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ORIGINAL RESEARCH ARTICLE

Long-Term Safety and Effectiveness of PF-05280014 (a Trastuzumab Biosimilar) Treatment in Patients with HER2-Positive Metastatic Breast Cancer: Updated Results of a Randomized, Double-Blind Study

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Abstract

Background PF-05280014 was compared with trastuzumab sourced from the European Union (trastuzumab-EU), each plus paclitaxel, as first-line treatment for human epidermal growth factor receptor 2-positive metastatic breast cancer in a phase III study. Equivalence between treatment groups was demonstrated.

Objective The aim of this study was to report long-term safety and overall survival (OS) over 6 years after the first patient was screened.

Patients and methods Randomized patients received intravenous PF-05280014 or trastuzumab-EU, each plus paclitaxel, until objective disease progression. OS, long-term safety, subgroup safety (patients ongoing after day 378), and time-to-treatment discontinuation (TTD) were assessed based on the final statistical analysis plan amended for the ad-hoc analyses.

Results Of 707 randomized patients ($n = 352$, PF-05280014; $n = 355$, trastuzumab-EU), 252 (71.6%) in the PF-05280014 and 251 (70.7%) in the trastuzumab-EU group discontinued treatment due to objective progression. Overall, 451 (63.8%) patients completed the study. Between groups (PF-05280014; trastuzumab-EU), estimated median TTDs were 12.25 and 12.06 months ($p = 0.692$); 61 (17.3%) and 67 (18.9%) patients died; stratified hazard ratio for OS was 0.929 (95% confidence interval 0.656–1.316; $p = 0.339$); estimated survival rates were 82.3 and 77.4% at 2 years and 77.2 and 75.3% at 3 years. The incidences of treatment-emergent adverse events (TEAEs) overall (98.6%; 96.6%) and for grades ≥3 (41.0%; 43.1%) were comparable between groups. In patients ($n = 265$; $n = 264$) ongoing after day 378, the incidences of any TEAEs, grade ≥3 TEAEs, and serious TEAEs were comparable between the treatment groups.

Conclusion Long-term safety and OS were consistent with previous results and demonstrated no clinically meaningful differences between treatment groups.

Trial registration ClinicalTrials.gov: NCT01989676 (21 November 2013); and EudraCT: 2013-001352-34 (18 December 2013).

1 Introduction

Trastuzumab is a recombinant humanized immunoglobulin G1 monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 (HER2); it has been used to treat HER2-positive breast cancer and gastric cancer [1, 2]. PF-05280014 (Trazimera™, Pfizer) is a trastuzumab biosimilar that has received regulatory approval in many countries globally, including the European Union (EU) [3], United States [4], Canada [5], Australia [6], New Zealand [7], and Japan [8]. All eligible indications of reference trastuzumab (Herceptin®), including HER2-positive breast cancer and HER2-positive metastatic gastric cancer are approved therapeutic indications of PF-05280014.

To obtain marketing authorization, biosimilars are required to demonstrate similarities in quality, safety, and efficacy compared with the licensed reference biologic products in analytical, nonclinical, and clinical studies [9–11]. Findings from nonclinical studies showed that compared with reference trastuzumab (Herceptin®) sourced from the EU (trastuzumab-EU) or from the United States (trastuzumab-US), PF-05280014 has similar chromatographic profiles in peptide mapping, similar in vitro inhibition of tumor cell growth, and similar in vivo pharmacokinetic (PK) and

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Key Points

PF-05280014 is a trastuzumab biosimilar used to treat human epidermal growth factor receptor 2 (HER2)-positive breast cancer in many countries globally.

PF-05280014 plus paclitaxel was compared with trastuzumab sourced from the EU plus paclitaxel in a randomized, double-blind trial for patients with HER2-positive breast cancer (NCT01989676), and equivalence of the two treatments was demonstrated.

Analysis using data collected over 6 years of this trial showed that long-term safety and overall survival were consistent with previous results and no clinically meaningful differences were observed between the two treatment groups.

immunogenicity characteristics [12]. Analytical testing has been additionally conducted by using trastuzumab sourced from Japan (trastuzumab-JP) and the results showed that the characteristics of PF-05280014 and trastuzumab-JP were similar [13]. In healthy male trial participants, PF-05280014 has demonstrated similar PK profiles and similar immunogenicity compared with trastuzumab-EU and trastuzumab-US [14]. Similar to reference trastuzumab, PF-05280014 was well tolerated without serious adverse events (AEs) reported [14].

As the confirmatory step in the biosimilarity assessment, a multinational, randomized, double-blind, parallel-group study, REFLECTIONS B327-02 (ClinicalTrials.gov: NCT01989676), was conducted and compared PF-05280014 with trastuzumab-EU, each in combination with paclitaxel, in the first-line treatment of HER2-positive metastatic breast cancer [15]. In the week 33 analysis, equivalence between the two treatment groups was demonstrated for the primary efficacy endpoint of objective response rate (ORR), evaluating responses achieved by week 25 and confirmed by week 33 (data cutoff 24 August 2016) [15]. In the week 53 analysis, which used data collected up to 378 days after randomization (data cutoff 11 January 2017), it was shown that there were no notable differences between the treatment groups in terms of progression-free survival (PFS), overall survival (OS), or duration of response, and no notable differences between the treatment groups in safety profile, PK, or immunogenicity [15]. In a separate supportive phase III study (ClinicalTrials.gov, NCT02187744), PF-05280014 was shown to be non-inferior to trastuzumab-EU in PK, and comparable in efficacy, safety, and immunogenicity as a neoadjuvant treatment in patients with operable HER2-positive breast cancer [16].

Trastuzumab treatment has been reported to be associated with cardiac toxicity that is most commonly presented as asymptomatic left ventricular ejection fraction (LVEF) decline [17, 18]. Therefore, cardiac safety assessment of trastuzumab has relevant clinical importance for its long-term use. In recent years, long-term follow-up data of trastuzumab clinical studies have shown that the number of cardiac events since randomization had not changed significantly with time [19], and adding trastuzumab did not cause long-term worsening of cardiac function [20]. To accumulate the information, long-term safety of trastuzumab biosimilars is an important consideration in the clinical trial setting.

In REFLECTIONS B327-02, patients who showed clinical benefit from study treatment had an opportunity to continue with trastuzumab therapy after the data cutoff date for the week 53 analysis. Updated data from this study population including treatment duration and OS will provide valuable information for HER2-positive breast cancer therapy. Thus, the current analysis aimed to assess long-term safety, treatment duration, and OS data collected beyond 6 years after the first patient was screened.

2 Methods

2.1 Study Design

This was a multinational, randomized, double-blind, phase III study conducted across 143 sites in 25 countries between February 2014 and June 2020 (Last Subject Last Visit: 27 June 2020). The study was conducted in accordance with the Declaration of Helsinki, as well as following all relevant local requirements. The protocol, its amendments, and informed consent documentation were reviewed and approved by the institutional review board(s) or independent ethics committee(s) at each site. Patients gave informed consent prior to undergoing any study-specific procedure.

Data were analyzed firstly when all patients had completed week 33 (the primary efficacy analysis) and secondly when all patients had completed week 53 (the secondary analysis) visit assessments. After the data cutoff date (11 January 2017) for the week 53 analysis, the study protocol was amended to delineate two treatment periods (treatment period 1 [TP1] and treatment period 2 [TP2]). TP1 for a patient began with the first dose of study treatment on cycle 1, day 1 and ended with the completion of the week 53 visit assessments and upon providing written, signed, and dated informed consent for the protocol amendment. The study elements required to achieve study objectives and endpoints (i.e., through week 53 visit assessments) were contained within TP1. TP2 was intended solely to provide access to study treatment for patients who continued to receive clinical

benefit beyond TP1. Patients who received study treatment beyond week 53 at the time of the protocol amendment and provided written informed consent for the protocol amendment, entered TP2 as soon as possible and no later than 28 days following the approval of the protocol amendment. During TP2, minimal protocol-required assessments and procedures were undertaken, and all other routine patient care assessments were at the discretion of the investigator based on local practice/standard of care (SoC). Patients were treated in TP2 in a blinded manner with the trastuzumab treatment to which they were initially randomized (PF-05280014 or trastuzumab-EU) until discontinuation. Continued treatment in the study was based on documented evidence of clinical benefit. The study design is shown in Supplementary Fig. 1 in the electronic supplementary material (ESM).

The study ended after marketing authorization for PF-05280014 was granted in several countries globally. Patients who continued to show clinical benefit were transferred to access programs as per regional regulations. The last dose of study treatment was administered on 30 May 2020.

2.2 Patient Population

The complete eligibility criteria have been reported [15]. In brief, eligible patients were women aged ≥ 18 years with metastatic, histologically confirmed breast cancer, documented HER2 gene amplification or overexpression, one or more measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, Eastern Cooperative Oncology Group (ECOG) status of 0–2, and normal LVEF. The key exclusion criteria included relapse within 1 year of last dose of previous adjuvant (including neoadjuvant) treatment (except endocrine therapy) and within 1 year before randomization; prior systemic treatment for metastatic breast cancer (except endocrine therapy); inflammatory breast cancer; prior cumulative dose of doxorubicin > 400 mg/m^2, epirubicin dose > 800 mg/m^2, or the equivalent dose for other anthracyclines or derivatives; and active or uncontrolled symptomatic central nervous system metastases confirmed by clinical symptoms, cerebral edema, and/or progressive growth.

2.3 Treatments

Patients were randomized 1:1 to receive intravenous PF-05280014 or trastuzumab-EU, each in combination with paclitaxel. The randomization was stratified by prior trastuzumab exposure (yes/no) and estrogen receptor status (positive/negative).

PF-05280014 or trastuzumab-EU was administered weekly (4 mg/kg loading dose on cycle 1 day 1; subsequent doses 2 mg/kg) on days 1, 8, 15, and 22 of each 28-day cycle until at least week 33 and when given together with paclitaxel. Paclitaxel was administered on days 1, 8, and 15 of each 28-day cycle (starting dose 80 mg/m^2, with provision for dose reduction). In the absence of disease progression or unacceptable toxicity in the judgment of the investigator, paclitaxel treatment was continued for ≥ 6 cycles, until maximal benefit of response was obtained, or until the patient completed TP1.

Following completion of the paclitaxel administration period and beginning no earlier than week 33, PF-05280014 or trastuzumab-EU could then be continued as monotherapy, and the weekly regimen could be changed to 6 mg/kg every 3 weeks. Study treatment with PF-05280014 or trastuzumab-EU was continued until objective disease progression as assessed by RECIST 1.1 in the judgment of the investigator or until the patient completed all week 53 visit assessments (i.e., end of TP1), whichever occurred first. Patients continuing to derive clinical benefit from study treatment after completing TP1 entered TP2; during TP2, all patients continued to receive PF-05280014 or trastuzumab-EU as monotherapy at a dose of 6 mg/kg every 3 weeks. Patients experiencing objective disease progression as assessed by RECIST 1.1 during TP2 were expected to discontinue study treatment.

2.4 Endpoints and Assessments

The primary and secondary endpoints and assessments have been described previously [15]. Secondary study endpoints of relevance to this analysis were OS (analyzed using time from date of randomization to death due to any cause) and safety evaluations.

AEs were classified using the medical dictionary for regulatory activities (MedDRA) classification system, version 23.0. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Treatment-emergent AEs (TEAEs) were defined as any AE that occurred, or any pre-existing AE that worsened, after beginning study treatment through 70 days after the last dose of study treatment. AEs of special interest included anaphylactic reaction, cardiac failure, ejection fraction decreased, infusion-related reaction, pyrexia, chills, pruritus, dyspnea, interstitial lung disease, and left ventricular dysfunction. AEs that occurred in ≥ 10% of patients in at least one treatment group and were not AEs of special interest were also evaluated.

As an ad-hoc analysis (supplemental to the original protocol), time to discontinuation from trastuzumab (defined as time from date of randomization to date of final administration of trastuzumab [i.e., PF-05280014 or trastuzumab-EU]) was also assessed as an indicator of effectiveness.

For follow-up, during TP1, survival status was collected by telephone contact every 2 months (± 14 days) up to 1

year from patient randomization and ≥ 6 months following last dose of study treatment. During TP1 and TP2, patients were followed for AEs for 6 months after the last dose of study treatment.

Tumor assessments were performed according to local SoC disease assessment frequency in TP2. A minimum interval of 4 months was recommended. Assessments of cardiac function via echocardiogram or multigated acquisition scan were also performed as per local SoC.

2.5 Statistical Analyses

The long-term safety and OS analyses were based on the final statistical analysis plan, which was amended to include the following ad-hoc analyses after reporting of data from the week 53 analysis.

Time-to-event endpoints were summarized using the Kaplan–Meier method in the intent-to-treat (ITT) population. The survival rate at 1, 2, and 3 years post-randomization was estimated. A 1-sided log-rank test was used to compare the survival distribution between the two treatments. For time to death, if there was no date of death for a patient, the patient was censored on the date of last contact. The time to discontinuation from trastuzumab was analyzed to estimate the median time on treatment, as well as the probability of still receiving trastuzumab at months 6, 9, and 12 after randomization. A 1-sided log-rank test was used to compare the curves representing the probability of remaining on treatment between the two treatment groups.

All patients treated with at least one dose of study treatment (PF-05280014 or trastuzumab-EU or paclitaxel) were included in the safety analysis. As long-term safety was of interest, most safety analyses were performed across all patients as well as for the subgroup of patients ongoing in the study after day 378 (which was the cutoff for inclusion in the previously presented week 53 analysis) [15]. When summarizing AEs for the subgroup, only those events that started after day 378 were included.

Data were summarized descriptively, where appropriate. Patients with an absolute decline in LVEF ≥ 10% and below the lower limit of normal (LLN) or with an absolute decline in LVEF ≥ 16% from baseline were summarized.

3 Results

3.1 Patient Characteristics and Disposition

Overall, 707 patients were randomized to PF-05280014 in combination with paclitaxel (PF-05280014 group; $n = 352$) or trastuzumab-EU in combination with paclitaxel (trastuzumab-EU group; $n = 355$) and included in the ITT population. Of these, 702 patients received study treatment and were included in the safety population (PF-05280014, $n = 349$; trastuzumab-EU, $n = 353$).

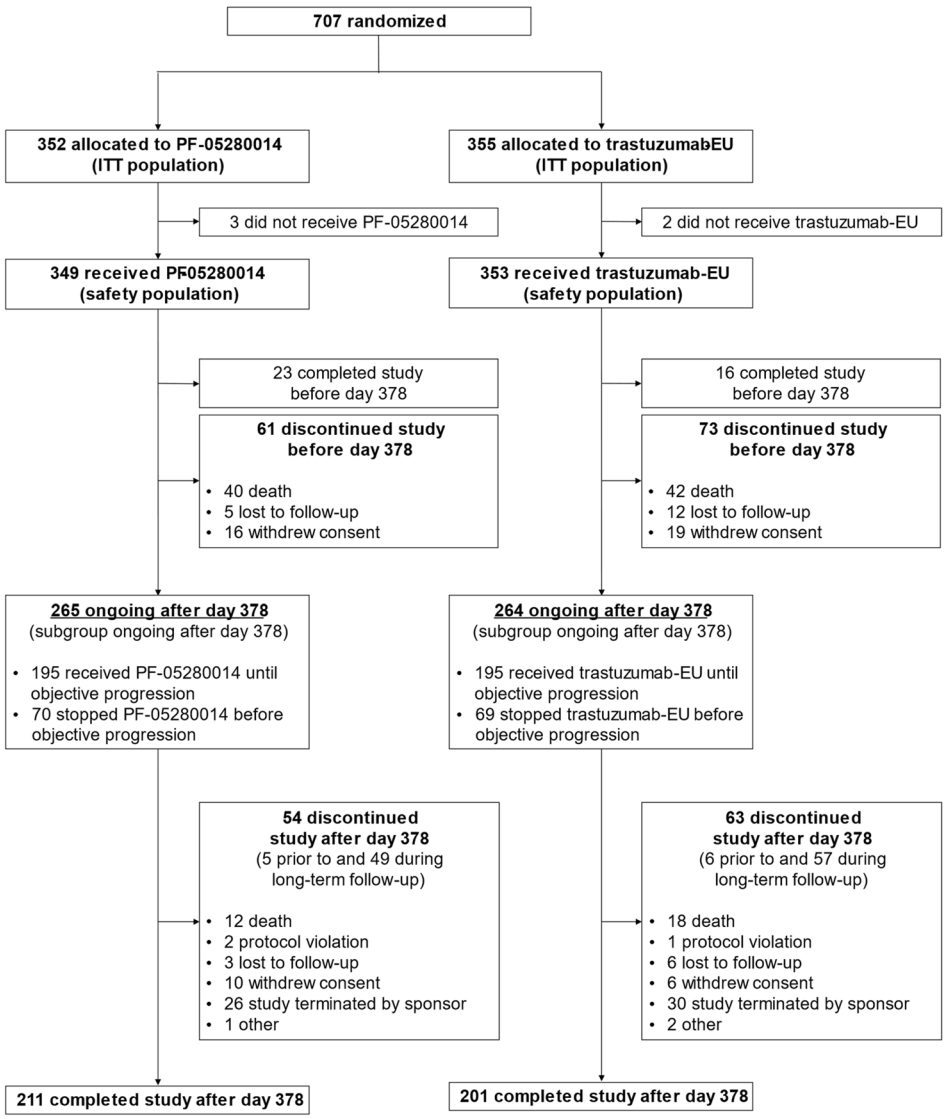
All patients had discontinued trastuzumab treatment (PF-05280014, $n = 352$ [100.0%]; trastuzumab-EU, $n = 355$ [100.0%]; includes the five patients who did not receive any study drug). The most frequent reason for discontinuing trastuzumab was objective progression (PF-05280014, $n = 252$ [71.6%]; trastuzumab-EU, $n = 251$ [70.7%]) (Fig. 1). Overall, 451 (63.8%) patients completed the study. Of the 256 (36.2%) patients who discontinued the study (including the five patients who did not receive any study drug), 53 (7.5%) patients discontinued prior to long-term follow-up and 198 (28.0%) patients discontinued during the long-term follow-up. Reasons for discontinuation from the study included death (112 [15.8%]), study terminated by Sponsor (56 [7.9%]), consent withdrawal (52 [7.4%]), lost to follow-up (26 [3.7%]), protocol violation (3 [<1.0%]), and 'other' reasons (7 [<1.0%]) (Fig. 1, Supplementary Table 1 in the ESM).

Baseline characteristics in the ITT population were well balanced between the treatment groups and have been reported previously [15]. All patients were adult females (≥ 18 years of age). The majority of patients were 45–64 years of age (61.2%) and of White race (67.3%). The most common diagnosis was ductal breast cancer (PF-05280014, $n = 278$ [79.0%]; trastuzumab-EU, $n = 277$ [78.0%]). In total, 31 (31/707, 4.4%) patients had a baseline ECOG score of 2. The stratification factors were comparable across treatment groups. There were 184 (52.3%) patients in the PF-05280014 group and 184 (51.8%) patients in the trastuzumab-EU group who had a positive estrogen receptor status at baseline. The corresponding numbers of patients with prior trastuzumab exposure were 33 (9.4%) and 39 (11.0%), respectively. Approximately half of the patients had received prior surgery for their primary diagnosis (353 [49.9%]). Overall, 309 (43.7%) patients had received previous systemic therapy; 232 (32.8%) patients had received prior radiation therapy. There were 152 (43.2%) patients in the PF-05280014 group and 157 (44.2%) in the trastuzumab-EU group who received previous neoadjuvant/adjuvant systemic therapy for breast cancer. For the subgroup of patients in the ITT population who were ongoing in the study after day 378, whether still receiving treatment or in follow-up (PF-05280014, $n = 265$; trastuzumab-EU, $n = 264$), baseline characteristics were also comparable between treatment groups (Table 1).

3.2 Treatment Exposure

In the safety population, the mean (standard deviation [SD]) duration of trastuzumab treatment was 74.7 (68.03) weeks in the PF-05280014 group and 78.3 (74.44) weeks in the trastuzumab-EU group. Corresponding mean (SD) durations

Fig. 1 Patient disposition



ITT intent-to-treat, *trastuzumab-EU* trastuzumab sourced from the European Union

of paclitaxel treatment were 31.5 (18.43) weeks and 33.0 (18.69) weeks.

3.3 Time to Discontinuation from Trastuzumab

In the ITT population, the estimated median time to discontinuation from trastuzumab was 12.25 months (95% confidence interval [CI] 11.93–14.52) for the PF-05280014 group and 12.06 months (95% CI 11.76–13.86) for the trastuzumab-EU group. There was no statistically significant difference in time to discontinuation from trastuzumab between the treatment groups (1-sided p value of the stratified log-rank test was 0.692). The hazard ratio when comparing time to discontinuation from trastuzumab between PF-05280014 and trastuzumab-EU was 1.039 (95% CI 0.894–1.207; Cox proportional hazards model, prior trastuzumab exposure [yes/no] and estrogen receptor status [positive vs negative] as strata) (Table 2; Fig. 2).

3.4 Overall Survival

OS results were based on long-term data from TP1 and TP2. The percentage of patients who died was comparable across treatment groups: 61 (17.3%) patients in the PF-05280014 group and 67 (18.9%) patients in the trastuzumab-EU group. The estimated survival rates (95% CI) at 1 year were 89.4% (85.6–92.2) for the PF-05280014 group and 87.5% (83.5–90.6) for the trastuzumab-EU group. Corresponding estimated survival rates at 2 years were 82.3% (77.2–86.3) and 77.4% (71.7–82.1), and at 3 years were 77.2% (70.5–82.6) and 75.3% (68.9–80.6). Median time to death could not be estimated in either treatment group (Fig. 3;

Table 1 Baseline demographic and other characteristics (ITT population)

	Overall population			Subgroup ongoing after day 378		
	PF-05280014 plus paclitaxel ($n = 352$)	Trastuzumab-EU plus paclitaxel ($n = 355$)	Total ($n = 707$)	PF-05280014 plus paclitaxel ($n = 265$)	Trastuzumab-EU plus paclitaxel ($n = 264$)	Total ($n = 529$)
Age, years						
Mean (SD)	54.0 (10.8)	54.1 (10.9)	54.1 (10.8)	54.1 (10.9)	54.2 (10.7)	54.1 (10.8)
Median (range)	55.0 (19–80)	54.0 (25–85)	54.0 (19–85)	55.0 (27–80)	54.0 (28–85)	55.0 (27–85)
Weight, kg						
Mean (SD)	69.1 (17.1)	68.1 (16.1)	68.6 (16.6)	68.8 (16.3)	67.9 (16.4)	68.3 (16.3)
Median (range)	68.2 (29–147)	66.0 (36–139)	67.0 (29–147)	68.1 (29–123)	65.0 (36–139)	67.0 (29–139)
Body mass index, kg/m^2						
Mean (SD)	27.4 (6.3)	26.8 (6.0)	27.1 (6.2)	27.2 (5.9)	26.8 (5.9)	27.0 (5.9)
Median (range)	26.5 (15.3–58.9)	25.7 (14.5–56.9)	26.1 (14.5–58.9)	26.5 (15.3–49.6)	25.9 (14.5–52.2)	26.3 (14.5–52.2)
Race, *n* (%)						
White	232 (65.9)	244 (68.7)	476 (67.3)	178 (67.2)	178 (67.4)	356 (67.3)
Black	5 (1.4)	8 (2.3)	13 (1.8)	5 (1.9)	7 (2.7)	12 (2.3)
Asian	104 (29.5)	84 (23.7)	188 (26.6)	76 (28.7)	65 (24.6)	141 (26.7)
Other	11 (3.1)	19 (5.4)	30 (4.2)	6 (2.3)	14 (5.3)	20 (3.8)
Time since initial diagnosis of breast cancer[a], *n*				259	260	519
Mean (SD), months	24.8 (37.8)	22.4 (29.8)	23.6 (34.0)	25.0 (38.1)	22.6 (30.6)	23.8 (34.6)
Median (range), months	6.7 (0–284)	6.1 (0–157)	6.5 (0–284)	5.4 (0–231)	4.8 (0–157)	4.8 (0–231)
Missing, *n*	9	7	16	6	4	10
Histopathological classification, *n* (%)						
Ductal	278 (79.0)	277 (78.0)	555 (78.5)	205 (77.4)	208 (78.8)	413 (78.1)
Lobular	14 (4.0)	17 (4.8)	31 (4.4)	12 (4.5)	13 (4.9)	25 (4.7)
Unknown	4 (1.1)	3 (< 1.0)	7 (< 1.0)	2 (< 1.0)	3 (1.1)	5 (< 1.0)
Other	56 (15.9)	58 (16.3)	114 (16.1)	46 (17.4)	40 (15.2)	86 (16.3)
Disease site[b], *n* (%)						
Lung	186 (52.8)	185 (52.1)	371 (52.5)	138 (52.1)	130 (49.2)	268 (50.7)
Liver	146 (41.5)	166 (46.8)	312 (44.1)	98 (37.0)	121 (45.8)	219 (41.4)
Lymph node	259 (73.6)	252 (71.0)	511 (72.3)	192 (72.5)	188 (71.2)	380 (71.8)
Skin	45 (12.8)	33 (9.3)	78 (11.0)	36 (13.6)	24 (9.1)	60 (11.3)
Bone	184 (52.3)	177 (49.9)	361 (51.1)	125 (47.2)	124 (47.0)	249 (47.1)
Brain	4 (1.1)	4 (1.1)	8 (1.1)	1 (0.4)	2 (0.8)	3 (0.6)
Breast	192 (54.5)	191 (53.8)	383 (54.2)	148 (55.8)	141 (53.4)	289 (54.6)
Other	68 (19.3)	81 (22.8)	149 (21.1)	53 (20.0)	54 (20.5)	107 (20.2)
Estrogen receptor status, *n* (%)						
Positive	184 (52.3)	184 (51.8)	368 (52.1)	147 (55.5)	140 (53.0)	287 (54.3)
Negative	168 (47.7)	171 (48.2)	339 (47.9)	118 (44.5)	124 (47.0)	242 (45.7)
Prior trastuzumab exposure, *n* (%)						
Yes	33 (9.4)	39 (11.0)	72 (10.2)	26 (9.8)	23 (8.7)	49 (9.3)
No	319 (90.6)	316 (89.0)	635 (89.8)	239 (90.2)	241 (91.3)	480 (90.7)
ECOG score, *n* (%)						
0	186 (52.8)	194 (54.6)	380 (53.7)	149 (56.2)	154 (58.3)	303 (57.3)
1	150 (42.6)	146 (41.1)	296 (41.9)	107 (40.4)	103 (39.0)	210 (39.7)
2	16 (4.5)	15 (4.2)	31 (4.4)	9 (3.4)	7 (2.7)	16 (3.0)
LVEF result, %						
Mean (SD)	65.4 (5.8)	65.3 (6.2)	65.3 (6.0)	65.6 (5.8)	65.6 (6.0)	65.6 (5.9)
Median (range)	65.0 (46–82)	65.0 (46–89)	65.0 (46–89)	65.0 (46–80)	65.5 (46–89)	65.0 (46–89)

ECOG Eastern Cooperative Oncology Group, *ITT* intent-to-treat, *LVEF* left-ventricular ejection fraction, *SD* standard deviation, *trastuzumab-EU* trastuzumab reference product sourced from the European Union

[a]Defined as time from initial diagnosis to first dose on cycle 1, day 1. Data were missing for 1 patient in the PF-05280014 group

[b]Data for disease sites recorded as 'no' or 'not assessed' are not presented

Supplementary Table 2 in the ESM). The stratified log-rank test resulted in a 1-sided *p* value of 0.339, indicating no statistically significant difference in OS between the treatment groups. Using a Cox proportional hazards model with prior trastuzumab exposure (yes/no) and estrogen receptor status (positive vs negative) as strata, the hazard ratio when comparing OS between PF-05280014 and trastuzumab-EU was 0.929 (95% CI 0.656–1.316).

3.5 Safety

The majority of patients, 344 (98.6%) in the PF-05280014 group and 341 (96.6%) in the trastuzumab-EU group, experienced one or more all-causality TEAE. In both the overall safety population and the subgroup of patients in the safety population who were ongoing in the study after day 378, the incidences of any TEAEs, grade 3 or higher TEAEs, and serious TEAEs were comparable between the treatment groups (Table 3). These results were consistent with those previously reported and no new clinically relevant findings were observed.

Table 2 Time to discontinuation from trastuzumab

	PF-05280014 plus paclitaxel ($n = 352$)	Trastuzumab-EU plus paclitaxel ($n = 355$)
Number censored	3 (< 1.0)	2 (< 1.0)
Reason for censorship		
Patient did not receive trastuzumab treatment	3 (< 1.0)	2 (< 1.0)
Primary reason for discontinuation from trastuzumab treatment, *n* (%)		
Objective progression	252 (71.6)	251 (70.7)
Global deterioration of health status	5 (1.4)	7 (2.0)
AE	23 (6.5)	19 (5.4)
Medication error without associated AE	0	0
Patient died	3 (< 1.0)	11 (3.1)
Protocol violation	1 (< 1.0)	5 (1.4)
Lost to follow-up	0	2 (< 1.0)
Patient no longer willing to continue treatment for reason other than AE	24 (6.8)	20 (5.6)
Study terminated by study sponsor	25 (7.1)	27 (7.6)
Other	16 (4.5)	11 (3.1)
Probability of on trastuzumab treatment		
At month 6[a] (95% CI[b])	77.65 (72.91–81.67)	80.17 (75.62–83.97)
At month 9[a] (95% CI[b])	67.62 (62.44–72.25)	68.56 (63.43–73.12)
At month 12[a] (95% CI[b])	54.15 (48.78–59.21)	51.28 (45.94–56.35)
Kaplan–Meier estimates of time to event (month)		
Quartiles (95% CI)[c]		
25%	7.16 (5.72–7.59)	7.43 (6.08–8.12)
50%	12.25 (11.93–14.52)	12.06 (11.76–13.86)
75%	23.03 (20.27–25.99)	23.20 (20.07–26.38)
Hazard ratio[d]	1.039	
95% CI of hazard ratio	0.894–1.207	
p value[e]	0.692	

AE adverse event, *CI* confidence interval, *trastuzumab-EU* trastuzumab sourced from the European Union

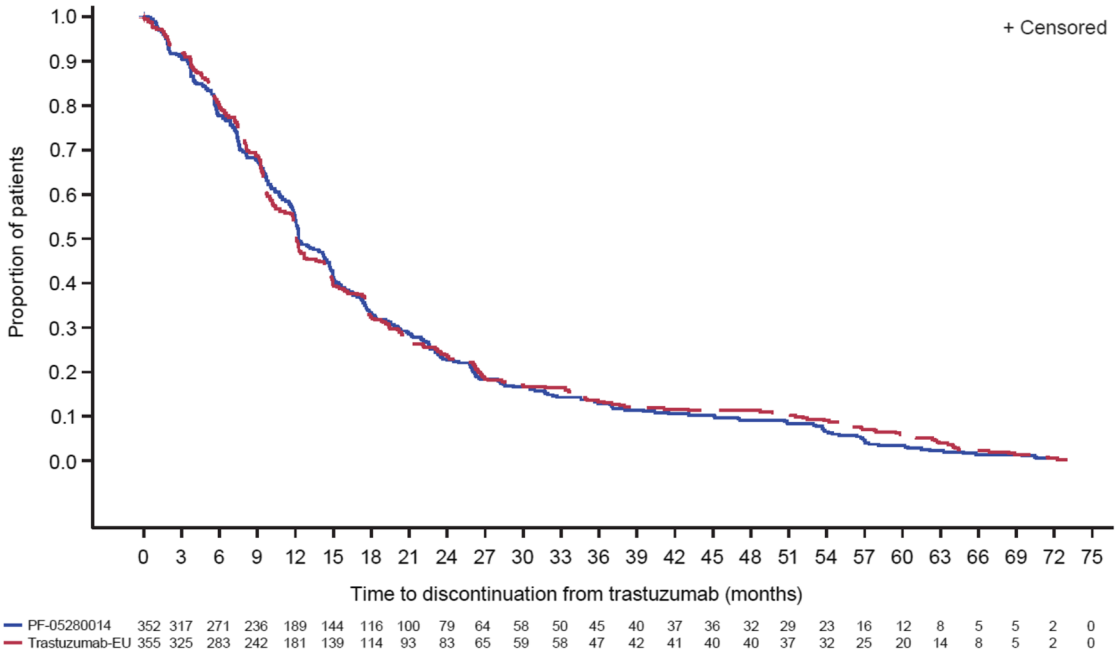
[a]Estimated from the Kaplan–Meier curve

[b]Calculated using the Greenwood formula

[c]Based on the Brookmeyer and Crowley Method

[d]Based on the Cox proportional hazards model stratified by prior trastuzumab exposure (yes/no) and estrogen receptor (ER) status (ER positive vs ER negative). Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor of PF-05280014; a hazard ratio >1 indicates a reduction in hazard rate in favor of trastuzumab-EU

[e]1-sided *p* value from the log-rank test stratified by prior trastuzumab exposure (yes/no) and ER status (ER positive vs ER negative)



ITT intent-to-treat, *trastuzumab-EU* trastuzumab sourced from the European Union

Fig. 2 Kaplan–Meier plot of time to discontinuation from trastuzumab (ITT population)

The most frequently reported TEAEs of special interest were ejection fraction decreased (49 [14.0%] patients in the PF-05280014 group and 47 [13.3%] patients in the trastuzumab-EU group), infusion-related reaction (34 [9.7%] and 32 [9.1%]), and pyrexia (29 [8.3%] and 24 [6.8%]) (Table 4). The incidences of TEAEs of special interest were generally comparable between the treatment groups in both the overall safety population and the subgroup (Table 4).

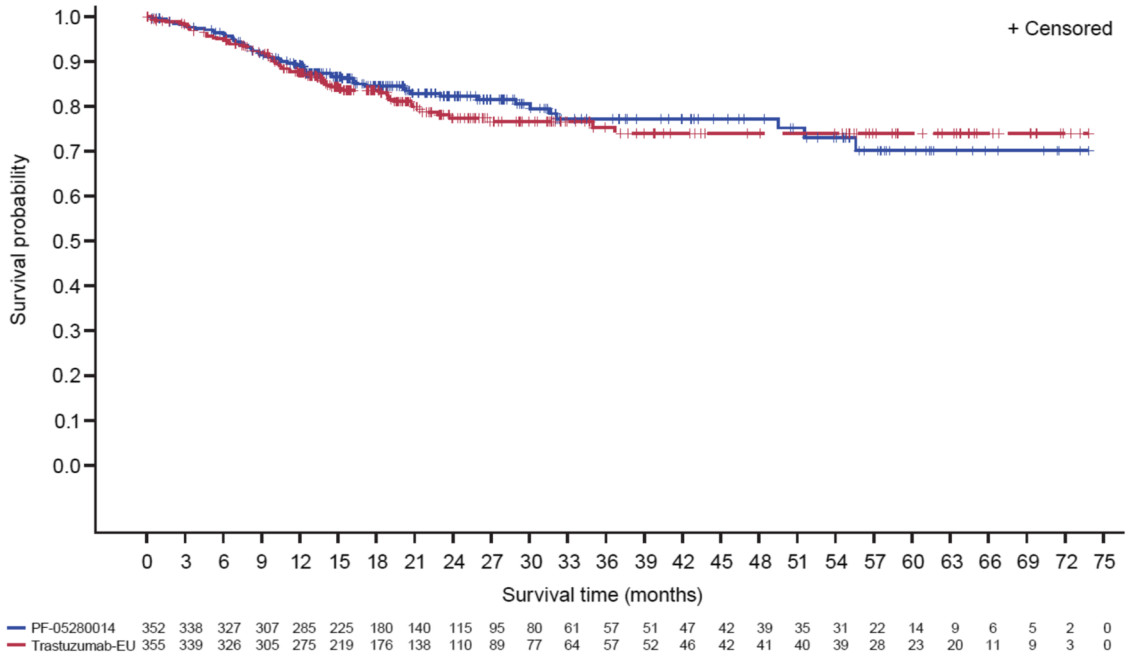
In the overall safety population, the most frequently reported TEAEs were alopecia (189 [54.2%] patients in the PF-05280014 group and 186 [52.7%] patients in the trastuzumab-EU group), anemia (124 [35.5%] and 136 [38.5%]), neutropenia (100 [28.7%] and 95 [26.9%]), and peripheral sensory neuropathy (93 [26.6%] and 85 [24.1%]) (Table 5). In the subgroup, the most frequently reported TEAEs (≥ 5% of patients in either treatment group) were anemia (19 [7.2%] in the PF-05280014 group and 16 [6.1%] patients in the trastuzumab-EU group), neutropenia (7 [2.6%] and 15 [5.7%]), upper respiratory tract infection (9 [3.4%] and 15 [5.7%]), and headache (15 [5.7%] and 18 [6.8%]) (Table 5).

With respect to cardiac function, in the overall safety population, ejection fraction decreased was reported in 49 (14.0%) and 47 (13.3%) patients treated with PF-05280014 and trastuzumab-EU, respectively. An absolute decrease in LVEF of ≥ 16% from baseline was reported in 22 (6.3%) and in 19 (5.4%) patients receiving PF-05280014 and trastuzumab-EU, whereas 14 (4.0%) and 18 (5.1%) patients had an absolute decrease in LVEF of ≥ 10% from baseline and below the LLN.

4 Discussion

PF-05280014 plus paclitaxel has demonstrated equivalence to trastuzumab-EU plus paclitaxel as a first-line treatment for HER2-positive metastatic breast cancer in terms of ORR in REFLECTIONS B327-02 [15]. The current analysis assessed data collected from REFLECTIONS B327-02 for longer than 6 years and no notable difference in OS was found between the treatment groups, which indicated that the long-term efficacy data were consistent with previously reported findings from this study [15]. Further, no notable difference was found in the time to discontinuation from trastuzumab (PF-05280014 or trastuzumab-EU).

Results of primary and secondary analyses in REFLECTIONS B327-02 have been reported previously [15]. In summary, the risk ratio for ORR was 0.940 (95% CI 0.842–1.049; which was within the pre-specified equivalence margin of 0.80–1.25), demonstrating equivalence of PF-05280014 plus paclitaxel to trastuzumab-EU plus paclitaxel as first-line treatment for HER2-positive metastatic breast cancer. No notable differences were found in PFS, OS, safety outcomes, or immunogenicity between treatment groups [15]. In the current analysis, PF-05280014



ITT intent-to-treat, *trastuzumab-EU* trastuzumab sourced from the European Union

Fig. 3 Kaplan–Meier plot of overall survival (ITT population)

plus paclitaxel provided a survival probability of 82% (95% CI 77–86) at 2 years and 77% (95% CI 70–83) at 3 years as a first-line therapy for HER2-positive metastatic breast cancer. For patients treated with trastuzumab-EU, the survival probability was 77% (95% CI 72–82) at 2 years and 75% (95% CI 69–81) at 3 years. These long-term survival probabilities were comparable between patients treated with PF-05280014 and trastuzumab-EU. Similar comparability of long-term OS between a trastuzumab biosimilar (trastuzumab-dkst, Ogivri®; Viatris Inc, Canonsburg, PA, USA) and the originator has been reported in the HERITAGE study [21].

To investigate the exposure to study treatment, we evaluated time to discontinuation of PF-05280014 and trastuzumab-EU. In the ITT population, a similar proportion of patients in each treatment group (71.6% in the PF-05280014 group and 70.7% in the trastuzumab-EU group) received study treatment until objective progression, with a similar estimated median time to discontinuation from trastuzumab (12.25 months and 12.06 months for the PF-05280014 and the trastuzumab-EU group, respectively). It has been reported that for patients with early-stage breast cancer, early trastuzumab discontinuation was an independent predictor of cardiac events, clinically significant relapse, and OS [22]. This suggests that time to discontinuation might also be an indicator of effectiveness of trastuzumab therapy in patients with metastatic breast cancer. In the current analysis, no notable difference in time to discontinuation was found between the treatment groups, which indicates that comparable time to discontinuation might be a possible explanation for the similar effectiveness of PF-05280014 and trastuzumab-EU.

In REFLECTIONS B327-02, safety data up to day 378 showed similar incidences for all categories of TEAEs and serious TEAEs between the treatment groups. No notable differences in the incidences of TEAEs of special interest, for instance, infusion-related reactions, cardiac failure, and decreased ejection fraction, were found between treatment groups [15]. Evaluation of long-term safety data of REFLECTIONS B327-02 showed comparable results between the overall safety population and the subgroup of patients who were ongoing in the study after day 378; no notable differences were found between treatment groups in incidences of TEAEs, grade 3 or higher TEAEs, serious TEAEs, and TEAEs of special interest.

Safety of long-term usage of trastuzumab has been reported, particularly in terms of cardiotoxicity. An earlier study reported that 13% of the patients receiving reference trastuzumab and paclitaxel had cardiac dysfunction [23]. Therefore, cardiac toxicity has been assessed as an important part of the safety profile of trastuzumab in later long-term investigations [17, 18, 24–26]. These studies showed that no significant difference in cardiac toxicity was found for patients who received trastuzumab for < 1 year compared

Table 3 TEAEs (safety population)

	Overall safety population		Subgroup ongoing after day 378[a]	
	PF-05280014 plus paclitaxel ($n = 349$)	Trastuzumab-EU plus paclitaxel ($n = 353$)	PF-05280014 plus paclitaxel ($n = 265$)	Trastuzumab-EU plus paclitaxel ($n = 264$)
Number of TEAEs	2692	2789	446	471
Any TEAEs	344 (98.6)	341 (96.6)	107 (40.4)	112 (42.4)
Grade 3 or higher TEAEs	143 (41.0)	152 (43.1)	31 (11.7)	39 (14.8)
Treatment-related TEAEs	321 (92.0)	316 (89.5)	52 (19.6)	60 (22.7)
Trastuzumab-related TEAEs	130 (37.2)	119 (33.7)	35 (13.2)	39 (14.8)
Treatment-related Grade 3 or higher TEAEs	84 (24.1)	92 (26.1)	8 (3.0)	5 (1.9)
Trastuzumab-related Grade 3 or higher TEAEs	15 (4.3)	11 (3.1)	5 (1.9)	1 (0.4)
TEAEs resulting in treatment discontinuation	57 (16.3)	52 (14.7)	10 (3.8)	12 (4.5)
Trastuzumab discontinuation	24 (6.9)	20 (5.7)	8 (3.0)	8 (3.0)
Treatment-related TEAEs resulting in treatment discontinuation	45 (12.9)	46 (13.0)	4 (1.5)	9 (3.4)
Trastuzumab discontinuation	11 (3.2)	13 (3.7)	2 (0.8)	5 (1.9)
Serious TEAEs	67 (19.2)	69 (19.5)	19 (7.2)	15 (5.7)
Treatment-related serious TEAEs	23 (6.6)	16 (4.5)	5 (1.9)	0
Trastuzumab-related serious TEAEs	8 (2.3)	5 (1.4)	3 (1.1)	0
Serious TEAEs resulting in treatment discontinuation	16 (4.6)	9 (2.5)	6 (2.3)	3 (1.1)
Trastuzumab discontinuation	11 (3.2)	8 (2.3)	5 (1.9)	3 (1.1)
Treatment-related serious TEAEs resulting in treatment discontinuation	8 (2.3)	3 (0.8)	2 (0.8)	0
Trastuzumab discontinuation	2 (0.6)	2 (0.6)	1 (0.4)	0
TEAEs resulting in treatment being temporarily stopped	153 (43.8)	159 (45.0)	32 (12.1)	29 (11.0)
Trastuzumab temporarily stopped	116 (33.2)	113 (32.0)	29 (10.9)	25 (9.5)
TEAEs resulting in trastuzumab infusion rate reduced	2 (0.6)	3 (0.8)	0	0

Values are number of patients *n* (%) unless stated otherwise. TEAE was defined as any event that occurred on or after the first dose of study treatment administration or any pre-existing event that worsened in severity after dosing. TEAE defined through last dose of PF-05280014 or trastuzumab-EU + 70 days. Treatment-related: related to trastuzumab and/or paclitaxel; trastuzumab related: related only to trastuzumab; paclitaxel related: related only to paclitaxel. Serious TEAE was recorded according to investigator assessment. Patients discontinued due to adverse events were those who permanently discontinued the study treatment. Except for the 'Number of TEAEs' row, patients were only counted once per treatment group per row for the overall safety population, and once per treatment group per row for the subgroup ongoing after day 378

TEAE treatment-emergent adverse event, *trastuzumab-EU* trastuzumab sourced from the European Union

[a]For the subgroup columns, only those TEAEs that started after day 378 are included

with those patients receiving trastuzumab for > 1 year [24]; for patients who received ≥ 5 years of trastuzumab for breast cancer or ≥ 3 years for gastric/gastroesophageal junction cancer, no serious cardiac AEs or marked changes in LVEF occurred, and the median overall worst LVEF was 57.0% (range 47–63%) [25]. The rate of trastuzumab-related cardiac AEs was low (2.2% [3/134]) among patients with HER2-positive metastatic or locally advanced breast cancer who received first-line trastuzumab for a median duration of 4.5 years (range 0.8–12.1 years) [26]. For the current analysis, the safety profile of PF-05280014 and trastuzumab-EU was comparable and there was limited concern about using trastuzumab with regards to cardiac events. In the overall safety population, ejection fraction decreased was reported in 14% of patients treated with PF-05280014 and 13% with trastuzumab-EU, respectively. Comparable proportions of patients between the treatment groups had one or more event of an absolute decrease in LVEF of ≥ 16% from baseline (6% of patients receiving PF-05280014 and 5% receiving trastuzumab-EU) and the proportions of patients who had an absolute decrease in LVEF of ≥ 10% from baseline and below the LLN were balanced across the treatment groups (4 and 5%, respectively). Similar findings have been reported for the trastuzumab biosimilar SB3 [27] and CT-P6 [28].

By end of July 2021, five trastuzumab biosimilars had obtained regulatory approval in the United States [29]. All these biosimilars are indicated for HER2-positive breast cancer with clinical trial data supporting the equivalence of the biosimilar compared with the reference trastuzumab, without additional safety concerns [30]. In the EU, six

Table 4 TEAEs of special interest (safety population)

System organ class and MedDRA preferred term	Overall population		Subgroup ongoing after day 378[a]	
	PF-05280014 plus paclitaxel ($n = 349$)	Trastuzumab-EU plus paclitaxel ($n = 353$)	PF-05280014 plus paclitaxel ($n = 265$)	Trastuzumab-EU plus paclitaxel ($n = 264$)
Cardiac disorders				
Left ventricular dysfunction	1 (0.3)	2 (0.6)	0	1 (0.4)
Cardiac failure	5 (1.4)	10 (2.8)	0	3 (1.1)
General disorders and administration-site conditions				
Pyrexia	29 (8.3)	24 (6.8)	5 (1.9)	4 (1.5)
Chills	4 (1.1)	5 (1.4)	0	1 (0.4)
Injury, poisoning, and procedural complications				
Infusion-related reaction	34 (9.7)	32 (9.1)	0	2 (0.8)
Investigations				
Ejection fraction decreased	49 (14.0)	47 (13.3)	13 (4.9)	12 (4.5)
Respiratory, thoracic, and mediastinal disorders				
Interstitial lung disease	1 (0.3)	1 (0.3)	1 (0.4)	0
Dyspnea	18 (5.2)	20 (5.7)	1 (0.4)	0
Skin and subcutaneous tissue disorders				
Pruritus	12 (3.4)	22 (6.2)	2 (0.8)	7 (2.7)

Values are *n* (%). TEAEs of special interest were pre-specified events of clinical importance that are maintained in a list in the product's safety review plan including anaphylactic reaction, cardiac failure, chills, dyspnea, ejection fraction decreased, infusion-related reaction, interstitial lung disease, left ventricular dysfunction, pruritus, and pyrexia. MedDRA (version 23.0) coding dictionary applied

TEAE treatment-emergent adverse event, *trastuzumab-EU* trastuzumab sourced from the European Union

[a]For the subgroup columns, only those TEAEs that started after day 378 are included

trastuzumab biosimilars have been approved by end of July 2021 for the treatment of HER2-positive early breast cancer and advanced breast and gastric cancer [31]. Currently (end of July 2021), three trastuzumab biosimilars are available for both HER2-positive breast cancer and metastatic gastric cancer in Japan [32].

With increasing numbers of available trastuzumab biosimilars, switching from the reference product to a biosimilar version has become an option for clinical practice [33]. The 2016 position paper on biosimilars published by the European Society for Medical Oncology stated that the decision to choose a biosimilar over the reference product should be made by the physician [34]. In 2018, the American Society of Clinical Oncology (ASCO) also published its statement regarding biosimilars in oncology [35]. The 2020 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Breast Cancer stated that trastuzumab biosimilars approved by the US Food and Drug Administration are an appropriate substitute when providing preoperative/adjuvant therapy for HER2-positive breast cancer or systemic therapy for stage IV or recurrent HR-negative, HER2-positive breast cancer [36, 37]. In the 2020 update of the ASCO Guideline for adjuvant chemotherapy and targeted therapy for early breast cancer, trastuzumab biosimilars are recommended for the treatment of HER2-positive breast cancer as adjuvant trastuzumab therapy [38].

This study has limitations. As the protocol amendment that defined TP1 and TP2 took place after the data cutoff date (11 January 2017) for the week 53 analysis, continuing patients were beyond week 53 at the time the protocol amendment was implemented. These patients would have been following a prior version of the protocol and would have had full assessments at defined intervals, may have been continuing on paclitaxel beyond week 53, and may have had study drug administered as a weekly dosing regimen. Since the intention of TP2 was to provide patients who showed clinical benefit from study treatment an opportunity to continue with therapy, only minimally required assessments and procedures were undertaken following local SoC guidelines. Therefore, the TP2 data were collected inconsistently, in that some patients had full assessments for a period of time whereas others had limited assessments depending on status of the amendment implementation at their sites. Furthermore, tumor assessments collected during TP1 underwent independent review by a central laboratory from which the primary analysis was based, whereas in TP2 only investigator-determined overall tumor assessments were collected; as a result, the data could not be combined to determine PFS or ORR. In addition, in TP2, there were longer

Table 5 Most common[a] TEAEs

System organ class and MedDRA preferred term	Overall safety population		Subgroup ongoing after day 378	
	PF-05280014 plus paclitaxel ($n = 349$)	Trastuzumab-EU plus paclitaxel ($n = 353$)	PF-05280014 plus paclitaxel ($n = 265$)	Trastuzumab-EU plus paclitaxel ($n = 264$)
Blood and lymphatic system disorders				
Anemia	124 (35.5)	136 (38.5)	19 (7.2)	16 (6.1)
Neutropenia	100 (28.7)	95 (26.9)	7 (2.6)	15 (5.7)
Leukopenia	37 (10.6)	46 (13.0)	–	–
Thrombocytopenia	18 (5.2)	13 (3.7)	–	–
Gastrointestinal disorders				
Diarrhea	61 (17.5)	66 (18.7)	–	–
Nausea	57 (16.3)	70 (19.8)	–	–
Vomiting	27 (7.7)	26 (7.4)	–	–
Constipation	24 (6.9)	31 (8.8)	–	–
Stomatitis	23 (6.6)	13 (3.7)	–	–
Dyspepsia	16 (4.6)	20 (5.7)	–	–
Abdominal pain	14 (4.0)	32 (9.1)	–	–
General disorders and administration-site conditions				
Asthenia	53 (15.2)	46 (13.0)	–	–
Fatigue	47 (13.5)	51 (14.4)	–	–
Edema peripheral	27 (7.7)	45 (12.7)	–	–
Infections and infestations				
Upper respiratory tract infection	36 (10.3)	46 (13.0)	9 (3.4)	15 (5.7)
Respiratory tract infection viral	23 (6.6)	13 (3.7)	–	–
Nasopharyngitis	21 (6.0)	19 (5.4)	–	–
Urinary tract infection	7 (2.0)	20 (5.7)	–	–
Investigations				
Alanine aminotransferase increased	42 (12.0)	45 (12.7)	–	–
Aspartate aminotransferase increased	36 (10.3)	31 (8.8)	–	–
Blood alkaline phosphatase increased	28 (8.0)	26 (7.4)	–	–
Weight increased	20 (5.7)	22 (6.2)	–	–
Metabolism and nutrition disorders				
Decreased appetite	23 (6.6)	21 (5.9)	–	–
Musculoskeletal and connective tissue disorders				
Arthralgia	44 (12.6)	38 (10.8)	–	–
Myalgia	26 (7.4)	35 (9.9)	–	–
Pain in extremity	22 (6.3)	24 (6.8)	–	–
Bone pain	20 (5.7)	14 (4.0)	–	–
Back pain	18 (5.2)	34 (9.6)	–	–
Nervous system disorders				
Peripheral sensory neuropathy	93 (26.6)	85 (24.1)	–	–
Headache	53 (15.2)	70 (19.8)	15 (5.7)	18 (6.8)
Dizziness	38 (10.9)	30 (8.5)	–	–
Neuropathy peripheral	35 (10.0)	34 (9.6)	–	–
Respiratory, thoracic, and mediastinal disorders				
Cough	33 (9.5)	31 (8.8)	–	–
Epistaxis	15 (4.3)	23 (6.5)	–	–
Skin and subcutaneous tissue disorders				
Alopecia	189 (54.2)	186 (52.7)	–	–
Rash	24 (6.9)	26 (7.4)	–	–
Vascular disorders				
Hypertension	36 (10.3)	31 (8.8)	–	–

Table 5 (continued)

Values are *n* (%)

TEAE treatment-emergent adverse event, *trastuzumab-EU* trastuzumab sourced from the European Union

[a]TEAEs that occurred in ≥5% of patients in at least one treatment group and were not AEs of special interest. MedDRA (version 23.0) coding dictionary applied. For the subgroup columns, only those TEAEs that started after day 378 with incidence ≥ 5% in any group are included. Cells with a '–' indicate the incidences were < 5%

and inconsistent intervals between the tumor assessments due to differences in local SoC guidelines, which would have affected the determination of time to PFS.

5 Conclusion

No clinically meaningful differences between PF-05280014 and trastuzumab-EU in long-term safety, time to discontinuation, and efficacy including OS data were observed. These results further support the similarity of PF-05280014 to reference trastuzumab (Herceptin) established in the PF-05280014 development program.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40259-021-00513-7.

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Declarations

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Conflict of interest Rubi K. Li received personal fees for giving lectures and being an advisory member from Pfizer Inc., Roche, Eli Lilly, Hi-Eisai, Novartis, AstraZeneca, and MSD. Eriko Tokunaga received fees from Chugai, AstraZeneca, and Eli Lilly. Hryhoriy Adamchuk, Vladimir Vladimirov, Eduardo Yanez, Igor Bondarenko, and Oleg Lipatov have no conflicts of interest to declare. Keun Seok Lee reports personal fees from Roche, Lilly, Novartis, Daiichi Sankyo, MSD, and Pfizer; and drug support from Dong-A ST, outside the submitted work. Fiona Hilton, Alicia Vana, and Tomofumi Ishikawa are employees of and have stock and/or other ownership interests in Pfizer. Kentaro Tajima is an employee of Pfizer Japan Inc.

Availability of data Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Code availability Not applicable.

Author contributions All authors had full access to all study data. All authors made important contributions to data acquisition, analysis, and/or interpretation of data. All authors reviewed manuscript drafts and have reviewed and approved the final version for submission.

Ethics approval This study was conducted in compliance with the ethical principles originating in, or derived from, the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines, and was reviewed and approved by institutional review boards and/or independent ethics committees. All local regulatory requirements were followed, particularly those affording greater protection to the safety of trial participants. The study was sponsored by Pfizer and is registered on ClinicalTrials.gov (Identifier: NCT01989676) and EudraCT (EudraCT Number: 2013-001352-34).

Consent to participate All patients provided informed consent before undergoing any study-specific procedures.

Consent for publication Not applicable.

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