

Supplementary File

Figure S1. Risk of bias graph about included RCTs about CDK 4/6 inhibitors on unresectable locally advanced or metastatic HR+, HER2- BC in the meta-analysis

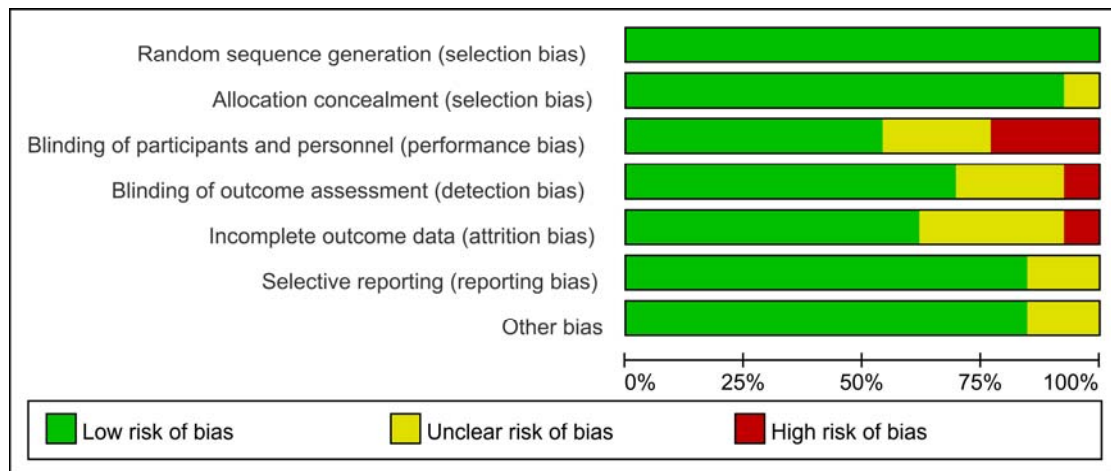


Figure S2. Risk of bias summary about included RCTs about CDK 4/6 inhibitors on unresectable locally advanced or metastatic HR+, HER2– BC in the meta-analysis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Albanell 2022	+	+	+	+	●	+	?
Finn 2015	+	+	●	+	+	?	+
Finn 2016	+	+	+	+	?	+	+
Goetz 2017	+	+	+	+	?	+	+
Hortobagyi 2016	+	?	+	?	+	+	+
Malorni 2018	+	+	●	+	?	?	+
Martin 2021	+	+	●	+	+	+	+
Park 2019	+	+	?	?	+	+	+
Slamon 2018	+	+	+	+	+	+	?
Sledge 2017	+	+	+	●	+	+	+
Tolaney 2020	+	+	?	+	?	+	+
Tripathy 2018	+	+	+	+	+	+	+
Turner 2015	+	+	?	?	+	+	+

Figure S3. Risk of bias graph about included RCTs about CDK 4/6 inhibitors on early HR+, HER2– BC in the meta-analysis.

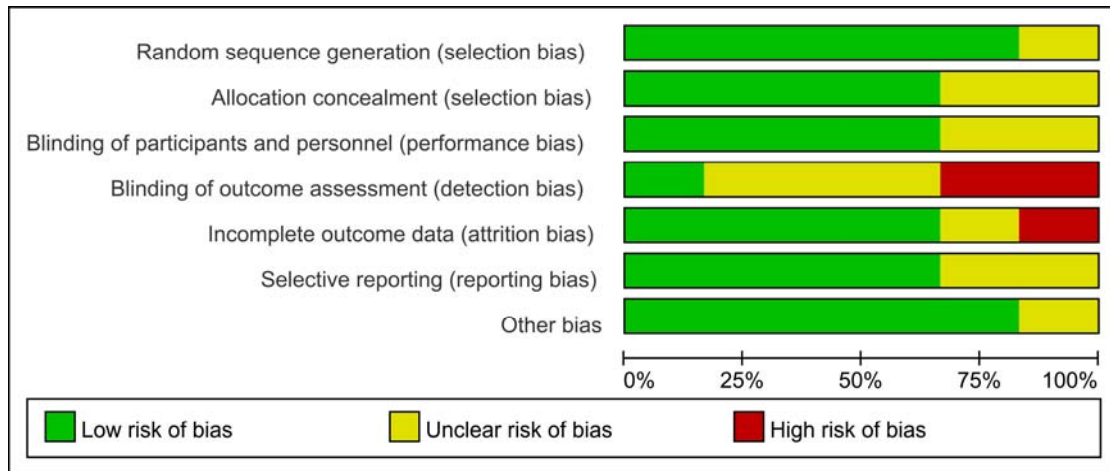


Figure S4. Risk of bias summary about included RCTs about CDK 4/6 inhibitors on early HR+, HER2– BC in the meta-analysis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cottu 2018	+	+	?	?	-	?	+
Johnston 2019	+	+	?	?	+	+	+
Johnston 2020	+	?	+	+	+	+	?
Loibl 2021	?	?	+	-	?	+	+
Mayer 2021	+	+	+	-	+	?	+
Prat 2020	+	+	+	?	+	+	+

Figure S5. Sensitivity analysis of the progression-free survival (PFS) of patients with unresectable locally advanced or metastatic HR+, HER2- BC on CDK4/6i combined with ET

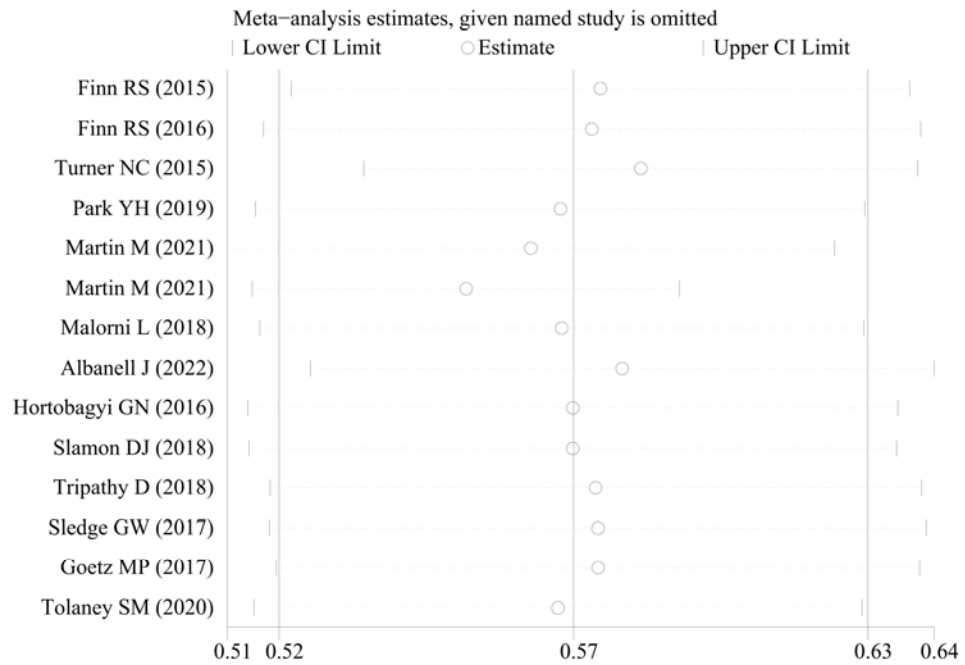


Figure S6. Publication bias of the progression-free survival (PFS) of patients with unresectable locally advanced or metastatic HR+, HER2- BC on CDK4/6i combined with ET

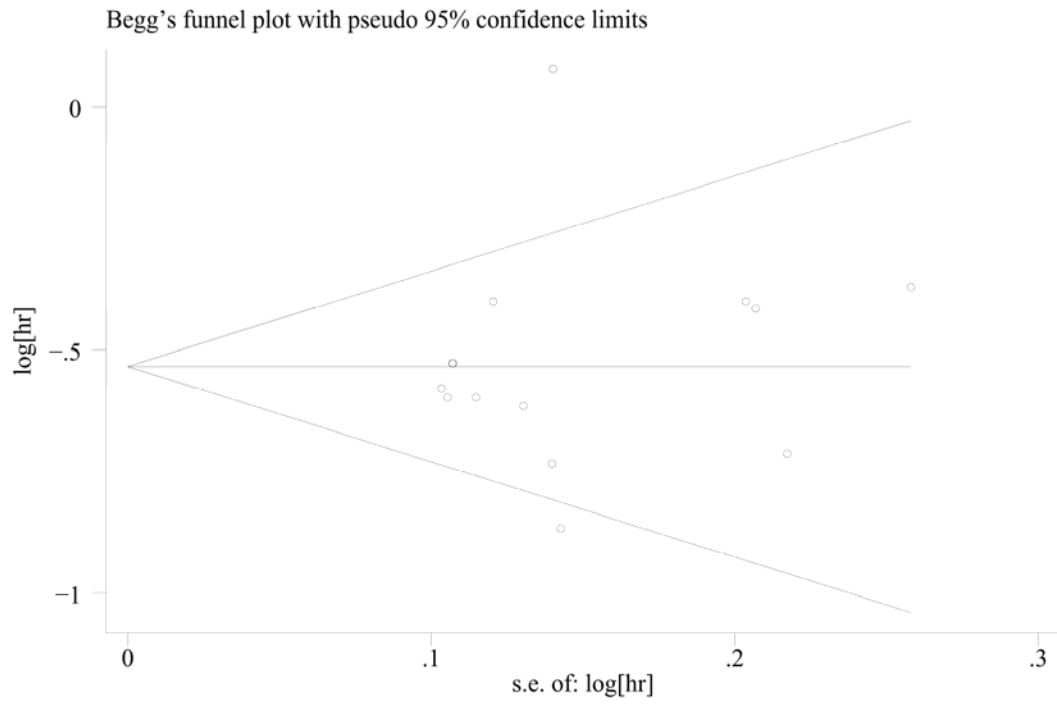


Table S1. Characteristics of included randomized controlled trials (RCTs) about cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors on HR+, HER2- advanced/metastatic breast cancer (BC) in the meta-analysis

Author, year	NCT	Masking	Median follow-up time (months)		Random allocation ratio	Trial duration	Median age (range) (years)		Other ids	Menstrual state/Sex
			Treatment	Control			Treatment	Control		
Finn, 2015	NCT00721409	None (open label)	29.6	27.9	1:1	2008.9–2017.11	63 (54–71)	64(56-70)	A5481003, 2008-002392-27	postmenopausal/female
Finn, 2016	NCT01740427	Quadruple (participant, care provider, investigator, outcomes assessor)	37.6	37.2	2:1	2013.12–2023.8	62 (30–89)	61 (28-88)	A5481008, 2012-004601-27	postmenopausal/female
Turner, 2015	NCT01942135	Triple (participant, care provider,	44.8	44.8	2:1	2013.9–2022.6	57 (30–88)	56 (29-80)	A5481023, 2013-002580-26	no requirement/female

Author, year	NCT	Masking	Median follow-up time (months)		Random allocation ratio	Trial duration	Median age (range) (years)		Other ids	Menstrual state/Sex
			Treatment	Control			Treatment	Control		
		investigator)								
Park, 2019	NCT02592746	None (open label)	17.0	17.0	1:1	2016.6–2021.6	44 (40–48)	44 (40–48)	KCSG-BR15-10, 2015-08-042	premenopausal/female
Martin, 2021	NCT02028507	None (open label)	13.5	18.9	1:1	2014.3–2021.1	60 (31–89)	60 (38–87)	GEICAM/2013-02, 2013-003170-27	postmenopausal/female
							62 (38–86)	60 (33–85)		
Malorni, 2018	NCT02549430	None (open label)	12.2	11.9	1:1	2012.10–2017.9	67 (37–82)	63 (45–81)	2011-005637-38	no requirement/female
Albanell, 2022	NCT02690480	Triple (participant, care provider, investigator)	28.6	28.6	1:1	2016.9–2023.12	64 (38–81)	64 (42–82)	GEICAM/2014-12, 2015-002437-21	postmenopausal/female

Author, year	NCT	Masking	Median follow-up time (months)		Random allocation ratio	Trial duration	Median age (range) (years)		Other ids	Menstrual state/Sex
			Treatment	Control			Treatment	Control		
Hortobagyi, 2016	NCT01958021	Quadruple (participant, care provider, investigator, outcomes assessor)	26.4	26.4	1:1	2013.11–2022.8	62 (23–91)	63 (29–88)	CLEE011A2301, 2013-003084-61	postmenopausal/female
Slamon, 2018	NCT02422615	Quadruple (participant, care provider, investigator, outcomes assessor)	39.4	39.4	2:1	2015.6–2022.9	63 (31–89)	63 (34–86)	CLEE011F2301, 2015-000617-43	postmenopausal/all

Author, year	NCT	Masking	Median follow-up time (months)		Random allocation ratio	Trial duration	Median age (range) (years)		Other ids	Menstrual state/Sex
			Treatment	Control			Treatment	Control		
Tripathy, 2018	NCT02278120	Quadruple (participant, care provider, investigator, outcomes assessor)	19.2	19.2	1:1	2014.11–2022.9	43 (25–58)	45 (29–58)	CLEE011E2301, 2014-001931-36	premenopausal/female
Sledge, 2017	NCT02107703	Double (participant, investigator)	47.7	47.7	2:1	2014.7–2024.1	59 (32–91)	62 (32–87)	15362, I3Y-MC-JPBL, 2013-004728-13	no requirement/female
Goetz, 2017	NCT02246621	Double (participant, care provider)	26.7	26.7	2:1	2014.11–2023.9	63 (38–87)	63 (32–88)	15417, I3Y-MC-JPBM, 2014-001502-18	postmenopausal/female

Author, year	NCT	Masking	Median follow-up time (months)		Random allocation ratio	Trial duration	Median age (range) (years)		Other ids	Menstrual state/Sex
			Treatment	Control			Treatment	Control		
Tolaney, 2020	NCT02675231	None (open label)	19.0	19.0	1:1	2016.5–2023.9	55 (47–62)	57 (47–67)	15804, I3Y-MC-JPBZ	no requirement/female

Table S2. Characteristics of included randomized controlled trials (RCTs) about cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors on early HR+, HER2– breast cancer (BC) in the meta-analysis

Author, year	NCT	Masking	Median follow-up time [years]		Random allocation ratio	Trial duration	Median age (range) (years)		Other ids	Menstrual state/Sex
			Treatment	Control			Treatment	Control		
Mayer, 2021	NCT02513394	none (open label)	23.7	23.7	1:1	2015.8–2025.9	52 (45–61)	52 (45–60)	AFT-05, ABCSG 42, BIG 14-03, 2014-005181-30	No requirement/all
Johnston, 2019	NCT02296801		NA	NA	3:2:2:2	2015.1–2019.3	64 (59–71)	66 (60–73)	NSABP FB-11, WI180455	Postmenopausal/female

Author, year	NCT	Masking	Median follow-up time [years]		Random allocation ratio	Trial duration	Median age (range) (years)		Other ids	Menstrual state/Sex
			Treatment	Control			Treatment	Control		
			none (open label)					64 (59–69)		
Loibl, 2021	NCT01864746	quadruple (participant, care provider, investigator, outcome assessor)	42.8	42.8	1:1	2013.11–2023.11	49 (22–76)	48 (19–79)	GBG78/BIG 1-13/NSABP-B-54-I, 2013-001040-62	No requirement/female
Cottu, 2018	NCT02400567	none (open label)	9.9	9.9	1:1	2015.1–2020.9	65 (49–78)	62 (48–80)	NeoPal-UC-0140/1404, 2014-002560-33, CARMINA04, NEOPAL	No requirement/female

Author, year	NCT	Masking	Median follow-up time [years]		Random allocation ratio	Trial duration	Median age (range) (years)		Other ids	Menstrual state/Sex
			Treatment	Control			Treatment	Control		
Prat, 2020	NCT03248427	none (open label)	NA	NA	1:1	2017.7–2019.7	63 (57–70)	64 (58–72)	SOLTI1402	Postmenopausal/female
Johnston, 2020	NCT03155997	none (open label)	15.5	15.5	1:1	2017.7–2029.6	51 (23–89)	51(22–86)	16338, I3Y-MC-JPCF, 2016-004362-26, NSABP B-58	No requirement/all

HR — hormone receptor; NA — not available