Supplementary Appendix

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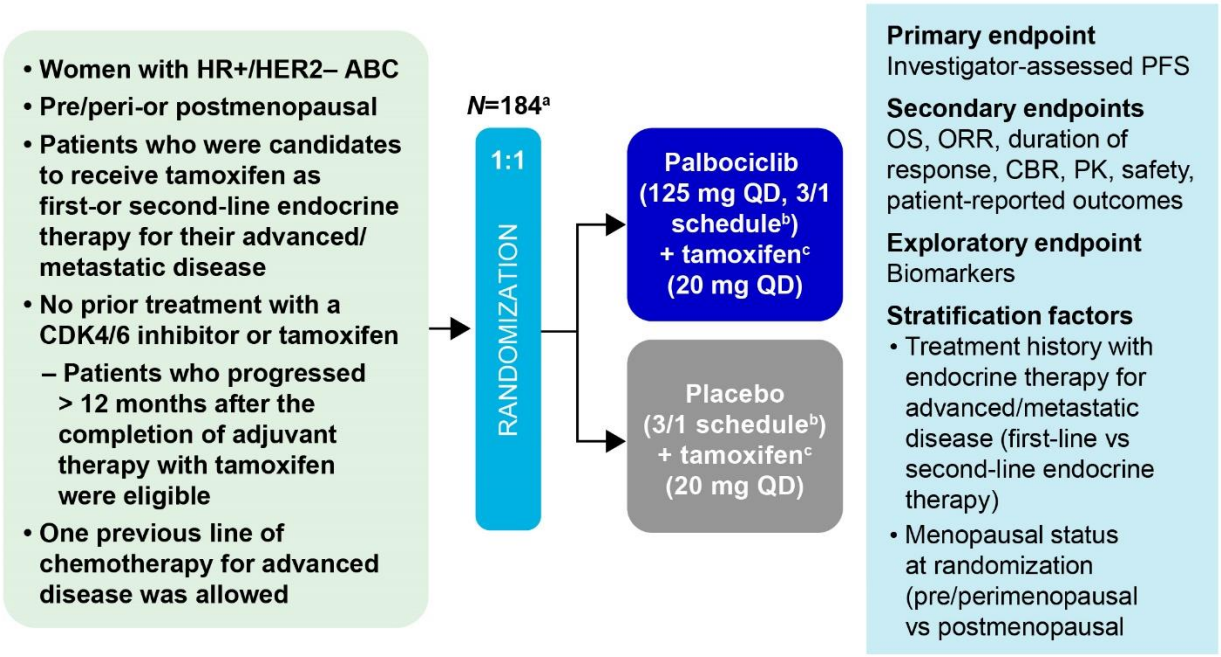
Supplementary Figure 1. Trial design.



[a]Actual.
[b]3/1 schedule defined as 3 weeks on and 1 week off therapy.
[c]Pre/perimenopausal women additionally received luteinizing hormone-releasing hormone agonist (goserelin).
ABC, advanced breast cancer; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4/6; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily.

Supplementary Table 1. Best overall response based on investigator assessment.

Treatment Group	*n*	Best Overall Response Based on Investigator Assessment, *n* (%)					Response Rate, *n* (%) (95%CI)[a]	Odds Ratio (95% CI)[b]
		CR	PR	SD	PD	NE		
Palbociclib-Tamoxifen	91	2 (2.2)	38 (41.8)	41 (45.1)	4 (4.4)	6 (6.6)	40 (44.0) (33.56–54.75)	2.02 (1.095–3.727)
Placebo-Tamoxifen	93	2 (2.2)	24 (25.8)	45 (48.4)	21 (22.6)	1 (1.1)	26 (28.0) (19.14–38.22)	

[a]Clopper Pearson method.

[b]Stratified odds ratio adjusted by the treatment history with endocrine therapy for advanced/metastatic disease and menopausal status at randomization.

CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Supplementary Table 2. Serious adiverse events related to study treatment, by severity grade and type.

Serious adverse event	Palbociclib–Tamoxifen Group (*n*=91)			Placebo–Tamoxifen Group (*n*=93)		
	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Any serious adverse events	2 (2.2)	1 (1.1)	0	3 (3.2)	1 (1.1)	1 (1.1)
Gastric ulcer	1 (1.1)	0	0	0	0	0
Peripheral swelling	0	0	0	1 (1.1)	0	0
Cellulitis	1 (1.1)	1 (1.1)	0	0	0	0
Erysipelas	1 (1.1)	1 (1.1)	0	0	0	0
Hypokalemia	0	0	0	1 (1.1)	1 (1.1)	0
Hyponatremia	0	0	0	1 (1.1)	0	1 (1.1)
Pulmonary embolism	0	0	0	1 (1.1)	1 (1.1)	0

Adverse events were graded by CTCAE v4.0.
Patient with more than one adverse event within the same level of MedDRA term was counted as one in its maximum grade.
CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

Supplementary Table 3. Adverse events leading to treatment discontinuation, by severity grade and type.

Adverse event leading to discontinuation	Palbociclib–Tamoxifen Group (*n*=91)			Placebo–Tamoxifen Group (*n*=93)		
	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Any adverse event leading to discontinuation	3 (3.3)	1 (1.1)	2 (2.2)	2 (2.2)	1 (1.1)	0
Septic shock	1 (1.1)	0	1 (1.1)	0	0	0
Femur fracture	1 (1.1)	1 (1.1)	0	0	0	0
Neutrophil count decreased	1 (1.1)	0	1 (1.1)	0	0	0
Thyroid cancer	0	0	0	1 (1.1)	1 (1.1)	0
Dizziness	0	0	0	1 (1.1)	0	0

Adverse events were graded by CTCAE v4.0.
Patient with more than one adverse event within the same level of MedDRA term was counted as one in its maximum grade.
CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

Supplementary Table 4. Follow-up anticancer therapy received by 3% or more of patients in either treatment group.

	Palbociclib–Tamoxifen *n*=91 *n* (%)	Placebo–Tamoxifen *n*=93 *n* (%)	Total *N*=184 *n* (%)
Any therapy	64 (70.3)	80 (86.0)	144 (78.3)
Any first subsequent therapy	64 (70.3)	80 (86.0)	144 (78.3)
Fulvestrant	11 (12.1)	7 (7.5)	18 (9.8)
Tamoxifen citrate	7 (7.7)	11 (11.8)	18 (9.8)
Abemaciclib, letrozole	3 (3.3)	8 (8.6)	11 (6.0)
Letrozole	5 (5.5)	5 (5.4)	10 (5.4)
Palbociclib, fulvestrant	3 (3.3)	6 (6.5)	9 (4.9)
Abemaciclib, fulvestrant	2 (2.2)	6 (6.5)	8 (4.3)
Anastrozole	5 (5.5)	2 (2.2)	7 (3.8)
Everolimus, exemestane	5 (5.5)	2 (2.2)	7 (3.8)
Tegafur/gimeracil/oteracil potassium	3 (3.3)	1 (1.1)	4 (2.2)
Palbociclib, letrozole	0	4 (4.3)	4 (2.2)
Paclitaxel	0	3 (3.2)	3 (1.6)
Any second subsequent therapy	38 (41.8)	53 (57.0)	91 (49.5)
Everolimus, exemestane	2 (2.2)	5 (5.4)	7 (3.8)
Fulvestrant	5 (5.5)	1 (1.1)	6 (3.3)
Capecitabine	1 (1.1)	5 (5.4)	6 (3.3)
Tegafur/gimeracil/oteracil potassium	4 (4.4)	1 (1.1)	5 (2.7)
Abemaciclib, fulvestrant	2 (2.2)	3 (3.2)	5 (2.7)
Paclitaxel	2 (2.2)	3 (3.2)	5 (2.7)
Exemestane	1 (1.1)	3 (3.2)	4 (2.2)
Palbociclib	0	4 (4.3)	4 (2.2)
Any third or greater subsequent therapy	31 (34.1)	42 (45.2)	73 (39.7)
Capecitabine	8 (8.8)	8 (8.6)	16 (8.7)
Eribulin mesylate	6 (6.6)	6 (6.5)	12 (6.5)
Everolimus, exemestane	1 (1.1)	10 (10.8)	11 (6.0)
Eribulin	4 (4.4)	6 (6.5)	10 (5.4)
Tegafur/gimeracil/oteracil potassium	5 (5.5)	2 (2.2)	7 (3.8)
Vinorelbine tartrate	4 (4.4)	3 (3.2)	7 (3.8)
Paclitaxel	4 (4.4)	2 (2.2)	6 (3.3)
Gemcitabine hydrochloride	2 (2.2)	4 (4.3)	6 (3.3)

Bevacizumab, paclitaxel	3 (3.3)	2 (2.2)	5 (2.7)
Abemaciclib, fulvestrant	3 (3.3)	1 (1.1)	4 (2.2)
Cyclophosphamide monohydrate, doxorubicin hydrochloride	1 (1.1)	3 (3.2)	4 (2.2)
Letrozole	1 (1.1)	3 (3.2)	4 (2.2)
Gemcitabine hydrochloride, paclitaxel	0	4 (4.3)	4 (2.2)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Abstract on pg 3
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	12
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Protocol
Participants	4a	Eligibility criteria for participants	12, 13
	4b	Settings and locations where the data were collected	12
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	13
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	14
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Protocol
Sample size	7a	How sample size was determined	15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
	8a	Method used to generate the random allocation sequence	13

Sequence generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	13
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	13
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	13
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	12
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	15
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	15
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	13, 14
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figures
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	5 to 7
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA

Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	7, 8
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	7, 8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	9 to 12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	9 to 12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	9 to 12
Other information			3
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	Supplement
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.