Electronic Supplementary Material

Article title: **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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Authors: Rubi K. Li[1], Eriko Tokunaga[2], HryhoriyAdamchuk[3], Vladimir Vladimirov[4], Eduardo Yanez[5], Keun Seok Lee[6], Igor Bondarenko[7], Alicia Vana[8], Fiona Hilton[8], Tomofumi Ishikawa[9], Kentaro Tajima[10], Oleg Lipatov[11]

[1]St. Luke's Medical Center, Quezon City, Metro Manila, Philippines; [2]Department of Breast Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [3]Kryvyi Rih Oncology Dispensary of Dnipropetrovsk Regional Council, Kryvyi Rih, Ukraine; [4]Pyatigorsk Oncology Dispensary, Pyatigorsk, Stavropol Region, Russian Federation; [5]Universidad de La Frontera, Temuco, Region de la Araucania, Chile; [6]Center for Breast Cancer, National Cancer Center, Korea; [7]Department of Oncology and Medical Radiology, Dnipropetrovsk Medical Academy, Dnipro, Ukraine; [8]Pfizer, New York, NY, USA; [9]Pfizer R&D, Tokyo, Japan; [10]Pfizer Japan Inc., Tokyo, Japan; [11]Republican Clinical Oncology Dispensary of the Ministry of Public Health of Bashkortostan Republic, Ufa, Republic of Bashkortostan, Russian Federation

Corresponding author: Rubi K. Li, Section of Medical Oncology, Cancer Institute, St. Luke's Medical Center, 279 E Rodriguez, Sr. Ave, Quezon City, 1112 Metro Manila, Philippines. Email: Rubikli@yahoo.com.

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Supplementary Table 1. Patient disposition

	Overall population			Subgroup ongoing after day 378		
	PF-05280014 plus paclitaxel	Trastuzumab-EU plus paclitaxel	Total	PF-05280014 plus paclitaxel	Trastuzumab-EU plus paclitaxel	Total
Randomized, *n*	352	355	707	265	264	529
Treated	349 (99.1)	353 (99.4)	702 (99.3)	265 (100.0)	264 (100.0)	529 (100.0)
Treated (trastuzumab) until objective progression	252 (71.6)	251 (70.7)	503 (71.1)	195 (73.6)	195 (73.9)	390 (73.7)
Treated (trastuzumab) stopped before objective progression	97 (27.6)	102 (28.7)	199 (28.1)	70 (26.4)	69 (26.1)	139 (26.3)
Study completion status						
Completed	234 (66.5)	217 (61.1)	451 (63.8)	211 (79.6)	201 (76.1)	412 (77.9)
Withdrawn after randomization but prior to treatment	3 (0.9)	2 (0.6)	5 (0.7)	0	0	0
Discontinued prior to long-term follow-up	23 (6.5)	30 (8.5)	53 (7.5)	5 (1.9)	6 (2.3)	11 (2.1)
Discontinued during long-term follow-up	92 (26.1)	106 (29.9)	198 (28.0)	49 (18.5)	57 (21.6)	106 (20.0)
Primary reason for discontinuation from trastuzumab treatment						
Objective progression	252 (71.6)	251 (70.7)	503 (71.1)	195 (73.6)	195 (73.9)	390 (73.7)
Global deterioration of health status	5 (1.4)	7 (2.0)	12 (1.7)	4 (1.5)	4 (1.5)	8 (1.5)
Adverse event(s)	23 (6.5)	19 (5.4)	42 (5.9)	11 (4.2)	13 (4.9)	24 (4.5)
Patient died	3 (<1.0)	11 (3.1)	14 (2.0)	0	1 (<1.0)	1 (<1.0)
Protocol violation	1 (<1.0)	5 (1.4)	6 (<1.0)	1 (<1.0)	1 (<1.0)	2 (<1.0)
Lost to follow-up	0	2 (<1.0)	2 (<1.0)	0	0	0
Patient withdrew consent	24 (6.8)	20 (5.6)	44 (6.2)	15 (5.7)	12 (4.5)	27 (5.1)
Study terminated by Sponsor	25 (7.1)	27 (7.6)	52 (7.4)	25 (9.4)	27 (10.2)	52 (9.8)
Other	19 (5.4)	13 (3.7)	32 (4.5)	14 (5.3)	11 (4.2)	25 (4.7)

Discontinued from study	118 (33.5)	138 (38.9)	256 (36.2)	54 (20.4)	63 (23.9)	117 (22.1)
Patient died	52 (14.8)	60 (16.9)	112 (15.8)	12 (4.5)	18 (6.8)	30 (5.7)
Protocol violation	2 (<1.0)	1 (<1.0)	3 (<1.0)	2 (<1.0)	1 (<1.0)	3 (<1.0)
Lost to follow-up	8 (2.3)	18 (5.1)	26 (3.7)	3 (1.1)	6 (2.3)	9 (1.7)
Patient withdrew consent	26 (7.4)	26 (7.3)	52 (7.4)	10 (3.8)	6 (2.3)	16 (3.0)
Study terminated by Sponsor	26 (7.4)	30 (8.5)	56 (7.9)	26 (9.8)	30 (11.4)	56 (10.6)
Other	4 (1.1)	3 (<1.0)	7 (<1.0)	1 (<1.0)	2 (<1.0)	3 (<1.0)
Analyzed for efficacy	352 (100.0)	355 (100.0)	707 (100.0)	265 (100.0)	264 (100.0)	529 (100.0)
Analyzed for adverse events	349 (99.1)	353 (99.4)	702 (99.3)	265 (100.0)	264 (100.0)	529 (100.0)

Values are *n* (%) unless stated otherwise

trastuzumab-EU trastuzumab sourced from the European Union

Supplementary Table 2. Overall survival – ITT population

	PF-05280014 plus paclitaxel (*n* = 352)	Trastuzumab-EU plus paclitaxel (*n* = 355)
Deaths, *n* (%)	61 (17.3)	67 (18.9)
Cause of death		
Disease under study	57 (16.2)	55 (15.5)
Study treatment toxicity	0	3 (<1.0)
Unknown	0	2 (<1.0)
Other	4 (1.1)	8 (2.3)
Number censored	291 (82.7)	288 (81.1)
Reason for censorship		
Patient no longer being followed for survival	291 (82.7)	288 (81.1)
Survival probability		
At month 6[a] (95% CI[b])	96.23 (93.59–97.79)	95.08 (92.21–96.92)
At month 9[a] (95% CI[b])	91.79 (88.3–94.26)	92.12 (88.71–94.53)
At month 12[a] (95% CI[b])	89.36 (85.56–92.21)	87.50 (83.46–90.61)
At month 24[a] (95% CI[b])	82.26 (77.21–86.29)	77.42 (71.73–82.10)
At month 36[a] (95% CI[b])	77.23 (70.47–82.63)	75.29 (68.87–80.57)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI)[c]		
25%	51.55 (28.95–NR)	36.70 (20.83–NR)
50%	NR	NR
75%	NR	NR
Versus trastuzumab-EU		
Hazard ratio[d]	0.929	
95% CI of hazard ratio	0.656–1.316	
p-value[e]	0.339	

Values are *n* (%) unless otherwise stated

[a]Estimated from the Kaplan–Meier curve

[b]Calculated from the product-limit method

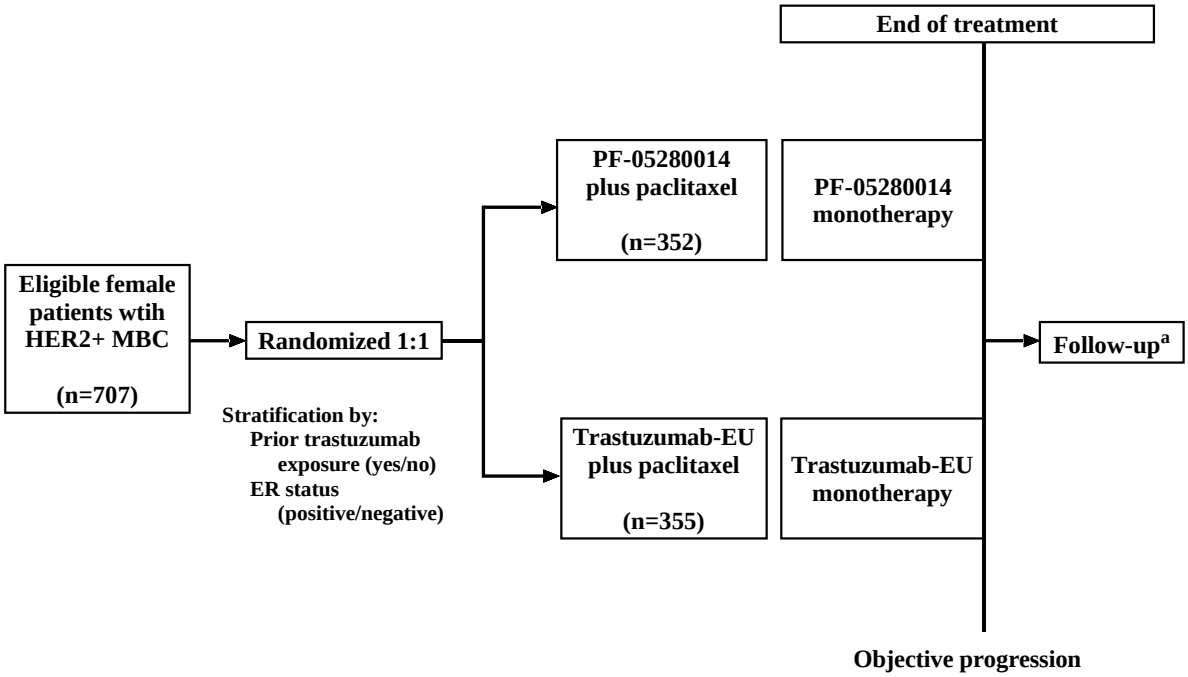
[c]Based on the Brookmeyer and Crowley Method

[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 less than 1 indicates a reduction in hazard rate in favor of PF-05280014; a hazard ratio greater than 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 estrogen receptor (ER) status (ER positive vs. ER negative)

CI confidence interval, *NR* not reached, *trastuzumab-EU* trastuzumab sourced from the European Union

Supplementary Fig. 1 Study design



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. 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 TP1. Patients continuing to derive clinical benefit from study treatment after completing TP1 entered TP2, during which 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.

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.

[a]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 TP2, minimal protocol required assessments and procedures were undertaken. Tumor assessments were performed according to local practice/standard of care disease assessment frequency. A minimum

interval of 4 months was recommended. Assessments of cardiac function via echocardiogram or multigated acquisition scan were also performed as per local standard of care. Cardiac safety (including left ventricular ejection fraction) findings were to be reported as adverse events. During TP1 and TP2, patients were followed for adverse events for 6 months after the last dose of study treatment.

ER estrogen receptor, *HER2+* human epidermal growth factor receptor 2-positive, *MBC* metastatic breast cancer, *RECIST* Response Evaluation Criteria in Solid Tumors, *TP* treatment period, *trastuzumab-EU* trastuzumab sourced from the European Union