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Breast Cancer

Efficacy and Safety of Pertuzumab and Trastuzumab Administered in a Single Infusion Bag, Followed by Vinorelbine: VELVET Cohort 2 Final Results

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Trastuzumab • Pertuzumab • Vinorelbine • Metastatic breast cancer • HER2-positive

Abstract

Background. VELVET Cohort 1 demonstrated the applicability of pertuzumab, trastuzumab, and vinorelbine as an alternative first-line treatment regimen for patients with HER2-positive locally advanced or metastatic breast cancer (MBC) who cannot receive docetaxel. Co-infusion of pertuzumab and trastuzumab may reduce clinic time and medical resource utilization. We report results from Cohort 2, in which pertuzumab and trastuzumab were co-infused, followed by vinorelbine.

Patients and Methods. During cycle 1, patients with HER2-positive locally advanced or MBC received loading doses of pertuzumab (840 mg) and trastuzumab (8 mg/kg) on consecutive days, followed by vinorelbine (25 mg/m^2) on days two and nine. From cycle 2 onwards, patients received a co-infusion of pertuzumab (420 mg) and trastuzumab (6 mg/kg) on day one, followed by vinorelbine (30–35 mg/m^2) on days one and eight (or days two and nine). The primary endpoint was objective response rate (ORR) in patients with measurable disease. Secondary endpoints included progression-free survival (PFS) and safety.

Results. Cohort 2 enrolled 107 patients. The ORR was 63.7% (95% confidence interval [CI] 53.0–73.6) in patients with measurable disease (91/107; 85.0%). Median PFS was 11.5 months (95% CI 10.3–15.8). The most common adverse events [AEs] were diarrhea (57.9%), neutropenia (57.0%), and nausea (41.1%). Grade $\geq$3 AEs occurred in 85 patients (79.4%) and serious AEs in 44 patients (41.1%). Eighteen patients (16.8%) had AEs suggestive of congestive heart failure.

Conclusion. These results support the feasibility of pertuzumab and trastuzumab co-infusion from a safety perspective and support Cohort 1 conclusions that vinorelbine offers an alternative chemotherapy companion for pertuzumab and trastuzumab. ***The Oncologist*** 2017;22:1160–1168

Implications for Practice: Combined treatment with pertuzumab, trastuzumab, and docetaxel is the standard of care for first-line HER2-positive metastatic breast cancer. However, some patients cannot, or choose not to, receive docetaxel. VELVET Cohort 2 results support the results from Cohort 1 that suggest that pertuzumab plus trastuzumab and vinorelbine is a suitable alternative for these patients. In addition to this, results from Cohort 2 support the feasibility of administering pertuzumab and trastuzumab together in a single infusion bag, which has the potential to offer greater patient convenience and reduce active health care professional time and medical resource utilization compared with administering them separately.

Introduction

The combination of pertuzumab, trastuzumab, and docetaxel is the standard of care for first-line HER2-positive metastatic breast cancer [1–3], based on the results of the pivotal Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study [4, 5]. Currently, all three drugs are administered separately. Co-infusion of drugs would potentially reduce clinic time for patients through reduced patient chair time and reduced post-infusion observation time. In addition to patient benefits, co-infusion may also reduce active health care professional time, medical resource utilization per patient, and increase patient flow through the clinic.

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While several small-molecule drugs, including chemotherapy drugs, are routinely co-infused in single infusion bags (based on supportive stability and compatibility data), little is known about the feasibility of administering multidrug combinations containing monoclonal antibodies (mAbs) [6]. Biophysical and analytical assays have demonstrated the physical and chemical stability of an admixture of pertuzumab and trastuzumab in a single infusion bag; no measurable changes in the admixture occurred for up to 24 hours at 5°C or 30°C [6].

The VELVET study was designed to explore the efficacy and safety of vinorelbine as a chemotherapy partner for pertuzumab and trastuzumab for the first-line treatment of HER2-positive locally advanced or metastatic breast cancer. In addition, VELVET is the first study to prospectively investigate the feasibility of co-infusing the two mAbs in the same infusion bag with the aim of improving convenience for patients.

VELVET used a two-cohort study design; results for Cohort 1, in which pertuzumab and trastuzumab were administered separately, followed by vinorelbine, were reported recently [7]. VELVET Cohort 1 showed that vinorelbine is an active and reasonably well-tolerated chemotherapy partner (no new or unexpected safety signals) for pertuzumab and trastuzumab for the first-line treatment of patients with HER2-positive metastatic breast cancer and offers an alternative for patients who cannot, or choose not to, receive docetaxel in this setting [7]. Here we report the final efficacy and safety results for VELVET Cohort 2, in which the co-infusion of pertuzumab and trastuzumab in a single infusion bag, followed by vinorelbine, was investigated.

Subjects, Materials, and Methods

Eligibility Criteria

Patients were ≥18 years old with HER2-positive locally advanced (not amenable to curative resection) or metastatic breast cancer. HER2-positivity was defined as immunohistochemistry (IHC) 3+ or *HER2* gene amplification by in situ hybridization (*HER2*:chromosome 17 ratio of ≥2) and was assessed by local laboratories on primary or metastatic tumor samples with subsequent central analysis (Targos Molecular Pathology GmbH, Kassel, Germany; central results were not required prior to study enrollment). All patients had at least one measurable lesion and/or nonmeasurable disease evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a left ventricular ejection fraction (LVEF) of at least 55% at baseline, and a life expectancy of at least 12 weeks were also required for enrollment. Patients were excluded if they had received prior systemic nonhormonal anticancer therapy in the metastatic or locally advanced setting, although up to two lines of hormonal therapy, one of which could have been in combination with everolimus, were permitted. Other exclusion criteria were prior breast cancer treatment with anti-HER2 drugs, except trastuzumab and/or lapatinib in the neoadjuvant or adjuvant setting, disease progression while receiving neoadjuvant or adjuvant trastuzumab and/or lapatinib, a disease-free interval of <6 months from completion of neoadjuvant or adjuvant nonhormonal therapy to time of disease recurrence, uncontrolled central nervous system metastases, and uncontrolled hypertension or clinically significant cardiovascular disease.

Study Design

VELVET was a two-cohort, open-label, multicenter, phase II, proof-of-concept trial evaluating the safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for the first-line treatment of HER2-positive locally advanced or metastatic breast cancer (NCT01565083). In Cohort 1, patients received PERJETA® (pertuzumab; F. Hoffmann-La Roche Ltd, Basel, Switzerland, www.roche.com) and Herceptin® (trastuzumab; F. Hoffmann-La Roche Ltd, www.roche.com), administered sequentially in separate infusion bags, followed by Bendarelbin (vinorelbine; Bendalis GmbH, Oberhaching, Germany). In Cohort 2, patients received pertuzumab and trastuzumab co-infused in a single saline infusion bag (from cycle 2 onwards), followed by vinorelbine (supplemental online Fig. 1). In Cohort 2, for co-infusion of the mAbs, pharmacists were required to adhere to strict study guidelines on dose preparation to ensure that the products were stable in the final compounded sterile preparation. Cohort 2 began enrolling after Cohort 1 was fully enrolled.

All study drugs were given intravenously on a 3-week schedule. During cycle 1, patients received 840 mg pertuzumab (loading dose) on day one followed by 8 mg/kg trastuzumab (loading dose) on day two, and 25 mg/m^2 of vinorelbine on days two and nine. From cycle 2 onwards, patients in Cohort 2 received 420 mg of pertuzumab (maintenance dose) and 6 mg/kg of trastuzumab (maintenance dose) in a single infusion bag on day one, followed by 30–35 mg/m^2 of vinorelbine on days one and eight (or days two and nine). Vinorelbine was administered in line with product labeling. The planned infusion and observation times for concomitant (Cohort 2) versus sequential infusion (Cohort 1) of pertuzumab and trastuzumab are shown in Figure 1.

Study drugs were given until investigator-assessed disease progression, unacceptable toxicity, withdrawal of consent, predefined study end, or death. If vinorelbine was discontinued, antibody therapy was allowed to be continued; if antibody therapy was discontinued, vinorelbine was allowed to be continued. Dose reductions were not permitted for pertuzumab or trastuzumab. For any grade 3–4 toxicities related to vinorelbine, treatment was delayed until toxicity improved to grade 1, after which the dose was reduced to 80%. In the event of elevated bilirubin (>2× the upper limit of normal) or transaminases (>3× the upper limit of normal), the dose of vinorelbine was reduced to 50% [8]. An independent data monitoring committee conducted safety reviews throughout the study. The final review occurred in March 2015.

VELVET was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki. Approval for the protocol and for any modifications was obtained from independent ethics committees/institutional review boards at each participating site. Written informed consent was obtained from each participant.

Assessments

Tumor response was evaluated according to RECIST v1.1; assessments were performed at baseline, every three cycles up to 36 months, and then every six cycles until disease progression. ECOG performance status was assessed at baseline, every three cycles, and 28 days after treatment discontinuation. LVEF was assessed by echocardiography (ECHO) or multigated acquisition (MUGA) scan during screening and every three cycles. Computed tomography or magnetic resonance imaging brain

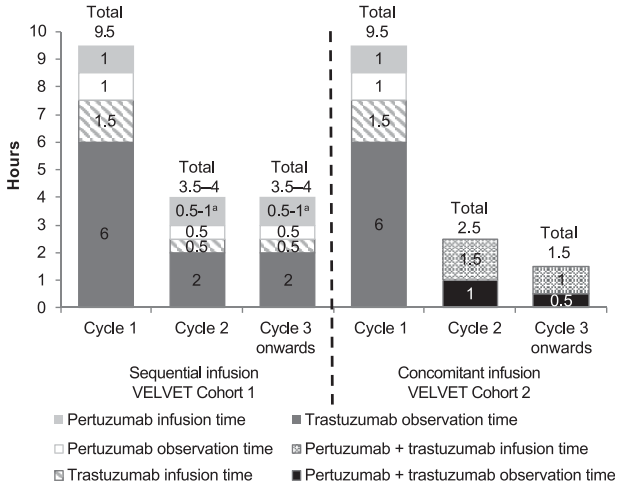

Figure 1. Planned maximum infusion times for combined versus sequential pertuzumab and trastuzumab infusion. Pertuzumab and trastuzumab were given as sequential infusions in cycle 1 of Cohort 1 and Cohort 2. In Cohort 1, pertuzumab and trastuzumab were given as sequential infusions from cycle 2 onwards; in Cohort 2, pertuzumab and trastuzumab were given as a co-infusion from cycle 2 onwards. [a]Pertuzumab time was 0.5–1 hour; maximum time is shown [15–17].

scans were performed during the screening period only in patients with clinical suspicion of brain metastases and during the study if clinically indicated. Blood counts and laboratory parameters were assessed at baseline, every cycle, and 28 days after treatment discontinuation. Adverse events (AEs) and serious AEs (SAEs) were monitored continuously until 28 days after treatment discontinuation. Study-related SAEs were collected until resolved. The AEs were graded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Study Endpoints

The primary endpoint was investigator-assessed objective response rate (ORR) according to RECIST v1.1 in patients with measurable disease (target lesion[s] present) at baseline, and was based on the best overall response (BOR), defined as the best response recorded from the start of study treatment until disease progression/recurrence or death. Patients required two consecutive assessments (at least 28 days apart) of partial response or complete response to be defined a responder. Secondary endpoints included time to response, duration of response (in responders), progression-free survival (PFS; defined as the time from first intake of any study treatment until the first radiographically documented progression of disease or death from any cause), time to progression (TTP; defined as the time from first intake of any study treatment until the first radiographically documented progression of disease or death due to progressive disease only), overall survival (OS; defined as the time from first intake of any study treatment to the date of death, regardless of the cause), safety and tolerability, and quality of life (not reported here). Safety analyses included the incidence and severity of AEs and SAEs, the incidence of congestive heart failure, changes in LVEF from baseline during the study, and laboratory test abnormalities.

Table 1. Baseline characteristics (intent-to-treat population)

Characteristic	Cohort 2: Pertuzumab and trastuzumab followed by vinorelbine $N = 107$
Median age, yr (range)	56 (21–90)
Gender	
Female, *n* (%)	106 (99.1)
Male, *n* (%)	1 (0.9)
Geographic region	
Europe, *n* (%)	63 (58.9)
North America, *n* (%)	12 (11.2)
South America (Brazil), *n* (%)	32 (29.9)
ECOG performance status	
0, *n* (%)	78 (72.9)
1, *n* (%)	29 (27.1)
Disease type at screening	
Visceral, *n* (%)	66 (61.7)
Nonvisceral, *n* (%)	41 (38.3)
Disease stage at initial diagnosis	
I, *n* (%)	14 (13.1)
II, *n* (%)	28 (26.2)
III, *n* (%)	39 (36.4)
IV, *n* (%)	26 (24.3)
Breast cancer diagnosis at study entry	
Locally advanced, *n* (%)	19 (17.8)
Metastatic, *n* (%)	88 (82.2)
Hormone receptor status	
Estrogen and/or progesterone receptor-positive, *n* (%)	64 (59.8)
Estrogen and progesterone receptor-negative, *n* (%)	43 (40.2)
HER2 status, local assessment	
Immunohistochemistry	
0 or 1+, *n* (%)	1 (0.9)
2+, *n* (%)	12 (11.2)
3+, *n* (%)	92 (86.0)
Not performed, *n* (%)	2 (1.9)
In situ hybridization	
Positive, *n* (%)	18 (16.8)
Negative, *n*	0
Not performed, *n* (%)	88 (82.2)
Missing, *n* (%)	1 (0.9)
Prior (neo)adjuvant systemic nonhormonal cancer therapy, *n* (%)	46 (43.0)
Chemotherapy, *n* (%)	35 (32.7)
Taxane[a], *n* (%)	23 (21.5)
Anthracycline[b], *n* (%)	31 (29.0)
Trastuzumab, *n* (%)	19 (17.8)

[a]Paclitaxel, docetaxel, nab-paclitaxel, or taxane (not otherwise specified).
[b]Epirubicin, doxorubicin, mitoxantrone, or anthracycline (not otherwise specified).
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

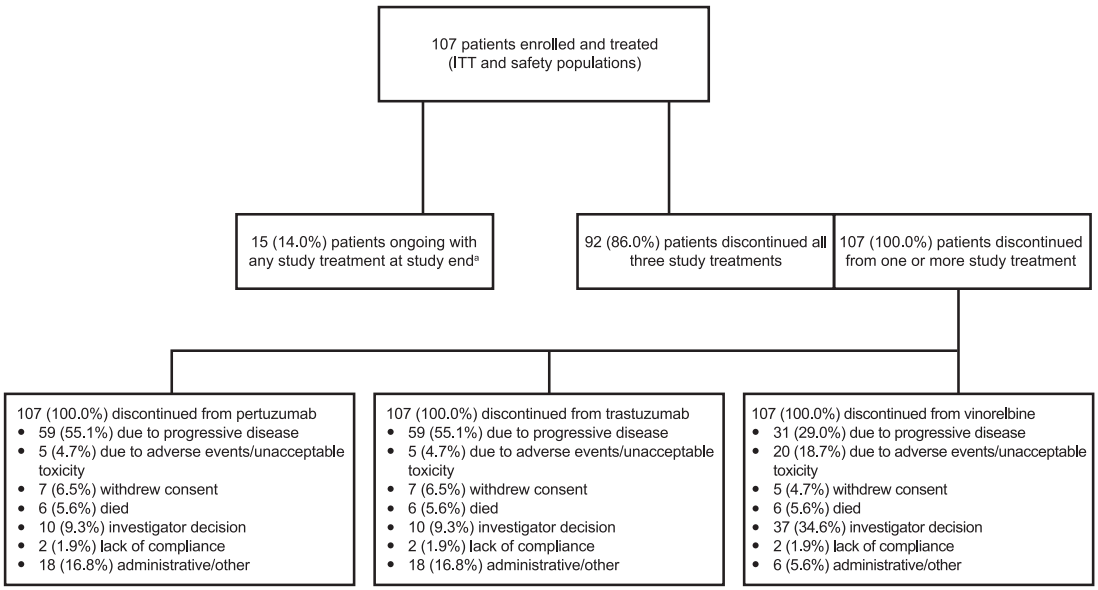

Figure 2. VELVET Cohort 2 study profile. [a]The 15 patients ongoing with any study treatment at time of study closure are also counted under administrative/other reasons.
Abbreviation: ITT, intent-to-treat.

Statistical Analysis

Assuming a preferable BOR rate of 70%–80% in each cohort (based on published data [4]), and aiming at a distance from the estimated proportion to the confidence interval (CI) limits of 8%–11%, 95 evaluable patients were required for each cohort. The observed BOR of 70% could be estimated to be between 59%–79% with a probability of 95% (Clopper–Pearson exact CIs), while the observed BOR of 80% could be estimated to be between 71%–88%. Adjusting for a withdrawal rate of approximately 10%, it was planned to enroll 105 patients in each cohort (calculated using analytic software [SAS, version 9.2, SAS, Cary, NC, https://www.sas.com/en_gb/home.html; nQuery, version 6, Statistical Solutions Ltd., Boston, USA, www.statsols.com]). The median time on study was estimated using the reverse censoring Kaplan–Meier method. Efficacy analyses were performed in the intent-to-treat (ITT) population (all enrolled patients) at study end (when all patients had been followed up with for at least 2 years after the last patient had enrolled, unless they were lost to follow-up, withdrew consent, or died). The BOR, PFS, and OS analyses were also conducted for the per-protocol population (all ITT patients who had received at least one dose of any study treatment and had at least one postbaseline tumor assessment with no major protocol deviations leading to exclusion from the per-protocol population). The ORR was summarized by the number and percentage of responders, together with two-sided 95% Clopper–Pearson CIs in patients with measurable disease at baseline. Secondary efficacy endpoints were estimated using the Kaplan–Meier approach. Predefined exploratory subgroup analyses were performed for ORR and PFS, according to prior trastuzumab treatment and by hormone receptor status. AEs were evaluated in the safety population (all patients who received at least one dose of any study treatment). All analyses presented are descriptive. VELVET Cohorts 1 and 2 were not intended to be formally compared, due to the nonrandomized nature of the study and imbalanced baseline characteristics; their data have therefore been published separately [7]. A pertuzumab extension study (NCT02320435) opened in February 2015 to provide continued access to pertuzumab for patients still benefiting from study treatment at the end of the study; this will collect long-term safety data.

Results

Study Population

Between April and September 2013, 107 patients were enrolled into Cohort 2 at 44 centers across Europe, North America, and South America (Brazil). All patients were included in the ITT and safety populations; 73 (68.2%) were included in the per-protocol population. Baseline characteristics are shown in Table 1; 58.9% of patients were from Europe, 29.9% from South America (Brazil), and 11.2% from North America. The majority of patients (82.2%) had metastatic disease, 59.8% had hormone receptor positive disease, and 43.0% had received prior nonhormonal systemic cancer therapy for early breast cancer (chemotherapy [32.7%] and/or trastuzumab [17.8%]). The cutoff date for data collection and the study end for Cohort 2 was November 13, 2015.

Treatment Summary

The median time on study was 26.5 months (95% CI 25.6–26.9). The median number of treatment cycles received was 15 (range 2–39) for pertuzumab, 15 (range 2–39) for trastuzumab, and 9 (range 2–39) for vinorelbine. One patient did not receive vinorelbine at cycle 1. The median vinorelbine dose intensity during the first six cycles was 17.34 mg/m^2 per week (range 8.4–21.3). Ninety-two (86.0%) patients discontinued all study treatment; the remaining 15 (14.0%) were still receiving at least one study treatment at the time of study closure. Progressive disease was the main reason for permanent discontinuation of all study treatment (Fig. 2).

Efficacy

In the 91 patients (85.0%) with measurable disease at baseline, investigator-assessed ORR was 63.7% (58/91 patients; 95% CI

Table 2. Investigator-assessed BOR and PFS for all patients and for predefined subgroup analyses stratified by prior trastuzumab treatment and hormone receptor status (intent-to-treat population)

	Cohort 2: Pertuzumab and trastuzumab followed by vinorelbine				
		History of prior trastuzumab therapy subgroups		Hormone receptor status subgroups	
	All patients *N* = 107	Prior trastuzumab therapy *n* = 19	No prior trastuzumab therapy *n* = 88	ER-positive or PR-positive *n* = 64	ER-negative and PR-negative *n* = 43
BOR					
Patients with measurable disease at baseline	91 (85.0)	16 (84.2)	75 (85.2)	52 (81.3)	39 (90.7)
Overall response rate	58 (63.7) [53.0–73.6]	6 (37.5) [15.2–64.6]	52 (69.3) [57.6–79.5]	31 (59.6) [45.1–73.0]	27 (69.2) [52.4–83.0]
Complete response	7 (7.7) [3.1–15.2]	3 (18.8) [4.0–45.6]	4 (5.3) [1.5–13.1]	2 (3.8) [0.5–13.2]	5 (12.8) [4.3–27.4]
Partial response	51 (56.0) [45.2–66.4]	3 (18.8) [4.0–45.6]	48 (64.0) [52.1–74.8]	29 (55.8) [41.3–69.5]	22 (56.4) [39.6–72.2]
Stable disease	27 (29.7) [20.5–40.2]	8 (50.0) [24.7–75.3]	19 (25.3) [16.0–36.7]	17 (32.7) [20.3–47.1]	10 (25.6) [13.0–42.1]
PFS					
Median, months (95% CI)	11.5 (10.3–15.8)	10.4 (6.8–19.0)	12.8 (10.3–17.1)	11.3 (9.8–15.0)	13.5 (9.6–26.9)
Number of patients with events	72 (67.3)	13 (68.4)	59 (67.0)	45 (70.3)	27 (62.8)

Data are presented as *n* (%) and [95% CI] unless noted otherwise.
BOR was assessed only in patients with measurable disease at baseline. PFS was assessed in the intent-to-treat population. Two patients (1.9%) had a missing progesterone receptor status and were considered as having a negative status.
Abbreviations: BOR, best overall response; CI, confidence interval; ER, estrogen receptor; PFS, progression-free survival; PR, progesterone receptor.

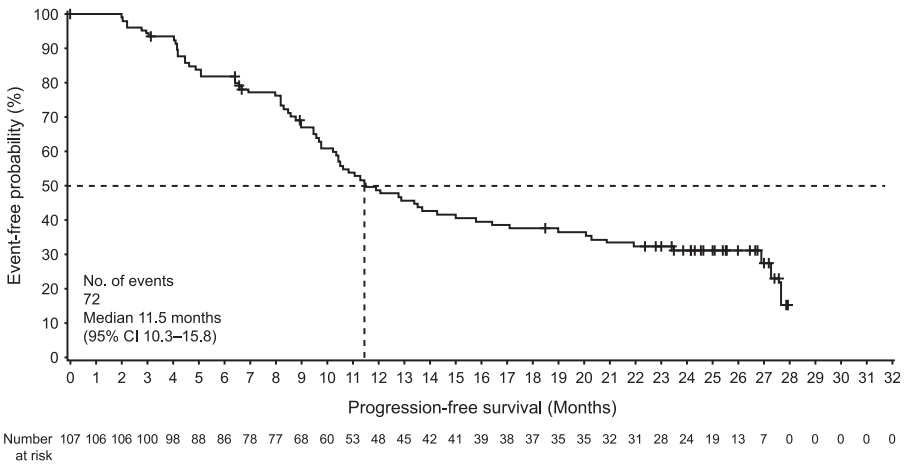

Figure 3. Progression-free survival (intent-to-treat population).
Abbreviation: CI, confidence interval.

53.0–73.6) with seven (7.7%) complete and 51 (56.0%) partial responses observed (Table 2). The median time to response for all 91 patients was 2.2 months (95% CI 2.1–4.4). The median duration of response in responders (58/91 patients) was 11.8 months (95% CI 7.5–17.9; supplemental online Fig. 2). At study end, 72 patients (67.3%) had progressed or died and the median PFS was 11.5 months (95% CI 10.3–15.8; Table 2; Fig. 3). The median TTP was 12.8 months (95% CI 10.4–17.1). Median OS was not reached by study end (data not shown), at which time 23 (21.5%) patients had died and 84 (78.5%) were censored. Per-protocol analyses for BOR, PFS, and OS were in line with the ITT analyses (data not shown).

Exploratory Analyses

In predefined exploratory subgroup analyses, a higher ORR and a longer median PFS were observed in trastuzumab-naïve patients compared with patients with prior trastuzumab treatment, and in patients with hormone receptor negative disease compared with patients with hormone receptor positive disease (Table 2). However, results should be interpreted with caution due to the small numbers of patients in subgroups and the noncomparative nature of the analysis.

The ORR and PFS were also assessed in a post hoc exploratory manner according to centrally assessed HER2 status. Seventy-four of 107 patients (69.2%) had HER2-positive disease

(of whom 67 [90.5%] were scored IHC 3+) and 15 (14.0%) were found to have HER2-negative disease by central assessment. The remaining 18 patients (16.8%) did not undergo central assessment for HER2-positivity. In the centrally confirmed HER2-positive patients with measurable disease at baseline (67 of 74; 90.5%), the ORR was 71.6% (48 of 67 patients; 95% CI 59.3–82.0) and the median PFS was 12.9 months (95% CI 9.8–21.9). In the IHC 3+ subgroup of patients with measurable disease at baseline (60 of 67; 89.6%), the ORR was 71.7% (43 of 60 patients; 95% CI 58.6–82.5). The median PFS in this subgroup was 15.8 months (95% CI 9.8–26.9).

Safety

All 107 patients were included in the safety population. AEs were reported in 106 patients (99.1%). The most frequently reported AEs were diarrhea (57.9%), neutropenia (57.0%), nausea (41.1%), fatigue (38.3%), and constipation (32.7%). AEs of any grade with an incidence of ≥20% are shown in Table 3. Grade ≥3 AEs were reported in 85 patients (79.4%; Table 3); neutropenia (31.8%) and hypertension (14.0%) were most commonly reported. Granulocyte-colony stimulating factor was administered concomitantly in 19 (17.8%) patients for neutropenia management. SAEs were experienced by 44 patients (41.1%), with pyrexia (5.6%), pneumonia (3.7%), neutropenia (2.8%), and febrile neutropenia (2.8%) reported in more than two patients (Table 3). Of note, the proportion of patients with an AE of hypertension was higher in South America (Brazil) than in Europe or North America (any grade: 43.8% vs. 22.2% vs. 25.0%; grade 3: 34.4% vs. 4.8% vs. 8.3%).

AEs were considered related to treatment in 81 patients (75.7%) treated with pertuzumab, 82 patients (76.6%) treated with trastuzumab, and 105 patients (98.1%) treated with vinorelbine. AEs led to study drug interruption in 85 patients (79.4%) and discontinuation in 25 patients (23.4%). The most commonly discontinued drug was vinorelbine, which was discontinued in 23 patients (21.5%), while pertuzumab and trastuzumab were discontinued in nine patients (8.4%) each. Of the 25 patients who discontinued study treatment, six (5.6%) discontinued due to neutropenia, two (1.9%) due to general physical health deterioration, two (1.9%) due to peripheral neuropathy, and 15 (14.0%) due to other AEs.

The incidence of cardiac AEs of all grades was 17.8% (19 patients) and of grade ≥3 AEs was 4.7% (five patients; one grade 3 cardiac failure [0.9%], two grade 3 left ventricular dysfunction [1.9%], one grade 3 tachycardia [0.9%], and one grade 4 supraventricular tachycardia [0.9%]). Additionally, ten patients (9.3%) had nonserious AEs, which were not reported as cardiac disorders but were classified as being suggestive of congestive heart failure according to Standardised MedDRA Queries; the majority had peripheral edema and two patients experienced Grade 2 decreased ejection fraction. During study treatment, the worst LVEF value of most patients (91.6%) remained >50% (supplemental online Table 1). Significant declines in LVEF (defined as a decline of ≥10% points from baseline to 50%–45%, in accordance with the study protocol) were observed in four patients (3.7%), with an additional two patients (1.9%) experiencing a decline to <45% (supplemental online Table 1). To make these findings comparable to the results of other pivotal studies, including CLEOPATRA, the incidence of LVEF declines by ≥10% points from baseline to <50% was also analyzed ($n = 4$ patients, 3.7%); the findings were expectedly consistent with prior data.

Table 3. AEs, grade ≥3 AEs (based on AEs of any grade with an incidence of ≥20%), and SAEs (based on SAEs of any grade with an incidence of >1 patient) (safety population)

	Cohort 2: Pertuzumab and trastuzumab followed by vinorelbine $N = 107$	
	Any grade	**Grade ≥3**
AE	106 (99.1)	85 (79.4)
Diarrhea	62 (57.9)	7 (6.5)
Neutropenia	61 (57.0)	34 (31.8)
Nausea	44 (41.1)	3 (2.8)
Fatigue	41 (38.3)	5 (4.7)
Constipation	35 (32.7)	1 (0.9)
Hypertension	31 (29.0)	15 (14.0)
Asthenia	29 (27.1)	3 (2.8)
Pain in extremity	29 (27.1)	0
Alopecia	28 (26.2)	0
Muscle spasms	28 (26.2)	0
Pyrexia	28 (26.2)	0
Back pain	27 (25.2)	0
Headache	27 (25.2)	0
Dyspnea	26 (24.3)	6 (5.6)
Mucosal inflammation	26 (24.3)	3 (2.8)
Stomatitis	26 (24.3)	2 (1.9)
Vomiting	25 (23.4)	0
Cough	24 (22.4)	0
Decreased appetite	24 (22.4)	0
Peripheral neuropathy	23 (21.5)	2 (1.9)
Upper abdominal pain	22 (20.6)	1 (0.9)
Eye disorders	22 (20.6)	2 (1.9)
Decreased weight	22 (20.6)	0
SAE	44 (41.4)	32 (29.9)
Pyrexia	6 (5.6)	0
Pneumonia[a]	4 (3.7)	3 (2.8)
Neutropenia	3 (2.8)	3 (2.8)
Febrile neutropenia	3 (2.8)	3 (2.8)
Device-related infection	2 (1.9)	2 (1.9)
Intestinal obstruction[a]	2 (1.9)	2 (1.9)
Nausea	2 (1.9)	2 (1.9)
Pleural effusion	2 (1.9)	2 (1.9)
Pulmonary embolism	2 (1.9)	2 (1.9)

Data are presented as *n* (%).
[a]Fatal AEs: pneumonia (three patients), intestinal obstruction (one patient). Other fatal AEs were meningitis (one patient) and septic shock (one patient).
Abbreviations: AE, adverse event; SAE, serious adverse event.

Twenty-three patients (21.5%) died during the study; most deaths (14.0%, 15 patients) were due to disease progression, with six deaths (5.6%) resulting from AEs while on treatment (three from pneumonia, one from intestinal obstruction, one

from meningitis, and one from septic shock). For two deaths (1.9%), the cause was not reported.

Anticancer Therapies After Discontinuation of Study Treatment

Seventy-six of 107 patients (71.0%) received anticancer therapies after the discontinuation of study treatment (supplemental online Table 2); trastuzumab was received by 45 patients (59.2%) and pertuzumab by 20 patients (26.3%).

Discussion

Changes in drug formulation and/or administration methods have the potential to improve convenience for both patients and health care providers while maintaining safety and efficacy [9–14]. Cohort 2 of the VELVET study is the first to provide evidence to support the feasibility of administering pertuzumab and trastuzumab together in a single infusion bag, followed by vinorelbine. Co-infusion is advantageous because it may offer patients greater convenience while also reducing time spent in the clinic. The dosing schedule of vinorelbine used in VELVET was the same as that used in the Herceptin Plus Navelbine or Taxotere (HERNATA) study [8], with the exception of a lower dose during cycle 1 in order to monitor safety with the addition of pertuzumab. Additionally, sequential infusion of pertuzumab and trastuzumab was required during cycle 1 for VELVET Cohort 2 in an effort to appropriately monitor safety during the initial infusion.

In VELVET, the potential time saving for co-infusion compared with standard sequential infusion of pertuzumab and trastuzumab after cycle 1 was 1–1.5 hours during cycle 2 (2.5 hours vs. 3.5–4.0 hours), and 2–2.5 hours from cycle 3 onwards (1.5 hours vs. 3.5–4.0 hours), including infusion and post-infusion observation time (Fig. 1) [15–17]. A time-and-motion study would help to confirm the time savings and medical resource utilization for the combined infusion.

The results from VELVET Cohort 2 show that co-infusion of pertuzumab and trastuzumab followed by vinorelbine is active and reasonably well tolerated for the first-line treatment of HER2-positive locally advanced or metastatic breast cancer with an investigator-assessed ORR of 63.7% (95% CI 53.0–73.6) and a median PFS of 11.5 months (95% CI 10.3–15.8) observed. Efficacy was lower than expected based on the results from Cohort 1 of the VELVET study, in which pertuzumab and trastuzumab were administered sequentially. Of note, a formal exploratory comparison between the cohorts was initially planned but was not performed due to the nonrandomized nature of the trial and important imbalances in baseline characteristics (proportion of patients with prior trastuzumab treatment or with locally advanced disease, and inter-regional differences with the inclusion of patients from South America [Brazil] in Cohort 2 but not in Cohort 1) [7]. Differences between the baseline characteristics were an anticipated consequence of the sequential recruitment that was conducted for the two cohorts and the different sites involved in each part of the study. Nonetheless, the ORR observed in Cohort 2 was in line with the protocol assumption of a BOR of 70% (95% CI 59–79), albeit at the lower end of the confidence interval.

The lower-than-expected efficacy may be due, in part, to discordance between local and central HER2 testing results since 14.0% of patients were found to have HER2-negative disease and 69.2% of patients to have HER2-positive disease by the central laboratory; the remaining patients (16.8%) did not have their HER2 status tested centrally. Post hoc exploratory subgroup analyses showed a higher ORR in patients with centrally versus locally confirmed HER2-positive disease (71.6% [95% CI 59.3–82.0] vs. 63.7% [95% CI 53.0–73.6], respectively) and a longer median PFS (12.9 months [95% CI 9.8–21.9] vs. 11.5 months [95% CI 10.3–15.8], respectively). When considering only those patients with HER2 IHC 3+ disease, the ORR was 71.7% (95% CI 58.6–82.5) vs. 67.1% (95% CI 55.6–77.3) and the median PFS was 15.8 months (95% CI 9.8–26.9) vs. 11.9 months (95% 9.8–16.4) with central and local assessment, respectively. Similar findings concerning improved efficacy in patients with centrally versus locally confirmed HER2-positive disease were also reported in other studies conducted in the early breast cancer setting [18]. These findings highlight the importance of following the standards for interpretation and reporting of HER2 testing [19], particularly in the context of a clinical trial investigation.

As expected, in exploratory subgroup analyses, trastuzumab-naïve patients had a higher ORR and longer median PFS than those who had prior trastuzumab treatment, although the number of trastuzumab-pretreated patients with measurable disease was small ($n = 16$) and CIs were wide and overlapping, limiting interpretation. Similarly, meaningful observations on efficacy cannot be drawn from the hormone receptor subgroup analyses due to the small numbers in each subgroup and wide and overlapping CIs.

The safety profile was consistent with the known toxicity profiles of each drug [16, 17, 20] and with VELVET Cohort 1 [7], and no unexpected safety signals were observed. This supports the feasibility of the co-infusion of pertuzumab and trastuzumab in a single infusion bag. Diarrhea and neutropenia were the most frequently reported AEs; however, treatment discontinuation due to these AEs was low (diarrhea: one patient; neutropenia: six patients). The incidence of hypertension (any grade: 31 patients [29.0%]; grade 3: 15 patients [14.0%]) was higher than expected; however, no patients discontinued treatment because of hypertension. The findings on hypertension are most likely attributable to a protocol and electronic case report form amendment that required vital signs to be assessed post-infusion. The amendment occurred after Cohort 1 finished enrolling and led to procedural differences between the cohorts, resulting in a much higher percentage of patients in Cohort 2 having post-infusion blood pressure measurements taken at cycle 1. Importantly, cardiac safety (incidence of cardiac dysfunction and LVEF declines $<50\%$) was in line with previous studies of pertuzumab and trastuzumab (standard sequential infusion) [7, 21, 22].

VELVET Cohort 2 is limited by the absence of a comparator arm and the relatively small number of patients; however, it adds to the large clinical trial datasets already available for each of the study drugs and provides the first efficacy and safety data for concomitant administration of two mAbs, pertuzumab and trastuzumab, in a single infusion bag.

Conclusion

Co-infusion of pertuzumab and trastuzumab is feasible from a safety standpoint and may offer patients greater convenience

and time savings compared with conventional sequential infusion. Consistent with VELVET Cohort 1, the results from VELVET Cohort 2 suggest that vinorelbine offers an alternative chemotherapy companion for pertuzumab and trastuzumab, particularly for those patients who cannot, or choose not to, receive docetaxel for the first-line treatment of HER2-positive locally advanced or metastatic breast cancer.

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Disclosures

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