth factor receptor (HER) 2 signaling pathways involved in tumorigenesis and cardiac survival. (A) In breast cancer cells, HER dimer formation results in cross-phosphorylation of the dimer tyrosine kinase domain and leads to the initiation of mitogenic cell signaling pathways, including activation of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt pathways [2]. While the HER2 to HER3 heterodimer is considered the most potent HER dimer with respect to strength of interaction, ligand-induced tyrosine phosphorylation, and downstream signaling, other dimer pairs do show weak mitogenic activity [3]. Blocking HER2 signaling with trastuzumab [4] or HER2 dimerization with pertuzumab [1] prevents activation of the signaling pathways that mediate cell proliferation and survival. (B) In cardiac myocytes, activation of cardiac stress pathways results in release of neuregulin that stimulates the formation of HER2:HER4 and HER4:HER4 dimers. These activate downstream signaling pathways, resulting in the promotion of cardiomyocyte growth and cardiac repair mechanisms [5–7]. However, under conditions of HER2 inhibition, the homeostatic cardioprotection afforded by the activation of these downstream pathways may be attenuated, resulting in vulnerability to cardiac stress. (C) Anthracycline exposure exerts direct cytotoxicity against cardiac myocytes, resulting in the cardiotoxic effects of these agents. Activation of the stress pathway described in panel B may afford some protection from the cytotoxic effects of anthracycline exposure. However, it is possible that HER2 inhibition in the presence of anthracycline stress may further attenuate the innate cardioprotective mechanisms by preventing the induction of HER2:HER4-mediated stimulation of cardiomyocyte growth and cardiac repair mechanisms, thus limiting the capacity for cardiac repair. Therefore, inhibition of HER2 dimerization in association with anthracycline therapy can exacerbate anthracycline-induced cardiac damage [8, 9].

therapy is thought to result primarily from a loss of tertiary organization of the contractile proteins [6], which explains the high rate of reversibility [21]. Discontinuation of trastuzumab and treatment of cardiac dysfunction with standard HF therapy may allow subsequent rechallenge with trastuzumab in selected patients [22], although not all patients recover completely, even with appropriate HF management [23, 24]. Conversely, exposure to anthracycline is associated with ultrastructural changes and LVSD that may be more permanent if not detected early and managed appropriately [25, 26]. It is likely that the underlying mechanism of anthracycline-induced cardiotoxicity is different from that resulting from anti-HER2 treatments [6]; however, the two types of cardiotoxicity are not completely independent, and anti-HER2 treatment has the potential to worsen anthracycline toxicity [6, 27]. This may be due to the inhibition by trastuzumab of the HER2:HER4 dimer-activated pathways that play a crucial role in cardiomyocyte growth and repair mechanisms during times of stress (Figure 1B and C) [8, 9, 18]. Moreover, the incidence of cardiac dysfunction is higher in patients who have had prior anthracycline treatment, a known cause of myocyte death, compared with those who have been previously treated with a taxane, suggesting that inhibition of cardiac repair mechanisms is a clinically relevant determinant of LVSD [28]. Nonetheless, in most cases, LVSD attributable to trastuzumab is recoverable with early identification and careful reassessment [22, 29, 30]. The cardiac safety of the oral small molecule HER1/HER2 inhibitor lapatinib has also been evaluated. In a pooled analysis of clinical trial data for 3689 healthy volunteers and patients with various cancers [31], the rate of adverse cardiac events was low and, events were generally reversible. A more recent study in patients with trastuzumab-refractory metastatic breast cancer (MBC) demonstrated a low level of symptomatic and asymptomatic cardiac events when lapatinib was given in combination with trastuzumab [32].

Pertuzumab has demonstrated promising efficacy in combination with trastuzumab in patients with MBC [33, 34]. In this report, we provide an exploratory but comprehensive analysis of the pertuzumab cardiac safety data currently available from the phase II clinical trials that were designed to explore the efficacy of pertuzumab as monotherapy and in combination with trastuzumab and other anticancer agents. Cardiac end points were included in these studies, facilitating an exploratory analysis of the cardiac safety of pertuzumab. The current analysis was undertaken to provide insight for clinicians and guidance for future studies.

materials and methods

The incidence of cardiac dysfunction is described from all completed and ongoing Roche and Genentech phase II studies in which full-dose pertuzumab was given as a single agent (Table 1). Data are also included from any study in which pertuzumab was combined with cytotoxic anti-epidermal growth factor receptor (EGFR) (erlotinib) or anti-HER2 (trastuzumab) therapies (Table 1), excluding ongoing studies where data analyses are yet to take place. The phase II studies were primarily designed to explore the efficacy of pertuzumab, but cardiac end points were included to assess for cardiac safety.

Cardiac exclusion criteria were similar across all studies with respect to baseline LVEF (<50%–55%) and maximum prior cumulative dose of anthracyclines (doxorubicin >360 mg/m^2, epirubicin >720 mg/m^2, mitoxantrone >120 mg/m^2, and idarubicin >90 mg/m^2) (Table 1). All patients underwent routine cardiac monitoring by echocardiography or multiple-gated acquisition scans in general every two to four cycles (Table 1).

As different definitions of LVSD and symptomatic HF were used across the studies included in the current analysis, data were reassessed to identify all patients in any study who met standardized criteria for LVSD, regardless of their cardiac status according to the original trial criteria. Asymptomatic LVSD was defined as a decrease from baseline in LVEF of ≥10 absolute percentage points to a value of <50% at any post-baseline LVEF assessment. LVEF readings were conducted and assessed by the participating study centers (local assessment) for all except one study (BO17929). For this study, central evaluations of LVEF were also conducted. HF was defined as symptomatic LVSD and was based on a decrease from baseline in LVEF of ≥10 absolute percentage points to a value of <50% at any post-baseline LVEF assessment accompanied by a physician diagnosis of a cardiac event, including any symptom plausibly associated with HF (including dyspnea, edema, and fatigue) and/or any recording of HF by an investigator.

pertuzumab as a single agent

Pertuzumab was given as a single agent in phase II studies in ovarian cancer, non-small-cell lung cancer (NSCLC), castration-resistant prostate cancer (CRPC), and MBC in which HER2 was not overexpressed [35–39]. Single-agent pertuzumab was also given to the third cohort of patients with HER2-positive MBC enrolling in the phase II BO17929 study, primarily investigating the efficacy and safety of pertuzumab plus trastuzumab [40] (Table 1). Patients included in these studies had experienced progression or recurrent disease despite previous treatment. Patients in studies TOC2689g, TOC2572g, TOC2682g, BO17004, and BO16934 had not received any prior HER2-targeted therapy [35–39], whereas those in BO17929 had progressed following trastuzumab-based chemotherapy [40, 45].

pertuzumab in combination with cytotoxic agents

Patients received pertuzumab in combination with non-anthracycline-containing cytotoxic therapy in phase I/Ib studies for various solid tumors and in phase II studies for ovarian cancer [41–44] (Table 1). Patients with advanced solid tumors were treated with pertuzumab in combination with cytotoxic agents following progression during or after standard therapy [41, 42], whereas patients with platinum-sensitive [44] or platinum-resistant [43] ovarian cancer were treated with pertuzumab plus cytotoxic agents after first-line therapy.

pertuzumab in combination with the anti-HER2 trastuzumab

Two studies have been reported in which patients with MBC who experienced disease progression during trastuzumab treatment received pertuzumab and trastuzumab together [33, 45]. In these studies, the majority of patients had also received prior anthracycline treatment. In one of these studies (BO17929), patients were stratified into one of the three treatment cohorts. Cohorts 1 and 2 received pertuzumab in combination with trastuzumab following disease progression on trastuzumab plus chemotherapy. A third patient cohort was included following a protocol amendment [40]. These patients received pertuzumab as monotherapy following disease progression on trastuzumab plus chemotherapy; if they experienced disease progression during pertuzumab monotherapy, they were switched to pertuzumab plus trastuzumab.

pertuzumab in combination with the anti-EGFR agent erlotinib

The combination of pertuzumab and erlotinib—an inhibitor of EGFR tyrosine kinase signaling—is being investigated in an ongoing study in patients with locally advanced or metastatic NSCLC that has progressed following chemotherapy [46] (Table 1).

Table 1. Overview of studies included in the analysis

Study no. (indication)	Combination partner(s)	*N*	Median age (range), years	Cardiac exclusion criteria	Key prior treatment exclusions	Cardiac monitoring (frequency and method)
Pertuzumab phase II single-agent studies						
TOC2689g [35] (ovarian), NCT00058552	None	123	57 (35–83)	LVEF <50%	HER-targeted agents; doxorubicin >360 mg/m^2 or equivalent	Before cycles 3, 5, 7, 9, 13, and 17 ECHO
TOC2572g [36] (NSCLC), NCT00063154	None	43	62 (39–77)	History of significant cardiac disease	HER-targeted agents	Before cycles 3, 5, 9, 13, and 17 ECHO
TOC2682g [37] (CRPC), NCT00058539	None	41	68 (45–81)	LVEF <50%	HER-targeted agents; doxorubicin >360 mg/m^2 or equivalent	Every four cycles, ECHO or MUGA
BO17004 [38] (CRPC)	None	68	72 (57–84)	LVEF <50%, known cardiac condition	HER-targeted agents; doxorubicin >360 mg/m^2 or equivalent	At end of cycles 2 and 4, and every four cycles thereafter, ECHO or MUGA
BO16934 [39] (HER2-negative MBC)	None	78	55 (33–78)	LVEF <50%, history of documented cardiac disease	HER-targeted agents; doxorubicin >360 mg/m^2 or equivalent	At cycles 2, 4, 8, 12, 16, and final visit, ECHO or MUGA
BO17929 cohort 3 [40] (HER2-positive MBC)	None	29	55 (38–65)	LVEF <55%, decline of LVEF to <50% with prior trastuzumab therapy, history of any cardiac AE related to trastuzumab therapy, history of congestive HF	Doxorubicin >360 mg/m^2 or equivalent	At the end of cycles 2, 4, 6, 8, and final visit, ECHO or MUGA
Pertuzumab in combination with cytotoxic agents						
BO17003 [41] (solid tumors)	Capecitabine	18	65 (39–72)	LVEF <50%	HER-targeted agents; doxorubicin >360 mg/m^2 or equivalent	Every two cycles, ECHO or MUGA
BO17021 [42] (solid tumors)	Docetaxel	17	59 (22–69)	LVEF <50%	Doxorubicin >360 mg/m^2 or equivalent	Every 6 weeks, ECHO or MUGA
TOC3258g [43] (ovarian), NCT00096993	Gemcitabine	65	58 (18–81)	LVEF <50%	HER-targeted agents; doxorubicin >360 mg/m^2 or equivalent	Every 6 weeks, ECHO or MUGA
BO17931 [44] (ovarian)	Carboplatin + gemcitabine or carboplatin + paclitaxel	75	59 (26–76)	LVEF <50%, history of NYHA ≥II HF	Any targeted therapy; doxorubicin >360 mg/m^2 or equivalent	At cycles 2, 4, and 6, and every four cycles thereafter, ECHO or MUGA

Table 1. (*Continued*)

Study no. (indication)	Combination partner(s)	*N*	Median age (range), years	Cardiac exclusion criteria	Key prior treatment exclusions	Cardiac monitoring (frequency and method)
Pertuzumab in combination with the anti-HER2 agent trastuzumab						
BO17929 cohorts 1 and 2 [45] (HER2-positive MBC)	Trastuzumab	66	55 (25–85)	LVEF < 55%, decline of LVEF to <50% with prior trastuzumab therapy, history of any cardiac AE related to trastuzumab therapy, history of HF	Doxorubicin >360 mg/m^2 or equivalent	At the end of cycles 1, 2, 4, 6, 8, and final visit, ECHO or MUGA
BO17929 cohort 3 [40] (HER2-positive MBC)[a]	Trastuzumab added following progression on pertuzumab monotherapy	16	55 (38–65)	LVEF <55%, decline of LVEF to <50% with prior trastuzumab therapy, history of any cardiac AE related to trastuzumab therapy, history of congestive HF	Doxorubicin >360 mg/m^2 or equivalent	At the end of cycles 2, 4, 6, 8, and final visit, ECHO or MUGA
TOC3487s [33], NCI-sponsored study (HER2-positive MBC)	Trastuzumab	11	53 (36–68)	LVEF <55%, clinical signs or symptoms of HF	Doxorubicin >360 mg/m^2 and/or liposomal doxorubicin	Every 3 weeks before treatment by electrocardiogram and ECHO. Cardiac MRI was carried out at baseline for patients who enrolled later in the trial and for those who had a reduction in LVEF by ECHO scan
Pertuzumab in combination with the anti-EGFR agent erlotinib						
WO20024 [46] (NSCLC)	Erlotinib	15	60 (43–78)	LVEF <50%	Agents targeting growth factors or their receptors; doxorubicin >360 mg/m^2 or equivalent	Day 15 of cycles 2, 4, and 6, and every four cycles thereafter, ECHO or MUGA

[a]These 16 patients are the subset of the total of 29 patients enrolled to cohort 3 who went on to receive trastuzumab on progression during pertuzumab monotherapy. AE, adverse event; CRPC, castration-resistant prostate cancer; ECHO, echocardiogram; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; HF, heart failure; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; MRI, magnetic resonance imaging; MUGA, multiple-gated acquisition scan; NCI, National Cancer Institute; NSCLC, non-small-cell lung cancer; NYHA, New York Heart Association.

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results

Information for 598 unique patients treated with pertuzumab alone or in combination was available for the current analysis (Table 2). Of these, 331 received pertuzumab as a single agent, 175 were treated with pertuzumab in combination with non-anthracycline-containing cytotoxic agents, 93 were treated with pertuzumab in combination with the anti-HER2 monoclonal antibody trastuzumab, and 15 were treated with pertuzumab in combination with the anti-EGFR agent erlotinib. Of the 93 patients receiving pertuzumab in combination with trastuzumab, 16 had already received pertuzumab as a single agent. The majority of patients in each of the MBC trials (>70%) had received prior anthracycline therapy (Table 2).

Exposure to pertuzumab in these clinical studies varied considerably depending upon the indication. The shortest exposures were in patients with prostate cancer (study BO17004), in whom the median treatment duration was 3 cycles, with a range of 2–11 cycles. The longest pertuzumab exposures were in patients with HER2-positive breast cancer (study BO17929). In this study, median pertuzumab exposure was 9 cycles, with a range of 1–26 cycles.

pertuzumab as a single agent

Data from 331 (231 non-breast cancer and 100 MBC) patients with available cardiac data who received pertuzumab as a single agent were included in the analysis. Studies in patients with ovarian cancer [35], NSCLC, and CRPC [36–38] demonstrated that pertuzumab was associated with a 5.6% (13/231) incidence of asymptomatic LVSD, with no documented cases of symptomatic HF. Similarly, among 100 patients with MBC and available post-baseline data who received pertuzumab [39, 40], asymptomatic LVSD occurred in 10.0% of patients (10/100) (Table 2). A single case of symptomatic HF was documented among patients treated with single-agent pertuzumab; this patient with MBC was a former smoker with hypertension and prior anthracycline therapy [39] (Table 3). Evidence of reduced LVEF was initially recorded on study day 290 after 14 cycles of pertuzumab (last dose given on day 275). The next cycle of pertuzumab was delayed by 4 weeks and was given on study day 323. An event of congestive HF was recorded on day 344 and, the patient was withdrawn from the study.

pertuzumab in combination with cytotoxic agents

Of the 175 patients treated with pertuzumab in combination with non-anthracycline-containing cytotoxic agents who had available cardiac data, a total of six patients (3.4%) developed asymptomatic LVSD. Two of these patients were being treated with pertuzumab plus docetaxel (Taxotere, sanofi-aventis, Bridgewater, NJ) for advanced solid tumors [42] and four with pertuzumab plus gemcitabine- or carboplatin-based chemotherapy for ovarian cancer [43, 44] (Table 2). In addition, two patients, both with ovarian cancer, developed symptomatic HF [43, 44]. One of these patients had no documented cardiac risk factors, whereas the other was a smoker with hypertension and hyperlipidemia (Table 3). The first of these two patients, a 41-year-old woman, was treated with pertuzumab in combination with paclitaxel (Taxol, Bristol-Myers Squibb Company, Princeton, NJ) and carboplatin. HF was recorded at cycle 2 and treatment was discontinued. The second patient, a 59-year-old female smoker with chronic obstructive pulmonary disease, hypertension, and hyperlipidemia received pertuzumab in combination with gemcitabine. A gradual decline in LVEF was noted between cycles 6 and 14 and therapy was withdrawn at cycle 15 due to HF.

pertuzumab in combination with the anti-HER2 agent trastuzumab

In total, 93 patients who received pertuzumab in combination with trastuzumab were analyzed for cardiac events. Asymptomatic LVSD was observed in six patients (6.5%), all of whom had MBC that had progressed following trastuzumab therapy [33, 45] (Table 2). In addition, one patient with MBC that had progressed after trastuzumab experienced symptomatic HF at cycle 2. This patient had extensive left chest wall disease and had been treated with left chest wall irradiation and prior anthracyclines (Table 3) [33].

Patients with refractory HER2-positive MBC that had relapsed on prior trastuzumab-containing therapy were examined in study BO17929 [45]. In this study, patients were selected for adequate cardiac function at baseline and treatment was associated with a low incidence of clinical cardiac events. Three of 66 patients (4.5%) in cohorts 1 and 2 experienced asymptomatic LVSD. No patient experienced systolic HF (Table 2), and in two patients, the asymptomatic LVSD resolved while continuing trastuzumab plus pertuzumab therapy [45]. One of 16 patients (6.3%) in cohort 3 who received pertuzumab and trastuzumab following progressive disease on pertuzumab monotherapy experienced asymptomatic LVSD (Table 2). Data from a smaller National Cancer Institute-sponsored study (TOC3487s) [33] demonstrated a higher incidence of left ventricular dysfunction, with 2 of 11 patients (18.2%) experiencing asymptomatic LVSD and 1 patient (9.1%) developing symptomatic HF (Table 2). However, in this trial, patients were not excluded if they had experienced previous trastuzumab-associated cardiac dysfunction, and cardiac monitoring was carried out more frequently than in study BO17929 (every 3 weeks versus every 6 weeks) (Table 1).

pertuzumab in combination with the anti-EGFR agent erlotinib

None of the 15 patients treated with a combination of pertuzumab and erlotinib who were assessable for cardiac toxicity demonstrated LVSD or HF (Table 2) [46].

timing of LVSD and HF events in relation to pertuzumab dosing

The median timing of LVSD and HF events was around cycle 4 (range 1–15 cycles) with 34/39 events (87%) occurring between cycles 1 and 7.

discussion

The results of this analysis demonstrate that pertuzumab (exposure ranging from a median of 3 cycles [range 2–11] to a median of 26 cycles [range 1–26]) was generally well tolerated. The incidence of LVSD was low, with most events being asymptomatic and detected at scheduled evaluations. The median timing of LVSD and HF was around cycle 4 (range 1–15)

Table 2. Incidence of asymptomatic left ventricular systolic dysfunction and symptomatic heart failure, by study

Study no. (indication)	Combination partner(s)	No. assessable for cardiac toxicity	Asymptomatic LVSD, *n* (%)	Symptomatic heart failure, *n* (%)
Pertuzumab phase II single-agent studies				
TOC2689g [35] (ovarian)	None	99	3 (3.0)	0
TOC2572g [36] (NSCLC)	None	30	1 (3.3)	0
TOC2682g [37] (HRPC)	None	38	3 (7.9)	0
BO17004 [38] (HRPC)	None	64	6 (9.4)	0
BO16934 [39] (MBC; 100% prior A)	None	71	8 (11.3)	1 (1.4)
BO17929 cohort 3 [40] (MBC progressing on trastuzumab; 72% prior A)	None	29	2 (6.9)[a]	0
Total single-agent		**331**	**23 (6.9) [95% CI 4.5–10.2]**	**1 (0.3)**
Pertuzumab in combination with cytotoxic agents				
BO17003 [41] (solid tumors)	Capecitabine	18	0	0
BO17021 [42] (solid tumors)	Docetaxel	17	2 (11.8)	0
TOC3258g [43] (ovarian)	Gemcitabine	65	2 (3.1)	1 (1.5)
BO17931 [44] (ovarian)	Carboplatin + gemcitabine or carboplatin + paclitaxel	75	2 (2.7)	1 (1.3)
Total in combination with cytotoxics		**175**	**6 (3.4) [95% CI 1.3–7.3]**	**2 (1.1)**
Pertuzumab in combination with the anti-HER2 agent trastuzumab				
TOC3487s [33], NCI-sponsored study (MBC progressing on trastuzumab; 82% prior A)	Trastuzumab	11	2 (18.2)	1 (9.1)
BO17929 cohorts 1 and 2 [45] (MBC progressing on trastuzumab; 70% prior A)	Trastuzumab	66	3 (4.5)[b]	0
BO17929 cohort 3 [40] (MBC progressing on trastuzumab; 72% prior A)	Trastuzumab (added following progression on pertuzumab monotherapy)	16	1 (6.3)	0
Total in combination with trastuzumab		**93**	**6 (6.5) [95% CI 2.4–13.5]**	**1 (1.1) [95% CI 0–5.8]**
Pertuzumab in combination with the anti-EGFR agent erlotinib				
WO20024 [46] (NSCLC)	Erlotinib	15	0	0
Total in combination with erlotinib		**15**	**0 [95% CI 0–21.8]**	**0 [95% CI 0–21.8]**
Total unique pertuzumab-treated patients[c]		598	35 (5.9) [95% CI 4.1–8.0]	4 (0.7) [95% CI 0.2–1.7]

[a]Of these, one had an LVEF decrease according to local readings only and one according to central readings only.
[b]Of these, one had an LVEF decrease according to local readings only and two according to central readings only.
[c]Sixteen patients received both pertuzumab monotherapy and pertuzumab in combination with trastuzumab. A, anthracycline; HER, human epidermal growth factor receptor; HRPC, hormone-resistant prostate cancer; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MBC, metastatic breast cancer; NCI, National Cancer Institute; NSCLC, non-small-cell lung cancer.

with 34/39 (87%) events occurring between cycles 1 and 7. Additionally, when pertuzumab was given in combination with trastuzumab or non-anthracycline-containing cytotoxic chemotherapy, there was no marked increase in observed cardiac dysfunction. In this analysis of 598 unique patients exposed to pertuzumab, 35 (5.9%) cases of asymptomatic LVSD and 4 (0.7%) cases of symptomatic HF were reported. There have been several recent publications examining HF rates among breast cancer patients receiving trastuzumab as adjuvant therapy as well as in patients with more advanced MBC [24, 30, 47]. In two studies, patients received trastuzumab in the adjuvant setting [30, 47]. In the first of these, Perez et al. [30] recorded an HF rate of 2.8% for patients with primary, operable HER2-positive breast cancer treated with paclitaxel followed by trastuzumab, and 3.3% for those treated with paclitaxel plus trastuzumab followed by trastuzumab alone. More recently, Russell et al. [47] reported a symptomatic HF rate of 2.0% for 133 patients receiving adjuvant trastuzumab therapy. In a study designed to evaluate the role of troponin I in predicting cardiac damage, Cardinale et al. [24] reported that among 251 women receiving treatment for early and advanced breast cancer with trastuzumab, 42 (16.7%) experienced trastuzumab-induced cardiotoxicity. In all three studies, whether patients were receiving adjuvant treatment or therapy for metastatic cancer, patients were selected on the basis of good

Table 3. Characterization of pertuzumab-treated patients experiencing symptomatic heart failure (all studies)

Study no. (indication)	Age, years/ gender	Treatment	Event term	LVEF (baseline/ nadir), %	Relevant medical history	Prior anthracyclines	Outcome
BO16934 [39] (MBC)	54/F	Pertuzumab	Systolic HF	55/30	Former smoker, hypertension	Yes	Pertuzumab discontinued. Improved with standard cardiac treatment
BO17931 [44] (ovarian)	41/F	Pertuzumab + paclitaxel/ carboplatin	Systolic HF	72/25	None	No	Pertuzumab discontinued
TOC3258g [43] (ovarian)	59/F	Pertuzumab + gemcitabine	Life-threatening systolic HF (3 episodes, with pulmonary edema)	76/32	Smoker, COPD with emphysema, hypertension, hyperlipidemia	No	Pertuzumab discontinued
TOC3487s [33] (NCI-sponsored MBC)	54/F	Pertuzumab + trastuzumab	Systolic HF	60/26	Former smoker, extensive involvement of the chest wall by recurrent breast cancer, left chest wall irradiation	Yes	Pertuzumab discontinued. Patient died of progressive disease, with HF

COPD, chronic obstructive pulmonary disease; F, female; HF, heart failure; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; NCI, National Cancer Institute.

performance status, adequate cardiac function (as indicated by baseline LVEF), and other indicators of physiological status, including adequate liver and bone marrow function and absence of significant medical history. Patients on these studies were, therefore, of broadly similar physiological status. Probably the major difference between these populations of patients receiving trastuzumab and, indeed, between these trastuzumab patients and those described in the current analysis who were treated with pertuzumab, however, is the difference in timing between the anthracycline and anti-HER2 therapies they received. Those patients receiving adjuvant therapy were more likely to have had recent exposure to anthracycline, whereas in those being treated for MBC, substantial periods of time (up to several years) may have elapsed since anthracycline exposure, and this should be considered when making comparisons between studies.

In one small study investigating pertuzumab plus trastuzumab in MBC progressing after trastuzumab-containing therapy [33], a higher rate of cardiac events was recorded than in any of the other studies. The reasons for this are unclear but may be a result of the lack of screening for adequate cardiac function during prior treatment with trastuzumab, closer monitoring, using a variety of monitoring methods, and a more stringent definition of LVSD (a decrease in LVEF of ≤55% from baseline).

It is likely that the careful selection of patients lacking cardiac comorbidities may contribute to the low rate of cardiac events observed in studies where pertuzumab and trastuzumab are combined. In study BO17929, patients were excluded if they had experienced LVEF declines during previous trastuzumab therapy [45], and in ongoing phase II and III breast cancer studies [NEOSPHERE (NCT00545688) and CLEOPATRA (NCT00567190), respectively], patients are excluded if they have any relevant cardiac history (including HF), uncontrolled hypertension, or poorly controlled diabetes mellitus. Furthermore, in these studies, patients must have a limited lifetime exposure to anthracyclines below 360 mg/m^2 for doxorubicin or liposomal doxorubicin or equivalent dosing for epirubicin, mitoxantrone, and idarubicin. It is anticipated that data from the CLEOPATRA study, which has a planned enrollment of 800 patients, will provide further insights into the safety profile of pertuzumab in combination with trastuzumab. It should also be noted that the presence of HER2-positive breast cancer tends to be skewed toward younger patients, who are less likely to have cardiovascular problems [48].

It is possible that pertuzumab may appear to have a relatively low cardiotoxic potential due to the timing of anthracycline and pertuzumab treatment. In the adjuvant trastuzumab trials, a shorter time between anthracycline and trastuzumab treatment appeared to bear a higher risk of trastuzumab-associated cardiotoxicity [8]. Due to the design of the studies in this analysis, the time between anthracycline and pertuzumab treatment was generally long—in most cases, several months or years. In the adjuvant trastuzumab trials, most patients received the first dose of trastuzumab between 3 and 12 weeks after the end of anthracycline-based therapy [33, 40, 45].

implications for use of anti-HER2 therapies

The results of this analysis indicate that pertuzumab has the potential to induce cardiac dysfunction and HF, although it is currently difficult to assess whether the rate is similar to that of

trastuzumab. The results also highlight that it is vital for physicians to examine the full medical history of patients before they receive anti-HER2 therapies, to identify potential risk factors for cardiac dysfunction, and an LVEF assessment before chemotherapy to identify patients at higher risk of anti-HER2 cardiotoxicity [49, 50]. Cardiac status should be optimized before treatment with anti-HER2 therapies, and the potential benefits of treatment should be balanced against any potential cardiac risk [51]. Recent preliminary evidence suggests that the preventative use of angiotensin-converting enzyme inhibitors in high-risk patients receiving high-dose chemotherapy (identified by elevations in troponin I cardiac markers) may prevent cardiac dysfunction with anti-HER2 therapy [51].

In the current analysis, most patients with breast cancer had received prior anthracycline therapy, but the majority of this exposure occurred early in the course of the disease (as either neoadjuvant or adjuvant therapy), and no patient had been exposed to anthracyclines beyond the established limits of lifetime exposure. A study [TRYPHAENA (NCT00976989)] is ongoing to evaluate the safety and efficacy of combined treatment of HER2-positive breast cancer with trastuzumab, pertuzumab, and epirubicin in the neoadjuvant setting.

In summary, as a single agent or in combination with cytotoxic agents, including trastuzumab, pertuzumab has been generally well tolerated by patients enrolled in the ongoing clinical trial program, with a low incidence of cardiac dysfunction, apparently similar to that associated with trastuzumab. Nonetheless, it is important that cardiac risk factors are taken into account when making a decision regarding treatment with pertuzumab.

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