Original Study

Results From the First Multicenter, Open-label, Phase IIIb Study Investigating the Combination of Pertuzumab With Subcutaneous Trastuzumab and a Taxane in Patients With HER2-positive Metastatic Breast Cancer (SAPPHIRE)

Natasha Woodward,[1] Richard H. De Boer,[2] Andrew Redfern,[3] Michelle White,[4] Jennifer Young,[5] Matt Truman,[6] Jane Beith[7]

Abstract

This open-label, non-randomized study examined the safety and tolerability of combination pertuzumab, subcutaneous trastuzumab (Herceptin), and taxane chemotherapy in previously untreated patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. Fifty patients were assessed. The overall response rate was 73.3% (95% confidence interval, 58.1%-85.4%), and the median progression-free survival was 17.0 months (95% confidence interval, 12.5-31.2 months). This combination has an acceptable safety and tolerability profile.

Introduction: The primary objective of this study was to assess the safety and tolerability of combination pertuzumab, subcutaneous trastuzumab (Herceptin), and investigator's choice of taxane chemotherapy in previously untreated patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. Efficacy was a secondary objective. **Patients and Methods:** This study was an open-label, non-randomized study of patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who had no previous systemic non-hormonal anti-cancer therapy for metastatic disease. The primary endpoints included adverse events (AE), serious AEs, and cardiac AEs. Secondary endpoints included overall response rate, progression-free survival, and overall survival. Patients were treated with pertuzumab and subcutaneous trastuzumab in 3-weekly cycles with taxane chemotherapy until disease progression, unacceptable toxicity, or withdrawal of consent and followed for a minimum of 24 months from initiation of study treatment. **Results:** Fifty patients were enrolled and included in the analysis. All patients experienced at least 1 AE, with diarrhea, fatigue, peripheral neuropathy, alopecia, rash, and nausea the most common. Three patients experienced at least 1 grade 3 event of suspected cardiac origin (cardiac failure, cardiomyopathy, hypertension). Six patients withdrew from therapy owing to AEs (cardiac failure, drug hypersensitivity, decreased left ventricular ejection fraction, syncope, and bullous dermatitis). Taxane chemotherapy comprised nab-paclitaxel (74.0% of patients), docetaxel (28.0%), or paclitaxel (4.0%). The overall response rate was 73.3% (95% confidence interval, 58.1%-85.4%), the median progression-free survival was 17.0 months (95% confidence interval, 12.5-31.2 months), and the median overall survival was not reached. **Conclusions:** Subcutaneous trastuzumab in this combination has an acceptable safety and tolerability profile, including cardiac safety profile. Safety and efficacy appear similar to previous studies of intravenous trastuzumab in this combination.

Clinical Breast Cancer, Vol. 19, No. 3, 216-24

Keywords: Cardiac safety profile, Dual targeting of HER2$^+$, First Line treatment, Human epidermal growth factor receptor 2, Metastases

[1]Mater Misericordiae Ltd/Mater Research Institute and the University of Queensland, Brisbane, Queensland, Australia
[2]Royal Melbourne Hospital, Parkville, Victoria, Australia
[3]Fiona Stanley Hospital, Murdoch, Western Australia, Australia
[4]Monash Cancer Centre, East Bentleigh, Victoria, Australia
[5]Roche Products, Pty Limited, Sydney, New South Wales, Australia
[6]OzBiostat Pty Ltd, Sydney, New South Wales, Australia
[7]Chris O'Brien Lifehouse, Camperdown, New South Wales, Australia

Submitted: Sep 26, 2018; Revised: Jan 31, 2019; Accepted: Feb 15, 2019; Epub: Feb 27, 2019

Address for correspondence: Natasha Woodward, MBBS, Level 3, Mater Hospital Brisbane, Raymond Tce, South Brisbane, Queensland 4101 Australia
E-mail contact: natasha.woodward@mater.org.au

1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2019.02.008

Introduction

In approximately 15% to 20% of primary breast cancers, human epidermal growth factor receptor 2 (HER2) is either amplified or overexpressed (HER2-positive [$HER2^+$]).[1] $HER2^+$ tumors have more aggressive biology. Treatment of $HER2^+$ breast cancer with anti-HER2-targeted therapy is standard of care for both early and metastatic breast cancer (mBC). Intravenous (IV) trastuzumab has proven clinical benefits in patients with $HER2^+$ mBC. Pertuzumab also targets HER2 through an independent epitope to that of trastuzumab and inhibits dimerization with other HER family members, particularly HER3.[2] The pivotal CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) study in $HER2^+$ mBC demonstrated acceptable toxicity and improved efficacy for pertuzumab IV in combination with trastuzumab IV and docetaxel compared with placebo, trastuzumab IV, and docetaxel.[3] The median PFS was 12.4 months (95% confidence interval [CI], 10.4-13.5 months) in the placebo group and 18.7 months (95% CI, 16.6-21.6 months) in the pertuzumab group. Overall survival (OS) was 40.8 months (95% CI, 35.8-48.3 months) in the placebo group and 56.5 months (95% CI, 49.3 months to not estimable) in the pertuzumab group (hazard ratio [HR], 0.68; 95% CI, 0.56-0.84; $P < .001$) after a median follow-up of 50 months in both groups. There was no increase in left ventricular systolic dysfunction, but the rates of grade 3 or worse febrile neutropenia and diarrhea were higher in the pertuzumab group.

Based on the results of the CLEOPATRA study, pertuzumab gained regulatory approval for use in Australia in combination with trastuzumab and docetaxel, but not with other taxanes. Pertuzumab was later funded for use in combination with trastuzumab and either docetaxel or paclitaxel. The subcutaneous formulation of trastuzumab (trastuzumab SC) had not been approved in Australia at the time this study was conducted, although the IV formulation was already standard of care. The safety and efficacy of other chemotherapy partners with pertuzumab IV and trastuzumab IV are now reported, notably for vinorelbine (the VELVET [A Study to Assess Efficacy and Safety of Pertuzumab Given in Combination With Trastuzumab and Vinorelbine in Participants With Metastatic or Locally AdVanced Human Epidermal GrowTh Factor Receptor (HER) 2-Positive Breast Cancer] study)[4] and for nab-paclitaxel and paclitaxel (the PERUSE [A Multicenter, Open-Label, Single-Arm Study of Pertuzumab in Combination With Trastuzumab and a Taxane in First Line Treatment of Patients With HER2-Positive Advanced (Metastatic or Locally Recurrent) Breast Cancer] study),[5] the latter in abstract alone.

The SAPPHIRE study was the first study to investigate the combination of trastuzumab SC with pertuzumab IV and taxane chemotherapy. Trastuzumab SC has the potential to reduce infusion chair time and thus be more convenient for patients. It has been shown to have a pharmacokinetic profile and efficacy that is non-inferior to the IV formulation and with a similar safety profile.[6,7] Patients have reported a preference for SC over IV administration.[8,9]

The primary objective of this study was to assess the safety and tolerability of the combination of pertuzumab, trastuzumab SC, and taxane chemotherapy of the investigator's choice (docetaxel, paclitaxel, or nab-paclitaxel) in patients with previously untreated $HER2^+$ mBC. Exploratory safety analyses by type of taxane chemotherapy administered were also conducted. The secondary objectives of this study were to assess the efficacy of the pertuzumab IV, trastuzumab SC, and taxane chemotherapy combination.

Patients and Methods

Trial Design

This open-label, multicenter, phase IIIb study of first-line treatment for $HER2^+$ mBC (NCT02019277) was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. The independent ethics committee for each participating center approved the protocol and amendments.

The primary endpoints were safety endpoints including adverse events (AEs), serious AEs, and cardiac AEs. Secondary endpoints included overall response rate (ORR; either confirmed complete response [CR] or partial response [PR] as determined by Response Evaluation Criteria In Solid Tumors [RECIST] criteria, version 1.1), PFS, and OS. PFS was defined as the time from the visit prior to treatment start until the first documented disease progression or death, whichever came first. Patients who had neither progressed nor died or who were lost to follow-up at the time of the analysis were censored at the date of their last tumor assessment where non-progression was documented or the last date of follow-up, whichever was later. OS was defined as the time from baseline until death from any cause. Patients still alive at the time of the analysis or lost to follow-up were censored at their last clinical assessment date.

Patient Population

Eligible patients were adults with $HER2^+$, histologically or cytologically confirmed adenocarcinoma of the breast with metastatic disease with at least 1 measurable lesion and/or non-measurable disease according to RECIST version 1.1. Patients were required to have immunohistochemistry 3+ (IHC3+) or in-situ hybridization-positive (ISH+) $HER2^+$ disease of the primary tumor or metastatic site. Patients who received docetaxel were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1, or 0, 1, or 2 for paclitaxel or nab-paclitaxel. Baseline left ventricular ejection fraction (LVEF) was required to be at least 50%. Previous use of either adjuvant or neoadjuvant anti-HER2 therapy was allowed. Hormonal therapy was allowed as per institutional guidelines but not in combination with taxane therapy.

Patients were ineligible to participate if they had received previous non-hormonal anti-cancer therapy for the treatment of mBC; were pregnant or breastfeeding; had current peripheral neuropathy grade 3 to 5 (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], version 4.0); had radiographic evidence of central nervous system metastases except where treated, stable for at least 3 months, and ongoing corticosteroid treatment was not required; or had concurrent serious diseases that may have interfered with planned treatment, including severe pulmonary conditions/illnesses.

Study Treatment

Pertuzumab (F. Hoffmann-La Roche Ltd) was administered every 3 weeks as an IV infusion; loading dose (840 mg) was given on Day 1 of the first 21-day treatment cycle, followed by 420 mg on Day 1 of each subsequent 21-day cycle, irrespective of body weight.

Fixed-dose trastuzumab SC (Herceptin, F. Hoffmann-La Roche Ltd; 600 mg/5 mL) was administered on Day 2 of the first treatment cycle, then once every 3 weeks. If both drugs were well-tolerated during the first treatment cycle, trastuzumab SC could be administered after pertuzumab IV on Day 1 of subsequent treatment cycles, followed by taxane chemotherapy. Commercially available docetaxel, paclitaxel, or nab-paclitaxel, as chosen by the investigator, were administered following the local product information for each drug and as per routine clinical practices. Doses of taxane chemotherapy were calculated according to the patient's body surface area using actual body weight; dosing schedule was in accordance with the local Product Information.

Patients with unacceptable toxicity or disease progression were switched to a standard treatment of the investigator's choice. If pertuzumab and trastuzumab SC were withheld for 2 cycles because of unacceptable toxicity, the patient was withdrawn from both study treatments. Taxane chemotherapy could be continued as first-line study treatment until disease progression. If taxane chemotherapy was permanently discontinued owing to unacceptable toxicity, pertuzumab and trastuzumab SC administration continued as first-line study treatment until disease progression.

Assessments

Routine tumor assessments (RECIST version 1.1) were performed by the investigator every 9 weeks from time of first dose of trastuzumab and pertuzumab until disease progression or death. Electrocardiograms and assessments of LVEF were performed every 12 weeks from the time of first dose of trastuzumab and pertuzumab and at the safety follow-up visit. Laboratory tests were performed every cycle and at the safety follow-up visit. Eastern Cooperative Oncology Group performance status was assessed every 3 cycles and at the safety follow-up visit. Patients were followed for a minimum of 24 months from initiation of study treatment. Survival status information was collected every 3 months.

AEs were reported throughout the treatment period and up to 28 days following the last dose of trastuzumab and pertuzumab. All AEs considered related to study treatment, and all cardiac AEs regardless of causality assessment, were required to be reported until study closure.

Statistical Considerations

No formal hypothesis testing was planned. The planned sample size of 50 patients was based on an acceptable level of precision for the incidence of AEs considered related to trastuzumab or pertuzumab of CTCAE grade 3 or worse. For 50 patients, an incidence of 10% would provide a 95% Clopper-Pearson CI of 3.3% to 21.8%, and an incidence of 50%, would provide a 95% CI of 35.5% to 64.5%.

All primary analyses were performed on the safety population, including all enrolled patients who received at least 1 dose of pertuzumab or trastuzumab. All baseline summaries and efficacy analyses were based on the intent-to-treat population, including all enrolled patients scheduled to receive pertuzumab and trastuzumab. The taxane chemotherapy subgroup (docetaxel, paclitaxel, or nab-paclitaxel) was defined at the time of enrollment. Patients who switched chemotherapy were assigned to the taxane group in which they had most cycles, or if equally administered, to their initial taxane group. Comparisons by taxane chemotherapy group are considered post-hoc analyses.

Endpoints related to AEs, serious AEs, cardiac AEs, and administration-associated reactions were summarized by number and percentage of patients having any event and 95% Clopper-Pearson CI.

Secondary efficacy endpoints included ORR, PFS, and OS. ORR was assessed by the number and proportion of responders and non-responders, together with 2-sided 95% CIs. Only patients with measurable disease at baseline (enrollment) were included in the analysis. Patients without a post-baseline assessment were considered non-responders. The analysis of PFS and OS was based on the survivor function, which is the probability of remaining event-free beyond a certain point in time. The survival function was estimated using the Kaplan-Meier method and summarized using the range, the 25th and 75th percentiles, the median, and a 95% CI for the median.

Results

Study Population

Fifty patients were enrolled in the study between December 2013 and October 2014 at 12 hospitals across Australia (Figure 1). The data cutoff date was March 21, 2017.

Selected patient baseline characteristics are presented in Table 1. No patients had brain metastases at baseline.

Treatment Exposure

Patients received a median of 19.0 cycles (range, 1-49 cycles) of trastuzumab and pertuzumab. Exposure to taxane chemotherapy was much lower, with a median of 6.0 cycles (range, 1-15 cycles). Nab-paclitaxel was received for 7.0 cycles (range, 1-11 cycles), docetaxel for 6.0 cycles (range, 1-15 cycles), and paclitaxel for 2.5 cycles (range, 1-4 cycles).

Thirty-seven (74.0%) patients received nab-paclitaxel during the study, 14 (28.0%) patients received docetaxel, and 2 (4.0%) patients received paclitaxel. Three patients switched taxane chemotherapy: 1 patient received nab-paclitaxel for 2 cycles then switched to paclitaxel for 1 cycle (included in nab-paclitaxel group); 1 patient received docetaxel for 1 cycle then switched to nab-paclitaxel for 14 cycles (nab-paclitaxel group); and 1 patient received docetaxel for 1 cycle then switched to nab-paclitaxel for 1 cycle (docetaxel group).

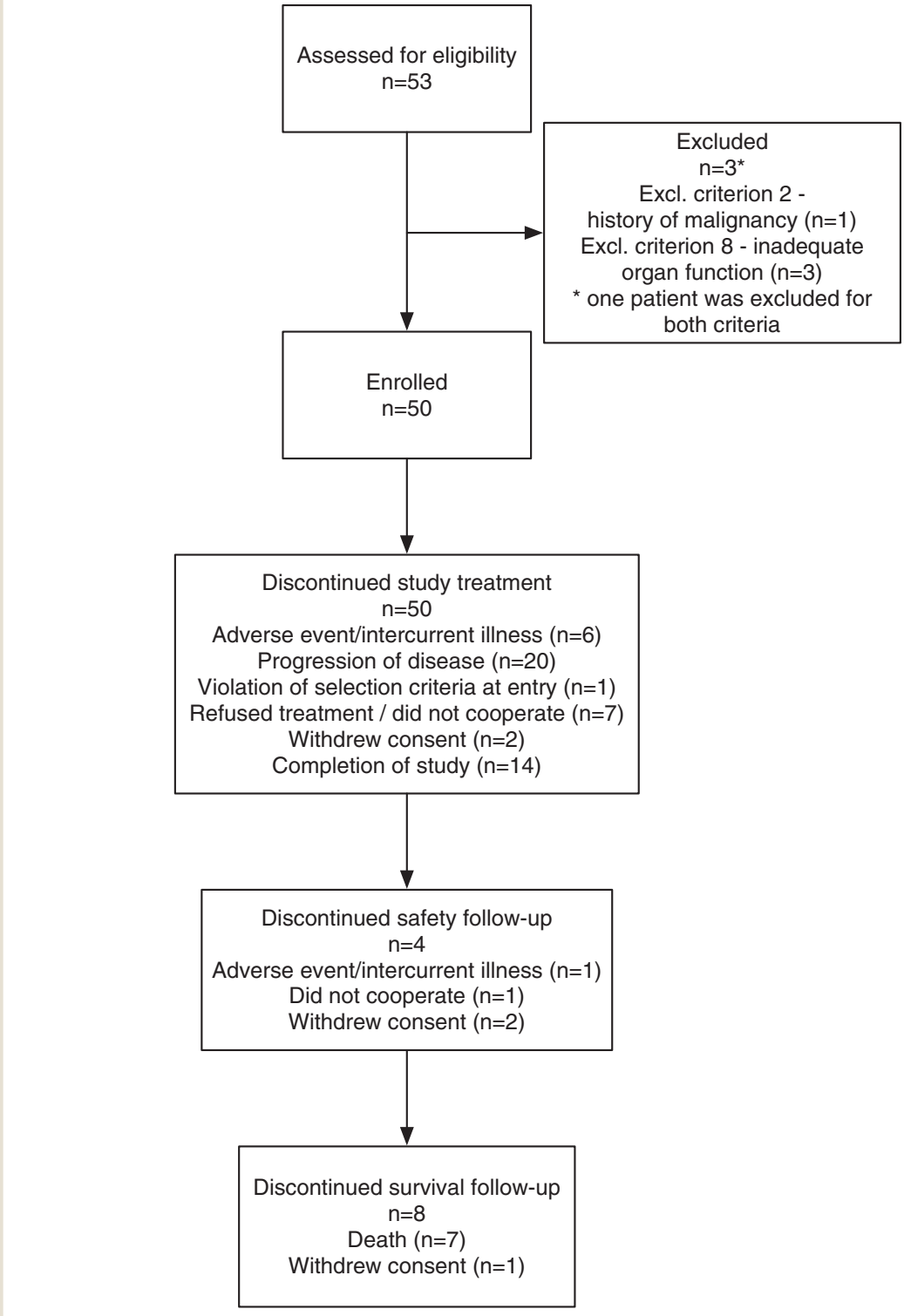
Thirty-six patients discontinued study treatment: 6 (12.0%) patients owing to AEs and 20 (40.0%) patients owing to progressive disease (Figure 1). Fourteen (28.0%) patients did not progress and switched to commercial stock of trastuzumab and pertuzumab at the completion of the study; no further data were collected from this point.

Thirty-one (62.0%) patients had hormone receptor-positive breast cancer; 15 patients received at least 1 hormonal therapy during the study, of whom 14 received hormonal therapy after stopping study taxanes.

Primary Safety Endpoints

All patients experienced at least 1 AE during the study, with diarrhea, fatigue, peripheral neuropathy, alopecia, rash, and nausea the most common events (Table 2). There were 349 AEs in the docetaxel group (27 events per patient), 707 in the nab-paclitaxel group (20 events per patient), and 6 in the paclitaxel group (6 events per patient).

Figure 1 Patient Flow Through the Study



CTCAE grade 3 or 4 AEs were experienced by 32 (64.0%) patients (Table 3). Serious AEs were experienced by 27 (54.0%) patients (Table 4). Notably, no patients in the nab-paclitaxel group experienced febrile neutropenia of CTCAE grade 3 or worse, or a serious AE of febrile neutropenia. In addition, only 1 (2.0%) patient, who received docetaxel, required concomitant granulocyte

Table 1 Demographics and Baseline Characteristics

Parameter	N (%)
Age, y (SD)	52.9 (12.0)
Gender	
Female	49 (98.0)
Male	1 (2.0)
Mean BMI (SD)	27.9 (6.4)
Race	
White	42 (84.0)
Asian	4 (8.0)
Other	4 (8.0)
Female reproductive status (N = 49)	
Childbearing	15 (30.6)
Surgically sterile	4 (8.2)
Post-menopausal	30 (61.2)
ECOG PS	
0	33 (66.0)
1	15 (30.0)
2	2 (4.0)
Disease presentation at screening	
De novo	23 (46.0)
Relapse	27 (54.0)
HER2 status at screening	
HER2$^+$	50 (100)
ISH+	44 (88)
IHC3+ (ISH not tested)	6 (12)
Hormone receptor status	
ER$^+$ or PR$^+$ or both	31 (62.0)
ER$^-$ and PR$^-$	19 (38.0)
Prior hormonal therapy in hormone-positive patients	20 (40.0)
Any anti-estrogen	15 (30.0)
Aromatase inhibitors	12 (24.0)
Gonadotropin and analogues	3 (6.0)
Conjugated estrogens and medroxyprogesterone	1 (2.0)
Prior chemotherapy/trastuzumab in adjuvant setting	23 (46.0)
Anthracyclines	17 (34.0)
Taxanes	17 (34.0)
Trastuzumab	15 (30.0)
Median time from last trastuzumab dose in eBC [n = 15], mos (range)	22.1 (0.5-62.3)

Abbreviations: BMI = body mass index; eBC = early breast cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; PR = progesterone receptor.

colony stimulating factors (filgrastim). Nine (18.0%) patients died owing to disease progression. No deaths were considered related to study treatments.

Six (12.0%) patients experienced a total of 12 AEs of suspected cardiac origin, of whom 4 (8.0%) patients experienced 8 adverse events considered by the investigator to be related to trastuzumab, pertuzumab, or both. Three (6.0%) patients experienced 5 CTC grade 3 events of suspected cardiac origin: 1 patient experienced cardiac failure and hypertension (both New York Heart Association [NYHA] Class II), 1 patient experienced cardiac failure and cardiomyopathy (both NYHA Class II), and 1 patient experienced cardiomyopathy (NYHA Class III). Of these 5 events, 3 remained unresolved at study completion (hypertension and cardiac failure in 1 patient and cardiomyopathy in 1 patient). The remaining 2 events, in 1 patient, resolved: 1 with sequelae (cardiomyopathy) and 1 without (cardiac failure). There were no grade 4 or 5 events of suspected cardiac origin.

Forty-one patients had a decrease in LVEF from baseline. The maximum decrease from baseline was less than 10% for 24 patients, and greater than 25% for 1 patient. There were 4 (8.0%) patients with a decrease in LVEF below 50% at any time during the study.

Six (12.0%) patients experienced a total of 8 administration-associated reactions, including 1 CTCAE grade 3 event of drug hypersensitivity reaction considered related to pertuzumab administration.

SC injection of trastuzumab was associated with only a small number of injection site reactions. Twelve (0.01%) of 1140 injections were associated with pain (3 events), erythema (2 events), or unspecified injection site reaction (7 events). There was no obvious link between injection site reactions and speed of injection.

AEs that led to withdrawal of trastuzumab and pertuzumab treatment were cardiac failure (2 patients), drug hypersensitivity, decreased ejection fraction, syncope, and bullous dermatitis (each 1 patient). Ten (20.0%) patients experienced an AE that led to withdrawal of taxane chemotherapy. Eight (22.2%) of 36 patients who received nab-paclitaxel and 2 (15.4%) of 13 patients who received docetaxel discontinued chemotherapy owing to AEs. No patients discontinued paclitaxel owing to AEs; however, only 2 patients received paclitaxel chemotherapy at any time during the study. Overall, the most common AEs leading to chemotherapy withdrawal were diarrhea and peripheral neuropathy.

Secondary Efficacy Endpoints

Forty-five patients had measurable disease at baseline. Thirty-three patients had a PR or CR to study treatment, giving an ORR of 73.3% (95% CI, 58.1%-85.4%). Eight (17.8%; 95% CI, 8.0%-32.1%) patients had stable disease (SD), and 3 (6.7%; 95% CI, 1.4%-18.3%) patients had progressive disease. One patient was not evaluated.

The clinical benefit rate,[10,11] which considers CR, PR, and SD, was 91.1% (95% CI, 78.8%-97.5%). In this study, clinical benefit was defined as CR, PR, and SD occurring at any time during treatment.

Thirty (60.0%) patients had a PFS event, with a median PFS of 17.0 months (95% CI, 12.5-31.2 months) (Figure 2A). Nine (18.0%) patients died during the study. The median OS was not reached during the study treatment period (95% CI, 31.3 months to not calculable) (Figure 2B).

Twenty-three patients started second-line therapy, the most commonly used therapies being trastuzumab (13 patients), trastuzumab emtansine (10 patients), capecitabine (8 patients), pertuzumab (5 patients), lapatinib (4 patients), and paclitaxel (4 patients).

Table 2 Any Grade Adverse Events Occurring in > 7 (15%) Patients in the Total Patient Population

Adverse Event Preferred Term	Docetaxel (n = 13), n (%)	Nab-paclitaxel (n = 36), n (%)	Paclitaxel (n = 1), n (%)	Total (N = 50), n (%)
Diarrhea	9 (69.2)	27 (75.0)	–	36 (72.0)
Fatigue	8 (61.5)	26 (72.2)	–	34 (68.0)
Peripheral neuropathy	3 (23.1)	24 (66.7)	1 (100.0)	28 (56.0)
Alopecia	7 (53.8)	20 (55.6)	–	27 (54.0)
Rash	7 (53.8)	18 (50.0)	1 (100.0)	26 (52.0)
Nausea	4 (30.8)	18 (50.0)	1 (100.0)	23 (46.0)
Upper respiratory tract infection	7 (53.8)	12 (33.3)	–	19 (38.0)
Myalgia	4 (30.8)	14 (38.9)	–	18 (36.0)
Headache	5 (38.5)	12 (33.3)	–	17 (34.0)
Vomiting	4 (30.8)	13 (36.1)	–	17 (34.0)
Muscle spasms	5 (38.5)	9 (25.0)	–	14 (28.0)
Arthralgia	5 (38.5)	6 (16.7)	1 (100.0)	12 (24.0)
Epistaxis	3 (23.1)	9 (25.0)	–	12 (24.0)
Gastroesophageal reflux disease	6 (46.2)	6 (16.7)	–	12 (24.0)
Nail disorder	4 (30.8)	8 (22.2)	–	12 (24.0)
Pain in extremity	4 (30.8)	7 (19.4)	–	11 (22.0)
Urinary tract infection	3 (23.1)	8 (22.2)	–	11 (22.0)
Back pain	2 (15.4)	8 (22.2)	–	10 (20.0)
Constipation	3 (23.1)	6 (16.7)	–	9 (18.0)
Cough	2 (15.4)	7 (19.4)	–	9 (18.0)
Dizziness	3 (23.1)	6 (16.7)	–	9 (18.0)
Pyrexia	2 (15.4)	7 (19.4)	–	9 (18.0)
Neutropenia	5 (38.5)	3 (8.3)	–	8 (16.0)
Dry skin	4 (30.8)	4 (11.1)	–	8 (16.0)

The second-line median OS from failure of first-line therapy until death from any cause was 21.3 months (95% CI, 14.9-29.0 months) (Figure 2C).

The median length of time on the study was 18.8 months (range, 0.76-34.5 months).

Discussion

The observed safety profile combination for trastuzumab SC and pertuzumab IV is similar to that in the CLEOPATRA study,[3] suggesting that the trastuzumab SC formulation in this combination has a comparable safety and tolerability profile. There were 2 notable differences in this study compared with the CLEOPATRA study: an apparent higher frequency of peripheral neuropathy and lower frequency of neutropenia. These differences are considered to be associated with the common use of nab-paclitaxel in this study, as opposed to docetaxel, which all patients received in the CLEOPATRA study. In the PERUSE study[5] of trastuzumab IV and pertuzumab and taxane of the investigator's choice, a lower frequency of neutropenia and higher frequency of peripheral neuropathy, considered related to the use of paclitaxel and nab-paclitaxel, was also observed.

Table 3 Grade 3+ Adverse Events in More Than 1 (2%) Patient in the Total Patient Population

Adverse Event Preferred Term	Docetaxel (n = 13), n (%)	Nab-paclitaxel (n = 36), n (%)	Paclitaxel (n = 1), n (%)	Total (N = 50), n (%)
Neutropenia	3 (23.1)	3 (8.3)	–	6 (12.0)
Febrile neutropenia	4 (30.8)	–	–	4 (8.0)
Diarrhea	1 (7.7)	2 (5.6)	–	3 (6.0)
Peripheral neuropathy	1 (7.7)	2 (5.6)	–	3 (6.0)
Anaemia	–	2 (5.6)	–	2 (4.0)
Cardiac failure	–	2 (5.6)	–	2 (4.0)
Cardiomyopathy	–	2 (5.6)	–	2 (4.0)
Cellulitis	–	2 (5.6)	–	2 (4.0)
Dyspnea	1 (7.7)	1 (2.8)	–	2 (4.0)
Pulmonary embolism	–	2 (5.6)	–	2 (4.0)
Pyrexia	1 (7.7)	1 (2.8)	–	2 (4.0)
Upper respiratory tract infection	1 (7.7)	1 (2.8)	–	2 (4.0)

Table 4 Serious Adverse Events Occurring in More Than 1 (2%) Patient in the Total Patient Population

Serious Adverse Event Preferred Term	Docetaxel (n = 13), n (%)	Nab-paclitaxel (n = 36), n (%)	Paclitaxel (n = 1), n (%)	Total (N = 50), n (%)
Pyrexia	2 (15.4)	5 (13.9)	–	7 (14.0)
Febrile neutropenia	4 (30.8)	–	–	4 (8.0)
Cellulitis	–	2 (5.6)	–	2 (4.0)
Pulmonary embolism	–	2 (5.6)	–	2 (4.0)
Upper respiratory tract infection	1 (7.7)	2 (5.6)	–	2 (4.0)

Nab-paclitaxel appears to be a valid alternative chemotherapy to docetaxel in combination with trastuzumab SC and pertuzumab IV, and was commonly chosen by Australian oncologists over docetaxel and paclitaxel in this study. There were no cases of neutropenic fever in the nab-paclitaxel group.

As in the CLEOPATRA study, a low incidence of cardiac AEs and decreased LVEF was observed in this study. In this study, 12.0% of patients experienced any event of suspected cardiac origin, and 6.0% experienced at least 1 CTCAE grade 3 event of suspected cardiac origin, compared with cardiac AEs experienced by 16.4% of patients in the placebo treatment group (3.8% CTCAE grade 3 or above) and 14.5% of patients in the pertuzumab treatment group (1.5% CTCAE grade 3 or above) in CLEOPATRA.[12] Only 4 (8.0%) patients had a decrease in LVEF below 50% at any time during this study, and in CLEOPATRA, 4.4% of patients receiving pertuzumab and 6.6% of patients receiving placebo had a LVEF decrease of $\geq$ 10% below 50%.[12]

The median OS was not reached in this study, consistent with the long OS observed in the CLEOPATRA study,[3] despite a higher percentage of patients in the SAPPHIRE study having received previous HER2-targeted therapy in the adjuvant setting. PFS was also similar to that observed in the CLEOPATRA study.

The clinical benefit rate of the combination in this study was over 90%. All patients in the study were fit enough at the end of the study to go onto another treatment, suggesting that the progression of disease on treatment was not rapid.

The SAPPHIRE study had less restrictive eligibility criteria than the CLEOPATRA study. Only 10% of patients in the CLEOPATRA study had had adjuvant trastuzumab compared with 30% in SAPPHIRE.

The ongoing MetaPHER (Phase IIIb Multicenter, open-label, single-arm safety study of subcutaneous trastuzumab in combination with Pertuzumab and docetaxel in patients with HER2-positive advanced breast cancer) study (NCT02402712) is a single-arm phase IIIB study that aims to evaluate the safety and efficacy of trastuzumab SC, pertuzumab IV, and docetaxel IV in first-line HER2$^+$ locally advanced or mBC. Data from the second interim analysis of 418 patients has been reported at the European Society for Medical Oncology 2018 meeting, and the interim safety and efficacy profiles appear consistent with the known safety profile of trastuzumab IV and pertuzumab IV. Final results are awaited.[13]

Limitations of the SAPPHIRE study include small sample size, non-randomized design with lack of comparator arm, and insufficient follow-up to determine OS. Comparisons of AEs by type of taxane chemotherapy were performed as post-hoc analyses. However, the study should be generalizable to standard clinical practice, with a representative sample of older and younger patients with breast cancer and patients with comorbid conditions, including cardiovascular conditions such as atrial fibrillation.

Conclusion

SAPPHIRE is the first study to report on the combination of trastuzumab SC, pertuzumab IV, and taxane of investigators' choice. Nab-paclitaxel was the most common physician choice and was observed to be an acceptable alternative to docetaxel with the combination. SAPPHIRE suggests that trastuzumab SC in this combination has an acceptable safety and tolerability profile, including cardiac safety profile, with efficacy appearing similar to previous studies of trastuzumab IV in the combination.

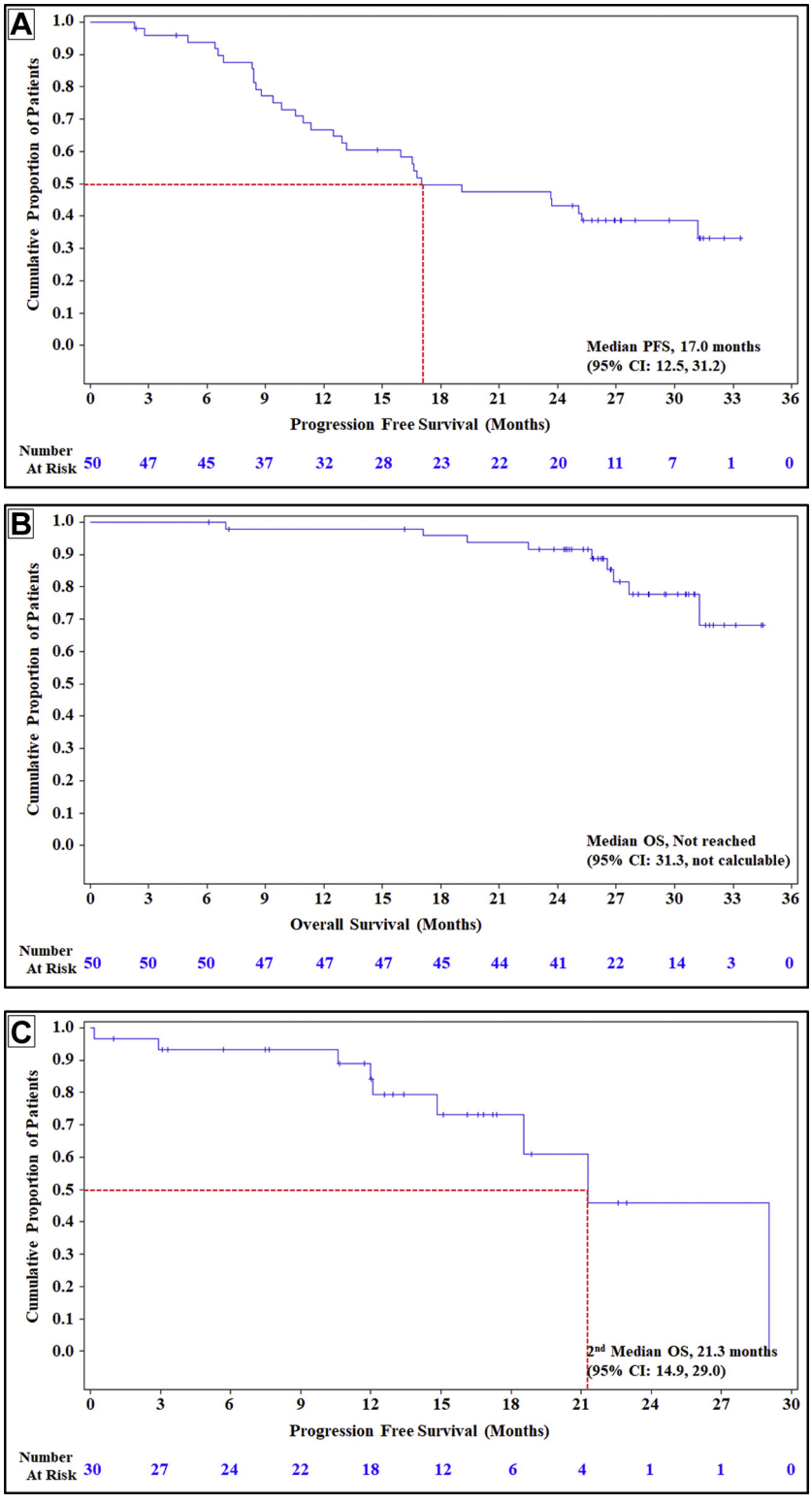
Clinical Practice Points

- Improved efficacy (both PFS and OS) with acceptable toxicity has been shown in mBC using pertuzumab IV in combination with trastuzumab IV and docetaxel.
- SAPPHIRE, an open-label, multicenter, phase IIIb study, was the first study to investigate `the combination of pertuzumab IV, trastuzumab SC, and clinician's choice of taxane chemotherapy in previously untreated patients with HER2$^+$ mBC. The study showed that this combination had acceptable safety and tolerability profile.
- Nab-paclitaxel appears to be a valid alternative chemotherapy to docetaxel in combination with trastuzumab SC and pertuzumab IV, and was commonly chosen over docetaxel and paclitaxel in this study.
- Notwithstanding the small sample size, of clinical interest is the low overall incidence of decreased LVEF in the study and the absence of grade 3+ febrile neutropenia in the nab-paclitaxel group.
- The clinical benefit rate of the combination in this study was over 90%. All patients in the study were fit enough at the end of the study to go onto another treatment, suggesting that the progression of disease on treatment was not rapid.

Acknowledgments

The study was sponsored by Roche Products, Pty Limited (Australia). The funder was involved in the study design, data management, analysis, and the preparation of the manuscript.

Figure 2 Kaplan-Meier Curve of PFS (ITT Population) (A), OS (ITT Population) (B), and OS (Second-line Therapy; ITT Population) (C)



Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival.

The authors thank all patients and investigators participating in this trial. The principal investigators were Dr Jacqui Adams, Dr Maree Colosimo, Dr Katharine Cuff, Dr Jeremy Power, Dr Mustafa Khasra, Dr Janine M Lombard, Dr Daphne Tsoi, Dr Jodi Lynch, and Dr Stephen Begbie. The authors also thank the Roche study team.

J. Steyne, of Novotech (Australia) Pty Limited, performed statistical analyses funded by Roche Products Pty Limited.

Sophie Gibb, PhD CMPP, of WriteSource Medical Pty Limited provided medical writing support, funded by Roche Products Pty Limited in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Disclosure

N. Woodward has stock or other ownership interest in the Commonwealth Serum Laboratories (CSL Limited); received research funding for her institution from Medivation; received remuneration for travel support from Roche Products Pty Limited and Novartis; has participated in speaker's bureau for Roche Products Pty Limited; and has received compensation for consultancy or advisory roles from Roche Products Pty Limited, Pfizer, and Novartis. R. De Boer has received compensation for consultancy or advisory roles from Roche Products Pty Limited and Amgen; and has participated in speaker's bureau for Novartis, Merck, and Roche Products Pty Limited. A. Redfern has received compensation for consultancy or advisory roles from Roche Products Pty Limited, Novartis, Eisai, and Pfizer; has participated in speaker's bureau for Eisai, Roche Products Pty Limited, and Novartis; and received travel or accommodations support to attend a conference from Amgen. M. White has received compensation for consultancy or advisory roles from Roche Products Pty Limited, Novartis, and Pfizer. J. Young is an employee of Roche Products Pty Limited. M. Truman has stock or other ownership interest in Roche Products Pty Limited and has received compensation for consulting or advisory role from Roche Products Pty Limited and Aurinia Pharmaceuticals; and received travel or accommodations support from Roche Products Pty Limited and Aurinia Pharmaceuticals. J. Beith has stock ownership interest in CSL Limited; and received remuneration for travel support from Roche Products Pty Limited, and has received compensation for consultancy or advisory roles from Roche Products Pty Limited, Pfizer, Lilly, and Specialised Therapeutics.

References

1. Wolff AC, Hammond MEH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. *J Clin Oncol* 2013; 31:3997-4013.
2. Franklin MC, Carey KD, Vajdos FF, Leahy DJ, de Vos AM, Sliwkowski MX. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell* 2004; 5:317-28.
3. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015; 372:724-34.
4. Perez EA, Lopez-Vega JM, Petit T, et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. *Breast Cancer Res* 2016; 18:126.
5. Miles D, Puglisi F, Schneeweiss A, et al. 1816 Preliminary safety results from PERUSE, a study of 1436 patients (pts) treated with first-line pertuzumab (P) combined with trastuzumab (H) and taxane therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mBC). *Eur J Cancer* 2015; 51:S271.
6. Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. *Lancet Oncol* 2012; 13:869-78.
7. Jackisch C, Kim SB, Semiglazov V, et al. Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: updated results from the phase III HannaH study. *Ann Oncol* 2015; 26:320-5.
8. Pivot X, Spano JP, Espie M, et al. Patients' preference of trastuzumab administration (subcutaneous versus intravenous) in HER2-positive metastatic breast cancer: results of the randomised MetaspHer study. *Eur J Cancer* 2017; 82:230-6.
9. Pivot X, Gligorov J, Muller V, et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. *Lancet Oncol* 2013; 14:962-70.
10. Amiri-Kordestani L, Cheng J, Zhang L, et al. Association of clinical benefit rate (CBR) with survival: a pooled-analysis of metastatic breast cancer (MBC) trials submitted to the US Food and Drug Administration (FDA): American Society of Clinical Oncology; 2016. *J Clin Oncol* 2016; 34(15 Suppl):e18091.
11. Verma S, McLeod D, Batist G, Robidoux A, Martins IR, Mackey JR. In the end what matters most? A review of clinical endpoints in advanced breast cancer. *Oncologist* 2011; 16:25-35.
12. Swain SM, Ewer MS, Cortes J, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. *Oncologist* 2013; 18:257-64.
13. Kümmel S, Tondini CA, Abraham J, et al. 323PSubcutaneous trastuzumab (H SC) with intravenous pertuzumab (P IV) and docetaxel (D IV) in HER2-positive advanced breast cancer (BC): MetaPHER second interim analysis. *Ann Oncol* 2018; 29, mdy272.313-mdy272.313.