Published in final edited form as:

Breast Cancer Res Treat. 2016 July ; 158(1): 91–97. doi:10.1007/s10549-016-3851-7.

Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer: overall survival and updated progression-free survival results from a phase II study

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Abstract

We previously reported progression-free survival (PFS) results on a phase II trial of weekly paclitaxel, trastuzumab, and pertuzumab in patients with human epidermal growth factor receptor 2(HER2)-positive metastatic breast cancer (MBC) treated in the first- and second-line setting. Here, we report results for overall survival (OS) and updated PFS after an additional year of follow-up. Patients with HER2-positive MBC with 0–1 prior treatment were eligible. Treatment consisted of paclitaxel (80 mg/m²) weekly, and trastuzumab (loading dose 8 mg/kg → 6 mg/kg) and pertuzumab (loading dose 840 mg → 420 mg) every 3 weeks, all given intravenously. Primary endpoint was 6-month PFS. Secondary endpoints included median PFS, 6-month and median OS. Evaluable patients received at least one full dose of treatment. From January 2011 to December 2013, 69 patients were enrolled: 51 (74 %) and 18 (26 %) treated in first- and second-line metastatic settings, respectively. As of July 1, 2015, the median follow-up was 33 months (range 3–49 months; 67 patients were evaluable for efficacy). The median OS was 44 months (95 % CI 37.5–NR) overall and 44 months (95 % CI 38.3–NR) and 37.5 months (95 % CI 30.3–NR) for patients with 0 and 1 prior metastatic treatment, respectively; 6-month OS was 98 % (95 % CI 90–1). The 6-month PFS was 86 % (95 % CI 75–93) overall and 89 % (95 % CI 76–95) and 78 % (95 % CI 51–91) for patients with 0 and 1 prior therapy, respectively; and median PFS was 21.4 months (95 % CI 14.1–NR) overall and 25.7 months (95 % CI 14.1–NR) and 16.9

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Compliance with ethical standards

Conflict of interest disclosures LMS, NMI, MFC, SMP, SP, CWL, DFA, JCS, SC, SMS, EAC, PD, TTS, JB, LN: no COI.CAH: Consulting- Genentech, CTD: Research funding-Genentech/Roche. TAT: Advisory-Genentech.DFA: Travel- Roche.

months (95 % CI 8.5–NR) for patients with 0–1 prior treatment, respectively. Treatment was well tolerated. Updated analysis demonstrates that weekly paclitaxel, when added to trastuzumab and pertuzumab, is associated with a favorable OS and PFS and offers an alternative to docetaxel-based therapy. <http://www.ClinicalTrials.gov> NCT0127604

Keywords

Breast cancer; Metastatic; HER2 positive; Pertuzumab; Trastuzumab; Paclitaxel

Introduction

Amplification of the *HER2* gene leading to human epidermal growth factor receptor 2(HER2) protein overexpression occurs in 20–30 % of breast cancers and is associated with an aggressive natural history and decreased overall survival [1, 2]. Outcomes of patients diagnosed with all stages of HER2-positive breast cancer have improved dramatically as therapies that specifically target HER2 have been approved [3, 4]. Trastuzumab is a humanized monoclonal antibody that binds the extracellular juxta membrane domain IV of HER2, preventing receptor dimerization and thus inhibiting proliferation and cell survival [5]. Pertuzumab, however, binds to domain II and prevents HER2 dimerization with other ligand-activated HER receptors [6–8]. These antibodies have a complementary mechanism of action and both stimulate antibody-dependent, cell-mediated cytotoxicity [9].

The combination of pertuzumab and trastuzumab with docetaxel has been shown to significantly improve progression-free survival (PFS) and overall survival (OS) for HER2-positive metastatic breast cancer [4, 10, 11]. In the adjuvant setting, weekly paclitaxel has been shown to be less toxic than docetaxel given every 3 weeks [12]. We conducted a phase II trial of paclitaxel with trastuzumab and pertuzumab, and the primary results of which demonstrated a favorable PFS that led to its inclusion in the National Comprehensive Cancer Network (NCCN) guidelines as an effective alternative in the first-line treatment of HER2-positive metastatic breast cancer [13, 14]. Notably, the regimen was well tolerated with no febrile neutropenia (FN) or symptomatic left ventricular systolic dysfunction [13]. With an additional year of follow-up, we now report the median OS as well as updated PFS results.

Methods

Patients

The full details of this study have been previously reported [13]. We conducted a phase II trial at Memorial Sloan Kettering Cancer Center. Our aim was to establish safety and efficacy of paclitaxel, trastuzumab, and pertuzumab in patients with HER2-positive metastatic breast cancer who had previously received 0–1 prior treatment. Patients were eligible for the study if they were 18 years or older, had an Eastern Cooperative Oncology Group performance status of 0–1, measurable or non-measurable disease, adequate organ function, and a baseline left ventricular ejection fraction (LVEF) of ≥ 50 % by echocardiogram within 4 weeks before enrollment. Patients may have had (neo) adjuvant trastuzumab and stable and treated brain metastasis ≥ 2 months before enrollment. Exclusion

criteria included a history of prior cardiac morbidities within 12 months (unstable angina, myocardial infarction, congestive heart failure, and uncontrolled ventricular arrhythmias), prior pertuzumab, and grade 2 neuropathy.

Study design and treatment

We administered paclitaxel 80 mg/m² once per week plus trastuzumab (8 mg/kg loading dose → 6 mg/kg) and pertuzumab (840 mg loading dose → 420 mg) once every 3 weeks, all given intravenously. One cycle consisted of three doses of weekly paclitaxel with one dose of every 3-weekly dual anti-HER2 antibody therapy (Fig. 1). Paclitaxel could be stopped after 6 months of therapy, if patients were deemed to be progression-free, and patients were maintained on antibodies alone until progression of disease. Upon progression of disease, they were permitted to restart paclitaxel with continued dual antibody therapy per the treating physician's discretion, but they were censored at the time of progression. Upon re-initiation of paclitaxel, chemotherapy dose was held and/or reduced as clinically warranted. Paclitaxel dose reductions were permitted (i.e., 80–60 and then 60–45 mg/m²).

Dose reductions of pertuzumab and trastuzumab were not permitted; however, doses could be held for significant asymptomatic LVEF decline of 10–15 % to less than 50 % or 16 % (from baseline) or for clinical heart failure, as defined by the study. Repeat echocardiogram or multigated angiogram within 3 weeks demonstrating recovery of LVEF, was required to restart anti-HER2 therapies.

Outcomes and assessments

Tumor assessments for primary and secondary endpoints were based on Response Evaluation Criteria in Solid Tumors version 1.1 and were done every 3 months. Adverse events were monitored continuously and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0). Patients were seen once per cycle with chemistry laboratory assessments performed every cycle, and a complete blood count was obtained before each chemotherapy dose. Echocardiogram with strain imaging was performed at screening, every 3 months and within 3 months of completion of treatment. Blood samples for exploratory cardiac biomarkers (troponin, brain natriuretic peptide, and neuregulin-β) were collected every other cycle at six time points.

Statistical methods

The primary endpoint for the trial was 6-month PFS. This endpoint was reached and previously reported. [13] Secondary endpoints included an analysis of median PFS, 6-month OS, and median OS using Kaplan–Meier methods and a detailed reporting of safety (including cardiac safety) and tolerability. Cardiac safety was defined as symptomatic left ventricular systolic dysfunction (LVSD), non-LVSD cardiac death, or probable cardiac death. Cardiac biomarkers were explored (previously reported) [15]. Herein, we report the median OS and updated PFS results. These analyses include one additional year of follow-up compared to the original clinical trial report. Overall survival was defined as the time period from enrollment to death from any cause and PFS was defined as the time period from enrollment to disease progression or death, whichever came first. For all analyses, evaluable patients included any patient who received at least one full dose of therapy. For

OS, patients who were alive were censored at the last known date they were alive, with a cutoff date of July 1, 2015. For PFS, patients who were alive without progression were censored at the last known clinical evaluation. The PFS and OS estimates were calculated using Kaplan–Meier methods. The SAS version 9.2 (SAS Institute, Cary, NC) and R v 3.1.1 were used for statistical analyses.

Results

Study population

Figure 2 shows the trial CONSORT diagram and Table 1 presents the patients' baseline characteristics. Of the 69 enrolled patients, two were not evaluable because they experienced immediate hypersensitivity reactions to paclitaxel and came off study on the same day they enrolled (before receiving antibody therapy). Thus, 67 patients had follow-up data available for efficacy and safety analysis.

Efficacy

With a median follow-up of 33 months (3–49 months) in the 67 evaluable patients, 21 (31 %) deaths had occurred. All deaths were attributable to progression of disease. Median OS was 44 months (95 % CI 37.5–NR) overall (Fig. 3a) and 44 months (95 % CI 38.3–NR) and 37.5 months (95 % CI 30.3–NR) for patients with 0 and 1 prior metastatic treatment, respectively (Fig. 3b). The 6-month OS was 98 % (95 % CI 90–1). At the time of data cutoff, 38 of 67 (57 %) evaluable patients had a progression-free survival event. Median PFS was 21.4 months (95 % CI 14.1–NR) overall (Fig. 4a) and 25.7 months (95 % CI 14.1–NR) and 16.9 months (95 % CI 8.5–NR) for patients with 0 and 1 prior therapy, respectively (Fig. 4b). Updated 6-month PFS was 86 % (95 % CI 75–93) overall and 89 % (95 % CI 76–95) and 78 % (95 % CI 51–91) for patients with 0 and 1 prior therapy, respectively.

Treatment exposure

In the evaluable population, 46 of 67 (69 %) received subsequent treatment for breast cancer after discontinuation of the study, and the median number of treatments received was 2 (range 1–7). Treatments received after discontinuation are detailed in Table 2.

In the safety population (i.e., those who received at least 1 dose of antibody therapy, $n = 67$), the median time on treatment was 17 months (range 1–53), with a median number of antibody cycles of 22 (range 2–70), and a median number of cycles of paclitaxel of 10 (range 2–29). Of the 32 patients who progressed on study, 10 (31 %) had paclitaxel restarted with continued dual antibody therapy after progression, 4 of which remain on therapy; these 10 patients were censored for progression before being reinitiated on paclitaxel as allowed by study to mimic real-life practice. The median number of cycles of paclitaxel received post-progression in this group was 3 (range 1–17).

Toxicity

Overall, with an additional year of follow-up since the first report [13], adverse events were relatively similar particularly with respect to grade 3 events. No new safety concerns were identified during the extended follow-up period. Compared with previous reporting of this

study, [13] adverse events did not change significantly (Table 3). The incidence of FN remained 0 % with longer follow-up.

In this study, median LVEF was preserved throughout and no patients experienced a cardiac event as defined by the protocol (symptomatic LVSD). Specific details of cardiac safety from this study are reported and discussed separately [15].

Serious adverse events were reported in 14 (21 %) of 67 patients who received pertuzumab, trastuzumab, and paclitaxel as follows: 3-G3 cellulitis, 3-symptomatic brain metastases requiring hospital admission (1-G4 cerebral edema, 1-G1 seizure, and 1-G1 headache), 1-G4 hypomagnesemia, 1-G4 hypersensitivity reaction to paclitaxel, 1-G4 AST/ALT elevation secondary to choledocholithiasis, 1-G3 diarrhea, 1-G3 pericardial effusion, 1-G3 macular edema, 1-G3 diverticulitis, and 1-G3 post-operative hematoma after breast implant exchange. No (0 %) deaths were attributable to an adverse event.

Discussion

With a median follow-up of 33 months, the median OS was 44 months (95 % CI 37.5–NR) overall and 44 months (95 % CI 38.3–NR) and 37.5 months (95 % CI 30.3–NR) for patients with 0 and 1 prior metastatic treatment, respectively, with weekly paclitaxel with trastuzumab and pertuzumab. With a longer follow-up, we also report a median PFS of 21.4 months (95 % CI 14.1–NR) overall and 25.7 months (95 % CI 14.1–NR) and 16.9 months (95 % CI 8.5–NR) for patients with 0–1 prior treatment, respectively. While we cannot compare results directly across trials, it is notable that with a similar duration of median follow-up (30 months) in the interim analysis of CLEOPATRA, median PFS was 18.7 months (16.6–21.6) [10]. Recently, the results of the VELVET study were reported demonstrating a median PFS of 11.5 months with vinorelbine, trastuzumab, and pertuzumab in the first-line setting [16]. In terms of survival, although median OS in CLEOPATRA had not yet been reached (95 % CI 42.4–NE) at the time of the interim analysis, in the intention to treat population the number of deaths among patients assigned to dual HER2 antibody therapy with docetaxel was 113 (28 %) of 402 patients, which was strikingly similar to the number of deaths in our study in which 21 of 69 (30 %) patients have expired [10].

A higher proportion of patients treated on this study had prior exposure to trastuzumab in both the neoadjuvant/adjuvant (32 %) and first-line metastatic settings (20 %) compared with 10 and 0 % respectively in CLEOPATRA. In fact, 9 % of our study population had previously received trastuzumab in both settings. CLEOPATRA only enrolled patients who had not received previous chemotherapy or anti-HER2 therapy for their metastatic disease; by comparison 26 and 17 % of patients treated on this study had already received first-line therapy with any therapy and chemotherapy with trastuzumab, respectively, for metastatic disease. Unsurprisingly, the med PFS and OS in our study were higher for those who were treated in the first-line setting of 25.7 months (95 % CI 14.1–NR) and 44 months (95 % CI 38.3–NR), respectively, versus in the second-line setting of 16.9 months (95 % CI 8.5–NR) and 37.5 months (95 % CI 30.3–NR), respectively. Despite the fact that this was a phase II non-randomized study, the efficacy results are encouraging and compare favorably with the seminal trial (CLEOPATRA).

Adverse events reported here with the additional follow-up were generally similar to those reported at the primary analysis [13]. Incidence of grade 3 fatigue, peripheral neuropathy, and diarrhea were 8, 5, and 3 % respectively. Notably the incidence of FN remained low at 0 %, which compared favorably to the FN rates of 2.8 % in the VELVET study [16, 17] and 13 % in CLEOPATRA [4, 10]. The serious adverse event rate (21 %) was also lower than that reported in CLEOPATRA (36 %) or in the VELVET study (29 % when dual HER2 antibodies were administered as separate infusions and 41 % when co-administered in a single infusion) [16–18]. Significantly there were no deaths attributable to an adverse event in this study compared with 2 and 3 % in each study arm of CLEOPATRA, of which FN or infections were the most frequent causes [4, 10]. There were no cardiac adverse events defined by the protocol (symptomatic LVSD) [13] or with longer follow-up.

Many studies thus far have demonstrated the efficacy of pertuzumab and trastuzumab combined with chemotherapy in HER2-positive breast cancer in the metastatic [4, 10, 13, 18] and neoadjuvant settings [19–21], and are currently under evaluation as adjuvant therapy [22, 23]. In the phase III randomized MARIANNE trial, T-DM1 and T-DM1 with pertuzumab treatments resulted in non-inferior, but not superior, PFS compared with trastuzumab plus a taxane in patients with locally advanced or metastatic HER2-positive breast cancer being treated in the first-line setting [24]. The results of these studies taken collectively confirm that a taxane combined with dual HER2 antibody therapy remains the optimal first-line regimen for metastatic HER2-positive breast cancer.

The final prespecified overall survival results of CLEOPATRA, with a median follow-up of 50 months, reported a 15.7 month improvement in OS with the addition of pertuzumab to trastuzumab and docetaxel (56.5 months [95 % confidence interval [CI], 49.3–NR] as compared with 40.8 months [95 % CI 35.8 to 48.3], hazard ratio favoring the pertuzumab group, 0.68; 95 % CI 0.56–0.84; $P < 0.001$) [11]. A further follow-up of our study with equally mature OS results will be reported. However, many patients will still progress and ultimately die of metastatic HER2-positive breast cancer, and thus, more work is ongoing to understand the mechanisms of resistance, as more therapies are explored for these patients.

In conclusion, the combination of dual HER2 blockade with weekly paclitaxel has shown promising efficacy and encouraging safety among our study population and offers another effective standard option in the treatment of metastatic HER2-positive breast cancer [13, 14].

Acknowledgments

We thank all the study investigators and their clinical teams for their contribution to this study, and the patients for agreeing to participate.

Funding This work was supported by Roche-Genentech. No grant applied.

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Fig. 1.
Treatment schema

Fig. 2.

Consort diagram. [†] *G4* Hypomagnesemia, *G3* Dry skin, *G3* Macular Edema secondary to paclitaxel, *G3* Diarrhea, *G2* Allergic reaction to paclitaxel, *G3* Asymptomatic LVEF decline and *G2* Edema

Fig. 3.

a Kaplan-Meier estimates of overall survival (evaluable population). Tick marks indicate censoring events. **b** Kaplan-Meier estimates of overall survival (evaluable population). Patients are stratified by previous treatment status

Fig. 4.
a Kaplan-Meier estimates of progression-free survival (evaluable population). **b** Kaplan-Meier estimates of progression-free survival (evaluable population). Patients are stratified by previous treatment status

Table 1Baseline characteristics of ITT population ($n = 69$)

Characteristic	No. (%)
Age (years)	
Median	53
Range	26–84
Race	
Asian	10 (14)
Black	15 (22)
White	44 (64)
ECOG PS	
0	41 (59)
1	27 (39)
2	1 (1)
Disease type at screening	
Non-visceral	20 (29)
Visceral	49 (71)
Measurable disease	57 (83)
Non-measurable disease	12 (17)
Hormone receptor status	
ER positive and/or PgR positive	44 (64)
ER negative and PgR negative	25 (36)
HER2 status assessed by IHC	
0 or 1+	3 (4)
2+	8 (12)
3+	56 (81)
Unknown	2 (3)
HER2 status assessed by FISH	
Positive	29 (42)
Negative	1 (1)
Unknown	39 (57)
Prior adjuvant or neoadjuvant therapy	
No	39 (57)
Yes ^a	30 (43)
Anthracycline	19 (28)
Taxane	25 (32)
Hormone	22 (32)
Trastuzumab	22 (32)
Other	1 (1)
Prior treatment of metastatic disease	
None	51 (74)
One prior therapy	18 (26)

Characteristic	No. (%)
Chemotherapy + trastuzumab	12 (17)
Endocrine therapy + trastuzumab	1 (1)
Chemotherapy + trastuzumab + lapatinib	1 (1)
Endocrine therapy alone	4 (6)

ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PgR, progesterone receptor

^aPatients may have received either adjuvant or neoadjuvant therapy

Table 2Breast cancer treatments received by patients who discontinued study treatment ($n = 46$)

Treatment	No. (%)
Anti-HER2 therapies	
Trastuzumab	42 (91)
Pertuzumab	25 (54)
TDM-1	19 (41)
Lapatinib	13 (28)
Neratinib	3 (7)
Chemotherapy Agents	
Taxane	15 (33)
Gemcitabine	15 (33)
Capecitabine	12 (26)
Vinorelbine	9 (20)
Eribulin	8 (17)
Carboplatin	6 (13)
Cyclophosphamide	5 (11)
Anthracycline	4 (9)
Methotrexate	4 (9)
Fluorouracil	4 (9)
Irinotecan	1 (2)
Others	
Hormone therapy	8 (17)
Phase 1 Study	4 (9)
Everolimus/Temsirolimus	4 (9)
Bevacizumab	3 (7)

Table 3Adverse events safety population ($n = 67$)

Adverse event	Grade 1 and 2 No. (%)	Grade 3 and 4, No. (%)
Diarrhea	58 (87)	2 (3)
Fatigue	57 (85)	5 (8)
Alopecia	57 (85)	0
Peripheral neuropathy	56 (84)	3 (5)
AST/ALT elevation	49 (73)	2 (3)
Cough	43 (64)	0
Dry skin	43 (64)	1 (1.5)
Arthralgia	42 (63)	0
Nausea	41 (61)	1 (1.5)
Acneiform rash	38 (57)	0
Mucositis	37 (55)	0
Peripheral edema	36 (54)	0
Hot flashes	36 (54)	0
Xerophthalmia	33 (49)	0
Dyspepsia	30 (45)	0
Epiphora	30 (45)	0
Epistaxis	29 (43)	0
Dyspnea	28 (42)	0
Anorexia	28 (42)	0
Hand-foot syndrome	25 (37)	2 (3)

Safety population includes all patients who received at least one dose of study drug. Adverse events of all grades shown have a frequency of 25 % or higher