Web appendix

Supplementary tables and figures

Supplement to: Fei Ma, et al. Pyrotinib versus placebo in combination with trastuzumab and docetaxel as first line treatment in patients with HER2 positive metastatic breast cancer (PHILA): a randomised, double blind, multicentre, phase 3 trial

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Figure S1. Kaplan-Meier curve of investigator-assessed progression-free survival by previous neoadjuvant or adjuvant trastuzumab

(A) Progression-free survival in patients with previous neoadjuvant or adjuvant trastuzumab. (B) Progression-free survival in patients without previous neoadjuvant or adjuvant trastuzumab. Hazard ratios are from unstratified analyses.

CI=confidence interval; NR=not reached.

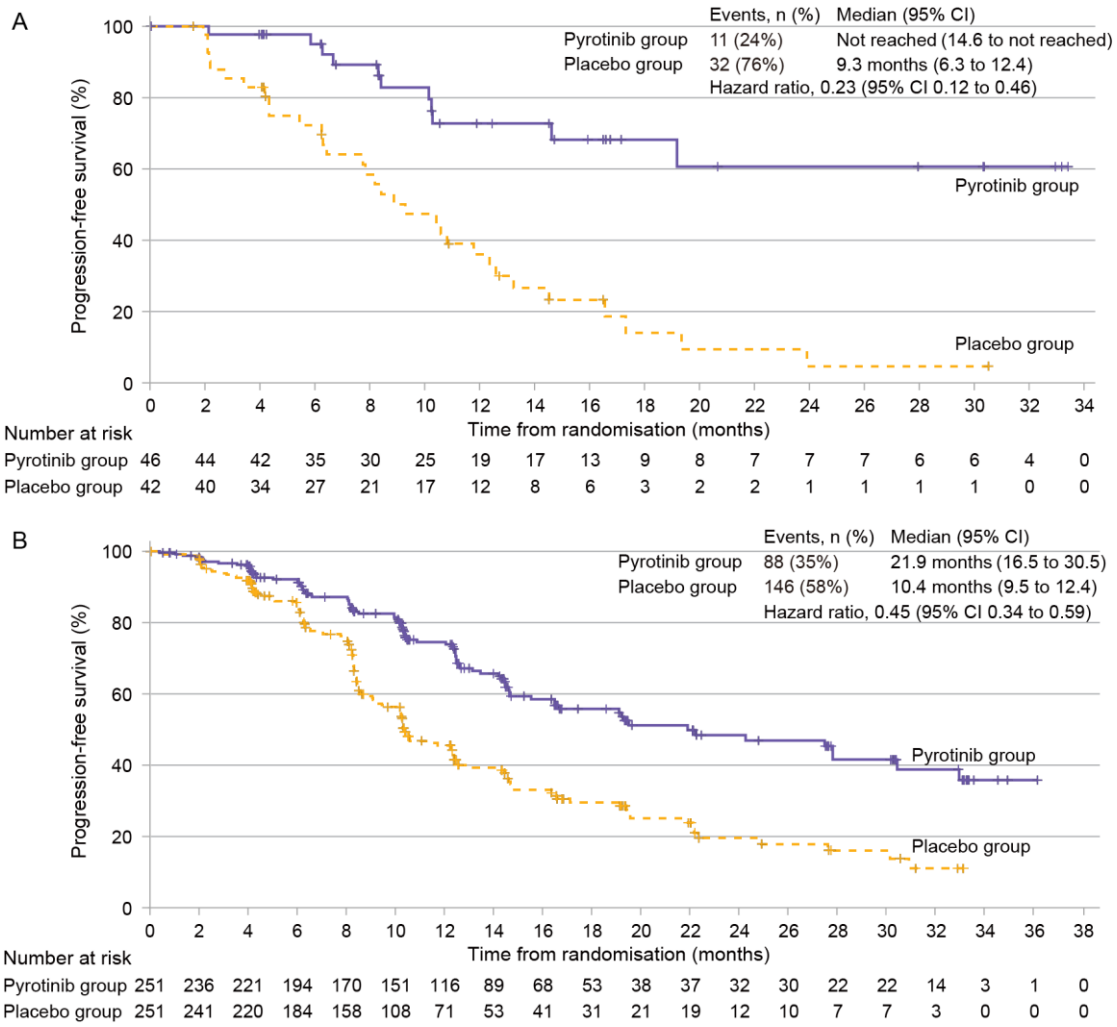

Figure S2. Kaplan-Meier curve of investigator-assessed progression-free survival by treatment-free interval of previous adjuvant therapy

(A) Progression-free survival in patients who had a treatment-free interval of ≥12 to <24 months for previous adjuvant therapy. (B) Progression-free survival in patients who had a treatment-free interval of ≥24 months for previous adjuvant therapy. Hazard ratios are from unstratified analyses.

CI=confidence interval; NR=not reached.

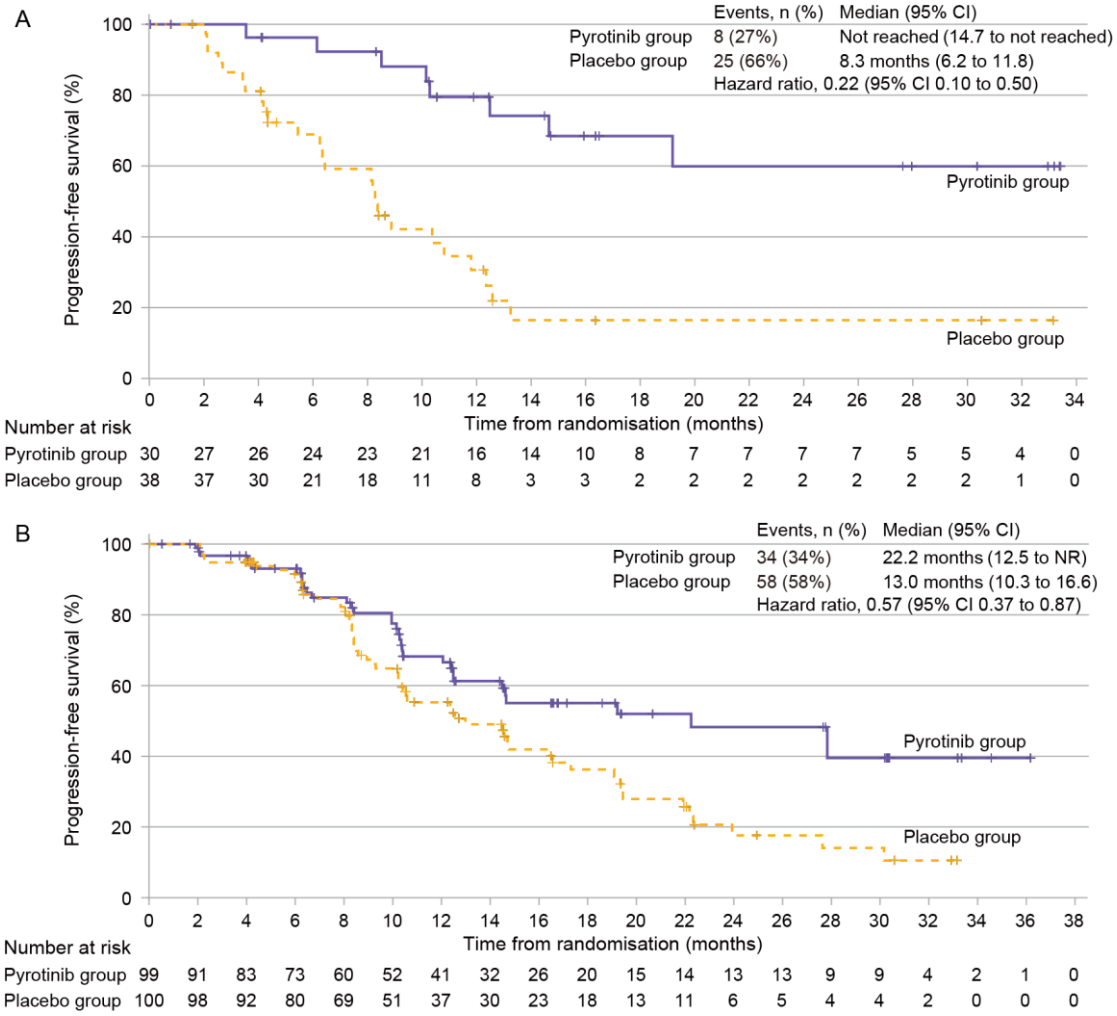

Table S1. List of participating sites, ethics committees, and approval IDs

Number of patients	Principal investigators	Participating sites	Name of the ethics committee	ID# of the approval
57	Min Yan	Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China	Ethics Committee of Henan Cancer Hospital	2019058-006
46	Wei Li	The First Hospital of Jilin University, Changchun, China	Ethics Committee of The First Hospital of Jilin University	19Y025-009
35	Quchang Ouyang	Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China	Ethics Committee of Hunan Cancer Hospital	2022-793
30	Zhongsheng Tong	Tianjin Medical University Cancer Institute & Hospital, Tianjin, China	Ethics Committee of Tianjin Medical University Cancer Institute & Hospital	E20220520
27	Yuee Teng	The First Hospital of China Medical University, Shenyang, China	Ethics Committee of The First Hospital of China Medical University	2019YL011-5H
22	Yongsheng Wang	Shandong Cancer Hospital & Institute, Jinan, China	Ethics Committee of Shandong Cancer Hospital & Institute	SDZLEC2019-032-09
22	Shusen Wang	Sun Yat-sen University Cancer Center, Guangzhou, China	Ethics Committee of Sun Yat-sen University Cancer Center	A2019-014-X06
21	Binghe Xu / Fei Ma	Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China	Ethics Committee of Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College	19-012/1797
20	Cuizhi Geng	The Fourth Hospital of Hebei Medical University and Hebei Tumor Hospital, Shijiazhuang, China	Ethics Committee of The Fourth Hospital of Hebei Medical University and Hebei Tumor Hospital	2019027-3
20	Ting Luo	West China Hospital, Sichuan University, Chengdu, China	Ethics Committee of West China Hospital	2019-6

Number of patients	Principal investigators	Participating sites	Name of the ethics committee	ID# of the approval
20	Jincai Zhong	The First Affiliated Hospital of Guangxi Medical University, Nanning, China	Ethics Committee of The First Affiliated Hospital of Guangxi Medical University	2022-065
17	Qingyuan Zhang	Harbin Medical University Cancer Hospital, Harbin, China	Ethics Committee of Harbin Medical University Cancer Hospital	2019-36
17	Qiang Liu	Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China	Ethics Committee of Sun Yat-sen Memorial Hospital	SYSYW-2022-072-01
16	Xiaohua Zeng	Affiliated Cancer Hospital of Chongqing University, Chongqing, China	Ethics Committee of Affiliated Cancer Hospital of Chongqing University	CZLS2019022-G
16	Tao Sun	Liaoning Cancer Hospital & Institute, Shenyang, China	Ethics Committee of Liaoning Cancer Hospital & Institute	20220518
16	Qinguo Mo	Guangxi Medical University Affiliated Tumor Hospital, Nanning, China	Ethics Committee of Guangxi Medical University Affiliated Tumor Hospital	KS2022-112
15	Hu Liu	The First Affiliated Hospital of USTC West District, Hefei, China	Ethics Committee of The First Affiliated Hospital of USTC West District	2019-24-09
14	Ying Cheng	Jilin Cancer Hospital, Changchun, China	Ethics Committee of Jilin Cancer Hospital	201902-008-08
13	Jing Cheng	Union Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China	Ethics Committee of Union Hospital	2019-44-4
13	Xiaojia Wang	Zhejiang Cancer Hospital, Hangzhou, China	Ethics Committee of Zhejiang Cancer Hospital	2022-563
12	Jianyun Nie	Yunnan Cancer Hospital, Kunming, China	Ethics Committee of Yunnan Cancer Hospital	YW201916
11	Jin Yang	The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China	Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University	XJTU1AF2019LSY-47-4
11	Xinhong Wu	Hubei Cancer Hospital, Wuhan, China	Ethics Committee of Hubei Cancer Hospital	2022-137
10	Xinshuai Wang	Henan Key Laboratory of Cancer Epigenetics,	Ethics Committee of The First Affiliated Hospital of	2022-355

Number of patients	Principal investigators	Participating sites	Name of the ethics committee	ID# of the approval
		Cancer Hospital, The First Affiliated Hospital, College of Clinical Medicine, Medical College of Henan University of Science and Technology, Luoyang, China	Medical College of Henan University of Science and Technology	
9	Huiping Li	Beijing Cancer Hospital, Beijing, China	Ethics Committee of Beijing Cancer Hospital	2019YW32-ZY05
9	Changsheng Ye	Southern Medical University Nanfang Hospital, Guangzhou, China	Ethics Committee of Southern Medical University Nanfang Hospital	NFEC-201904-Y7-06
8	Qianjun Chen / Liping Ren	Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, China	Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine	AF2019-022-13
8	Xian Wang	Zhejiang University School of Medicine Sir Run Run Shaw Hospital, Hangzhou, China	Ethics Committee of Zhejiang University School of Medicine Sir Run Run Shaw Hospital	2022-0072
8	Kunwei Shen	Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China	Ethics Committee of Ruijin Hospital	2019-22-4
8	Ru Zeng	The First Affiliated Hospital of Xiamen University, Xiamen, China	Ethics Committee of The First Affiliated Hospital of Xiamen University	XMYY-2019Y024-16
8	Xichun Hu	Fudan University Shanghai Cancer Center, Shanghai, China	Ethics Committee of Fudan University Shanghai Cancer Center	1904199-1-2208E
7	Yongmei Yin	The First Affiliated Hospital with Nanjing Medical University, Nanjing, China	Ethics Committee of The First Affiliated Hospital with Nanjing Medical University	2019-MD-073.A5
6	Peifen Fu	The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China	Ethics Committee of The First Affiliated Hospital	2022-231
4	Lili Zhang	Jiangsu Cancer Hospital, Nanjing, China	Ethics Committee of Jiangsu Cancer Hospital	2019-001-05
4	Gang Hu	Sichuan Provincial People's Hospital, Chengdu, China	Ethics Committee of Sichuan Provincial People's Hospital	2019-9-6

Number of patients	Principal investigators	Participating sites	Name of the ethics committee	ID# of the approval
3	Liqun Jia	China-Japan Friendship Hospital, Beijing, China	Ethics Committee of China-Japan Friendship Hospital	2019-32-Y04-36
3	Ai'min Zang	Affiliated Hospital of Hebei University, Baoding, China	Ethics Committee of Affiliated Hospital of Hebei University	HDFY-LL-2022-115
2	Xianfu Liu	The First Affiliated Hospital of Bengbu Medical College, Bengbu, China	Ethics Committee of The First Affiliated Hospital of Bengbu Medical College	2021-080X02
1	Qiuyun Xiong	The Third Hospital of Nanchang, Nanchang, China	Ethics Committee of The Third Hospital of Nanchang	2019-10-1
1	Li Sun	Xuzhou Central Hospital, Xuzhou, China	Ethics Committee of Xuzhou Central Hospital	XZXY-LY-20220316-2020068

Table S2. Interruption of treatment for each component

	Pyrotinib group	Placebo group
Pyrotinib/Placebo, days		
n	297	293
Mean (SD)	1.4 (5.0)	0.3 (0.8)
Median (range)	0.2 (0.0–63.0)	0.0 (0.0–5.25)
Trastuzumab, days		
n	286*	288*
Mean (SD)	21.9 (1.6)	21.6 (0.9)
Median (range)	21.4 (19.6–39.0)	21.3 (20.0–26.0)
Docetaxel, days		
n	286*	288*
Mean (SD)	21.8 (1.7)	21.6 (0.9)
Median (range)	21.3 (19.6–39.0)	21.3 (20.0–26.4)

SD=standard deviation.

The data presented represent the "mean or median duration of treatment interruption per cycle." Pyrotinib/placebo is administered once daily continuously without rest periods. For each participant, "duration of treatment interruption per cycle" is calculated by summing the total treatment interruption time during their treatment period and dividing it by the total number of treatment cycles, each calculated as 21 days. Trastuzumab and docetaxel are administered once every 21 days. For each participant, "duration of treatment interruption per cycle" is calculated by summing the total treatment interruption time during their treatment period and dividing it by the total number of recorded treatment cycles. The asterisk (*) denotes the number of participants excluded those who received only 1 cycle of trastuzumab or docetaxel.

Table S3. Treatment related serious adverse events

	Pyrotinib group (n=297)	Placebo group (n=293)
Total	74 (24.9)	18 (6.1)
Diarrhoea	15 (5.1)	0
Alanine aminotransferase increased	10 (3.4)	1 (0.3)
Febrile neutropenia	9 (3.0)	5 (1.7)
Neutrophil count decreased	6 (2.0)	1 (0.3)
Vomiting	5 (1.7)	0
White blood cell count decreased	5 (1.7)	0
Aspartate aminotransferase increased	5 (1.7)	0
Anaemia	4 (1.3)	1 (0.3)
Hypokalaemia	4 (1.3)	0
Decreased appetite	4 (1.3)	0
Pneumonia	4 (1.3)	2 (0.7)
Intestinal obstruction	3 (1.0)	0
Nausea	2 (0.7)	1 (0.3)
Platelet count decreased	2 (0.7)	0
Acute kidney injury	2 (0.7)	0
Abdominal pain	1 (0.3)	0
Gastrointestinal haemorrhage	1 (0.3)	0
Gastritis	1 (0.3)	0
Tooth development disorder	1 (0.3)	0
Electrocardiogram QT prolonged	1 (0.3)	0
Hypoalbuminemia	1 (0.3)	0
Electrolyte imbalance	1 (0.3)	0
Cystitis	1 (0.3)	0
Cellulitis	1 (0.3)	0
Carbuncle	1 (0.3)	0
Depressed level of consciousness	1 (0.3)	0
Syncope	1 (0.3)	0
Neuropathy peripheral	1 (0.3)	0
Chronic kidney disease	1 (0.3)	0
Pneumonitis	1 (0.3)	0
Pulmonary fibrosis	1 (0.3)	0
Asthenia	1 (0.3)	0
Oedema peripheral	1 (0.3)	0
Arrhythmia	1 (0.3)	0
Left ventricular dysfunction	1 (0.3)	0
Cholecystitis	1 (0.3)	0
Spinal compression fracture	1 (0.3)	0
Fistula	1 (0.3)	0
Hypertension	1 (0.3)	0
Post procedural infection	0	1 (0.3)

	Pyrotinib group (n=297)	Placebo group (n=293)
Infection	0	1 (0.3)
Diabetic hyperosmolar coma	0	1 (0.3)
Pleural effusion	0	2 (0.7)
Ventricular extrasystoles	0	1 (0.3)
Sinus tachycardia	0	1 (0.3)
Hypersensitivity	0	1 (0.3)

Data are n (%).

Table S4. Treatment related adverse events that led to treatment discontinuation

	Pyrotinib group (n=297)	Placebo group (n=293)
Any	39 (13.1)	21 (7.2)
Anaemia	7 (2.4)	1 (0.3)
Hand-foot syndrome	3 (1.0)	3 (1.0)
Oedema peripheral	3 (1.0)	3 (1.0)
Asthenia	2 (0.7)	2 (0.7)
Weight decreased	2 (0.7)	0
Platelet count decreased	2 (0.7)	0
Intestinal obstruction	2 (0.7)	0
Pain in extremity	2 (0.7)	0
Rash	1 (0.3)	2 (0.7)
Hypoesthesia	1 (0.3)	2 (0.7)
Infusion related reaction	1 (0.3)	1 (0.3)
Pneumonia	1 (0.3)	1 (0.3)
Onychomadesis	1 (0.3)	1 (0.3)
Nail disorder	1 (0.3)	1 (0.3)
Electrocardiogram QT prolonged	1 (0.3)	1 (0.3)
Decreased appetite	1 (0.3)	1 (0.3)
White blood cell count decreased	1 (0.3)	0
Ejection fraction decreased	1 (0.3)	0
Blood creatinine increased	1 (0.3)	0
Neutrophil count decreased	1 (0.3)	0
Cystatin C increased	1 (0.3)	0
Nausea	1 (0.3)	0
Diarrhoea	1 (0.3)	0
Vomiting	1 (0.3)	0
Abdominal pain upper	1 (0.3)	0
Gastrointestinal haemorrhage	1 (0.3)	0
Cellulitis	1 (0.3)	0
Paronychia	1 (0.3)	0
Carbuncle	1 (0.3)	0
Hypoalbuminemia	1 (0.3)	0
Hypocalcaemia	1 (0.3)	0
Hyponatremia	1 (0.3)	0
Epistaxis	1 (0.3)	0
Pulmonary fibrosis	1 (0.3)	0
Ventricular arrhythmia	1 (0.3)	0
Left ventricular dysfunction	1 (0.3)	0
Conjunctival hyperaemia	1 (0.3)	0
Lacrimation increased	1 (0.3)	0
Acute kidney injury	1 (0.3)	0

	Pyrotinib group (n=297)	Placebo group (n=293)
Hypersensitivity	0	2 (0.7)
Nail discoloration	0	1 (0.3)
Localised oedema	0	1 (0.3)
Cardiac dysfunction	0	1 (0.3)

Data are n (%).

Table S5. Summary of data on diarrhoea

	Pyrotinib group (n=297)	Placebo group (n=293)
Diarrhoea incidence	293 (98.7)	159 (54.3)
Grade 1	36 (12.1)	100 (34.1)
Grade 2	118 (39.7)	48 (16.4)
Grade 3	138 (46.5)	11 (3.8)
Grade 4/5	0	0
Unknown*	1 (0.3)	0
Time to onset, median (IQR), days		
All grade	3 (2–5)	6 (4–24)
Grade 3	8 (6–15)	71 (23–178)
Duration per event, median (IQR), days		
All grade	2 (1–3)	2 (1–4)
Grade 3	1 (1–1)	1 (1–1)
Having diarrhoea >3 times		
All grade	263 (88.6)	54 (18.4)
Grade 3	41 (13.8)	0
Cumulative duration, median (IQR), days		
Grade 3	3 (2–6)	1 (1–2)
Treatment or dose modification for pyrotinib or placebo due to diarrhoea		
Treatment interruption	74 (24.9)	2 (0.7)
Dose reduction	51 (17.2)	0
Treatment discontinuation	1 (0.3)	0
Treatment or dose modification for trastuzumab due to diarrhoea		
Treatment discontinuation	1 (0.3)	0
Treatment or dose modification for docetaxel due to diarrhoea		
Dose reduction	1 (0.3)	0
Treatment discontinuation	1 (0.3)	0

Data are n (%), unless otherwise specified.

IQR=interquartile range.

*Medical record card of follow-up for this patient was lost, so the detailed information about diarrhoea were unknown.