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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)

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CONFLICT OF INTEREST

N Woodward has stock or other ownership interest in the Commonwealth Serum Laboratories (CSL Limited); received research funding for her institution from Medivation, and 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 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 and 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.

DECLARATIONS

Ethics approval and consent to participate

This study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent prior to participation in the study. The independent ethics committee for each participating center approved the protocol and amendments (Hunter New England Research Ethics and Governance Unit on behalf of centers in New South Wales and Victoria, Human Research Ethics Committee (Tasmania Network), Human Research Ethics Committee Basil Hetzel Institute, Royal Perth Hospital Human Research Committee, St John of God Health Care Ethics Committee).

Consent for publication

Not applicable (no individual patient data presented).

Availability of data and material

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)

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Authors' contributions

N Woodward contributed to conception and design, collection and assembly of data and data analysis, manuscript writing, approved the final manuscript and agrees to be accountable for all aspects of the work, which includes ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

R De Boer contributed to collection of data and data analysis, manuscript writing, approved the final manuscript and agrees to be accountable for all aspects of the work, which includes ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. A Redfern contributed to collection of data and data analysis, manuscript writing, approved the final manuscript and agrees to be accountable for all aspects of the work, which includes ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

M White contributed to collection of data and data analysis, manuscript writing, approved the final manuscript and agrees to be accountable for all aspects of the work, which includes ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

J Young contributed to data analysis, manuscript writing, approved the final manuscript and agrees to be accountable for all aspects of the work, which includes ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

M Truman contributed to conception and design, collection and assembly of data and data analysis, manuscript writing, approved the final manuscript and agrees to be accountable for all aspects of the work, which includes ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

J Beith contributed to data analysis, manuscript writing, approved the final manuscript and agrees to be accountable for all aspects of the work, which includes ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

MICROABSTRACT

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 HER2-positive metastatic breast cancer. Fifty patients were assessed. Overall response rate was 73.3% (95% CI: 58.1-85.4%), median progression free survival was 17.0 months (95% CI: 12.5--31.2 months). This combination has acceptable safety and tolerability profile.

ABSTRACT

Purpose: The primary objective was to assess the safety and tolerability of combination pertuzumab, subcutaneous trastuzumab (Herceptin®) and investigator's choice taxane chemotherapy in previously untreated HER2-positive metastatic breast cancer (mBC) patients. Efficacy was a secondary objective.

Methods: An open-label, non-randomized study of HER2-positive mBC patients who had no previous systemic non-hormonal anti-cancer therapy for metastatic disease. Primary endpoints included adverse events (AE), serious adverse events and cardiac adverse events. Secondary endpoints included overall response rate (ORR), progression free survival (PFS) and overall survival (OS). Patients were treated with pertuzumab and subcutaneous trastuzumab in three-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 one AE, with diarrhea, fatigue, peripheral neuropathy, alopecia, rash and nausea the most common. Three patients experienced at least one grade 3 event of suspected cardiac origin

(cardiac failure, cardiomyopathy, hypertension). Six patients withdrew from therapy due 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%). ORR was 73.3% (95% CI: 58.1-85.4%), median PFS was 17.0 months (95% CI: 12.5-31.2 months) and median OS 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.

Trial registration: ClinicalTrials.gov, NCT02019277. Registered 24 December 2013, https://clinicaltrials.gov/ct2/show/NCT02019277

Keywords: Pertuzumab; subcutaneous trastuzumab; breast cancer; human epidermal growth factor receptor 2 (HER2), metastases

LIST OF ABBREVIATIONS

CI: confidence interval; CR: complete response; CTC: Common Terminology Criteria; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ITT: intent-to-treat; IV: intravenous; LVEF: left ventricular ejection fraction; mBC: metastatic breast cancer; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA: New York Heart Association; ORR: overall response rate; OS: overall survival; PFS: progression free survival; PR: partial response; SC: subcutaneous; SD: stable disease.

BACKGROUND

In approximately 15% to 20% of primary breast cancers, human epidermal growth factor receptor 2 (HER2) is either amplified or overexpressed (HER2-positive).[1] HER2-positive tumors have more aggressive biology. Treatment of HER2-positive 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-positive 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 study in HER2-positive mBC demonstrated acceptable toxicity and improved efficacy for pertuzumab IV in combination with trastuzumab IV and docetaxel compared to placebo, trastuzumab IV and docetaxel.[3] The median PFS was 12.4 months (95% CI 10.4 to 13.5 months) in the placebo group and 18.7 months (16.6 to 21.6 months) in the pertuzumab group. Overall survival (OS) was 40.8 months (95% CI 35.8 to 48.3 months) in the placebo group and 56.5 months (95% CI 49.3 to not estimable) in the pertuzumab group (hazard ratio 0.68, 95% CI 0.56 to 0.84; P<0.001) 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 intravenous 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 study)[4], and for nab-paclitaxel and paclitaxel (the PERUSE 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 so be more convenient for patients. It has been shown to have a pharmacokinetic profile and efficacy that is non-inferior to the intravenous formulation and with a similar safety profile.[6, 7] Patients have reported a preference for subcutaneous over intravenous 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-positive 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-positive 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, serious adverse events and cardiac adverse events. Secondary endpoints included overall response rate (ORR; either

confirmed complete response (CR) or partial response (PR) as determined by 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-positive, histologically or cytologically confirmed adenocarcinoma of the breast with metastatic disease with at least one 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-positive disease of the primary tumor or metastatic site. Patients who received docetaxel were required to have an Eastern Cooperative Oncology Group (ECOG) 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 3-5 (National Cancer Institute Common Terminology Criteria for Adverse Events (NCI 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; 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 three 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 three 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 standard treatment of the investigator's choice. If pertuzumab and trastuzumab SC were withheld for two 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 due 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 nine weeks from time of first dose of trastuzumab and pertuzumab until disease progression or death. Electrocardiograms (ECGs) and assessments of left ventricular ejection fraction (LVEF) were performed every 12 weeks from 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. ECOG performance status was assessed every three 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 three months.

Adverse events were reported throughout the treatment period and up to 28 days following last dose of trastuzumab and pertuzumab. All adverse events considered related to study treatment, and all cardiac adverse events 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 adverse events considered related to trastuzumab or pertuzumab of NCI CTCAE grade 3 or worse. For 50 patients, an incidence of 10% would provide a 95% Clopper-Pearson confidence interval (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 one dose of pertuzumab or trastuzumab. All baseline summaries and efficacy analyses were based on the intent-to-treat (ITT) 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 enrolment. 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 adverse events, serious adverse events, cardiac events 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 two-sided 95% CIs. Only patients with measurable disease at baseline (enrolment) 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 25^{th} and 75^{th} 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 (see Figure 1). The data cut-off date was 21 March 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 (min to max: 1 to 49 cycles) of trastuzumab and pertuzumab. Exposure to taxane chemotherapy was much lower with a median of 6.0 cycles (1 to 15 cycles). Nab-paclitaxel was received for 7.0 cycles (1 to 11 cycles), docetaxel for 6.0 cycles (1 to 15 cycles) and paclitaxel for 2.5 cycles (1 to 4 cycles).

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

Thirty-six patients discontinued study treatment: 6 patients (12.0%) due to adverse events and 20 patients (40.0%) due to progressive disease (Figure 1). Fourteen patients (28.0%) 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 one hormonal therapy during the study of whom 14 received hormonal therapy after stopping study taxanes.

Primary Safety Endpoints

All patients experienced at least one adverse event during the study, with diarrhea, fatigue, peripheral neuropathy, alopecia, rash and nausea the most common events (Table 2). There were

349 adverse events 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).

CTC grade 3 or 4 adverse events were experienced by 32 patients (64.0%) (Table 3). Serious adverse events were experienced by 27 patients (54.0%) (**Table *4***). Notably no patients in the nab-paclitaxel group experienced febrile neutropenia of CTC grade 3 or worse, or a serious adverse event of febrile neutropenia. In addition, only one patient (2.0%), who received docetaxel, required concomitant granulocyte colony stimulating factors (filgrastim). Nine patients (18.0%) died due to disease progression. No deaths were considered related to study treatments.

Six patients (12.0%) experienced a total of 12 adverse events of suspected cardiac origin of whom four patients (8.0%) experienced eight adverse events considered by the investigator to be related to trastuzumab, pertuzumab or both. Three patients (6.0%) experienced five CTC grade 3 events of suspected cardiac origin: one patient experienced cardiac failure and hypertension (both New York Heart Association (NYHA) Class II), one patient experienced cardiac failure and cardiomyopathy (both NYHA Class II) and one patient experienced cardiomyopathy (NYHA Class III). Of these five events, three remained unresolved at study completion (hypertension and cardiac failure in one patient and cardiomyopathy in one patient). The remaining two events, in one patient, resolved: one with sequelae (cardiomyopathy) and one 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 one patient. There were four (8.0%) patients with a decrease in LVEF below 50% at any time during the study.

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

Subcutaneous injection of trastuzumab was associated with only a small number of injection site reactions. Twelve of 1140 injections (0.01%) 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.

Adverse events that led to withdrawal of trastuzumab and pertuzumab treatment were cardiac failure (two patients), drug hypersensitivity, decreased ejection fraction, syncope and bullous dermatitis (each one patient). Ten patients (20.0%) experienced an adverse event that led to withdrawal of taxane chemotherapy. Eight of 36 patients (22.2%) who received nab-paclitaxel and two of 13 patients (15.4%) who received docetaxel discontinued chemotherapy due to adverse events. No patients discontinued paclitaxel due to adverse events; however, only two patients received paclitaxel chemotherapy at any time during the study. Overall, the most common adverse events 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 partial or complete response to study treatment giving an ORR of 73.3% (95% CI 58.1% to 85.4%). Eight patients had stable disease (SD; 17.8% (95% CI 8.0% to 32.1%)) and three patients had progressive disease (6.7% (95% CI 1.4% to 18.3%). One patient was not evaluated.

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

Thirty patients (60.0%) had a PFS event with a median PFS of 17.0 months (95% CI 12.5 to 31.2 months) (Figure 2A). Nine patients (18.0%) died during the study. 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). Second line median OS from failure of first-line therapy until death from any cause was 21.3 months (95% CI: 14.9 to 29.0 months) (Figure 2C).

The median (min to max) length of time on the study was 18.8 months (0.76 to 34.5 months).

DISCUSSION

The observed safety profile combination trastuzumab SC and pertuzumab IV is similar to that in the CLEOPATRA study [3] suggesting that the subcutaneous trastuzumab formulation in this combination has a comparable safety and tolerability profile. There were two 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 intravenous trastuzumab 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.

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 adverse events 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 one CTC grade 3 event of suspected cardiac origin, compared with cardiac adverse events experienced by 16.4% of patients in the placebo treatment group (3.8% CTC grade 3 or above), and 14.5% of patients in the pertuzumab treatment group (1.5% grade 3 or above) in CLEOPATRA.[12] Only four patients (8.0%) 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]

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 study (NCT02402712) is a single arm phase IIIB study which aims to evaluate 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 ESMO 2018 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-randomised design with lack of comparator arm, and insufficient follow-up to determine OS. Comparisons of adverse events 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 breast cancer patients 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 progression free survival and overall survival) with acceptable toxicity has been shown in metastatic breast cancer using intravenous pertuzumab in combination with intravenous trastuzumab and docetaxel.
- SAPPHIRE an open-label, multicenter, phase IIIb study was the first study to investigate `the combination of intravenous pertuzumab, subcutaneous trastuzumab and clinician's choice taxane chemotherapy in previously untreated patients with HER2-positive metastatic breast cancer. 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 left ventricular ejection fraction 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.

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Tables

Table 1: Demographics and baseline characteristics

Parameter	
Age, years (SD)	52.9 (12.0)
Sex, n (%)	
Female	49 (98.0)
Male	1 (2.0)
BMI, mean (SD)	27.9 (6.4)
Race, n (%)	
White	42 (84.0)
Asian	4 (8.0)
Other	4 (8.0)
Female reproductive status [N=49], n (%)	
Childbearing	15 (30.6)
Surgically Sterile	4 (8.2)
Post-Menopausal	30 (61.2)
ECOG PS, n (%)	
0	33 (66.0)
1	15 (30.0)
2	2 (4.0)
Disease presentation at screening, n (%)	
De novo	23 (46.0)
Relapse	27 (54.0)
HER2 status at screening, n (%)	
HER2+	50 (100)
ISH+	44 (88)
IHC3+ (ISH not tested)	6 (12)
Hormone receptor status, n (%)	
ER^+ or PR^+ or both	31 (62.0)
ER^- and PR^-	19 (38.0)
Prior hormonal therapy in hormone positive patients, n (%)	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, n (%)	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], months (min, max)	22.1 (0.5, 62.3)

eBC early breast cancer

Table 2: Any grade adverse events occurring in > 7 patients (15%) in the total patient population

AE preferred term	Docetaxel n = 13	Nab-Paclitaxel n = 36	Paclitaxel n =1	Total N = 50
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)

Table 3: Grade 3+ adverse events in more than 1 patient (2%) in the total patient population

AE preferred term	Docetaxel n = 13	Nab-Paclitaxel n = 36	Paclitaxel n =1	Total N = 50
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)

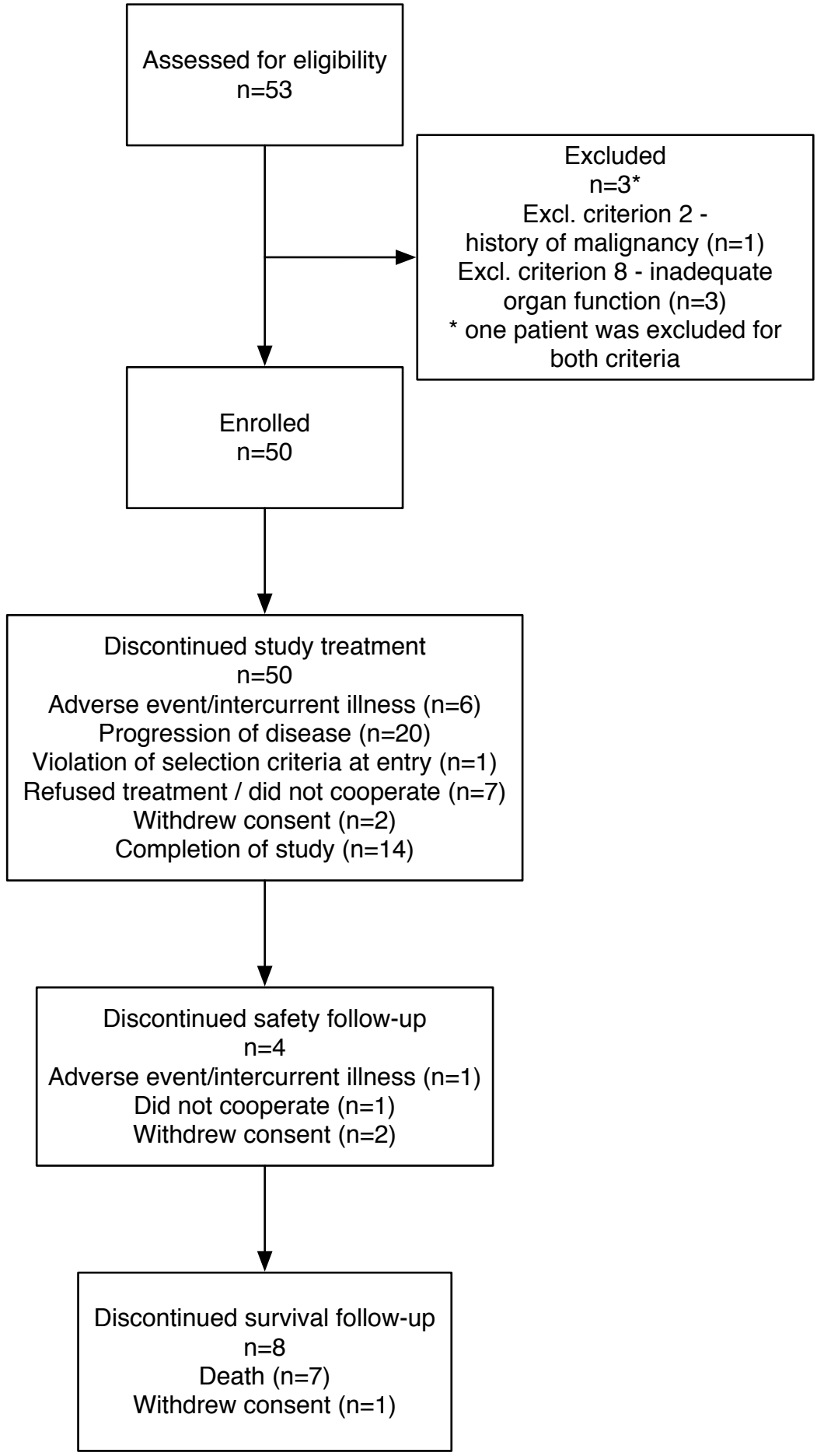
Table 4: Serious adverse events occurring in more than 1 patient (2%) in the total patient population

SAE preferred term	Docetaxel n = 13	Nab-Paclitaxel n = 36	Paclitaxel n =1	Total N = 50
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)

Figure Legends

Figure 1: Patient flow through the study

Figure 2: Kaplan-Meier curve of a) PFS (ITT population), b) OS (ITT population) and c) OS (second-line therapy; ITT population)


Assessed for eligibility
n=53
Excluded
n=3*
Excl. criterion 2 -
history of malignancy (n=1)
Excl. criterion 8 - inadequate
organ function (n=3)
* one patient was excluded for
both criteria
Enrolled
n=50
Discontinued study treatment
n=50
Adverse event/intercurrent illness (n=6)
Progression of disease (n=20)
Violation of selection criteria at entry (n=1)
Refused treatment / did not cooperate (n=7)
Withdrew consent (n=2)
Completion of study (n=14)
Discontinued safety follow-up
n=4
Adverse event/intercurrent illness (n=1)
Did not cooperate (n=1)
Withdrew consent (n=2)
Discontinued survival follow-up
n=8
Death (n=7)
Withdrew consent (n=1)