Title: Place in Therapy of Cyclin-dependent Kinase 4/6 Inhibitors in Breast Cancer: A Targeted Literature Review

Supplementary Information

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Running Header: Place in Therapy of CDK4/6i in Breast Cancer: A Targeted Literature Review

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Figure Legends

Fig. 1 PRISMA Study Selection Flow Diagram

Abbreviations: EudraCT = European Union Drug Regulating Authorities Clinical Trials Database; WHO = World Heath Organization. Source: Adapted from The PRISMA 2020 statement.

Fig. 2 Median Progression-free Survival on CDK4/6i Treatments in 1L

Median PFS for CDK4/6i treatment are presented in the 1L setting. Each included patient population is presented along X-axis with a unique reference number. The size of each bubble represents sample size. Complete list of included studies and reported PFS are presented in **Table 3**.
Abbreviations: CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; PFS = progression-free survival (months); Ref # = reference number.

Fig. 3 Median Progression-free Survival on CDK4/6i Treatments in 1L+ to 2L

Median PFS for CDK4/6i treatment are presented in the 1L+ to 2L setting. Each included patient population is presented along X-axis with a unique reference number. The size of each bubble represents sample size. Data were further grouped and color-coded by the treatment received prior to CDK4/6i treatment. Complete list of included studies and reported PFS are presented in **Table 3**.
Abbreviations: #L = # of line of therapy; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CT = chemotherapy; ET = endocrine therapy; NR = not reported; PFS = progression-free survival (months); Ref # = reference number.

Fig. 4 Median Progression-free Survival on CDK4/6i Treatments in 2L+ to 3L

Median PFS for CDK4/6i treatment are presented in the 2L+ to 3L setting. Each included patient population is presented along X-axis with a unique reference number. The size of each bubble represents sample size. Data were further grouped and color-coded by the treatment received prior to CDK4/6i treatment. Complete list of included studies and reported PFS are presented in **Table 3**.
Abbreviations: #L = # of line of therapy; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CT = chemotherapy; NR = not reported; PFS = progression-free survival (months); Ref # = reference number.

Fig. 5 Median Progression-free Survival on CDK4/6i Treatments in 3L+

Median PFS for CDK4/6i treatment are presented in the 3L+ setting. Each included patient population is presented along X-axis with a unique reference number. The size of each bubble represents sample size. Data were further grouped and color-coded by the treatment received prior to CDK4/6i treatment. Complete list of included studies and reported PFS are presented in **Table 3**.
Abbreviations: #L = # of line of therapy; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CT = chemotherapy; ET = endocrine therapy; NR = not reported; PFS = progression-free survival (months); Ref # = reference number.

Fig. 6 Median Overall Survival on CDK4/6i Treatments in 1L

Median OS for CDK4/6i treatment is presented in the 1L setting. Each included patient population is presented along X-axis with a unique reference number. The size of each bubble represents sample size. Complete list of included studies and reported OS are presented in **Table 4**.
Abbreviations: #L = # of line of therapy; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; OS = overall survival (months); Ref # = reference number.

Fig. 7 Median Overall Survival on CDK4/6i Treatments in 1L+ to 2L

Median OS for CDK4/6i treatment is presented in the 1L+ to 2L setting. Each included patient population is presented along X-axis with a unique reference number. The size of each bubble represents sample size. Data were further grouped and color-coded by the treatment received prior to CDK4/6i treatment. Complete list of included studies and reported OS are presented in **Table 4**.
Abbreviations: #L = # of line of therapy; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; ET = endocrine therapy; OS = overall survival (months); Ref # = reference number.

Fig. 8 Median Overall Survival on CDK4/6i Treatments in 2L+

Median OS for CDK4/6i treatment is presented in the 2L+ setting. Each included patient population is presented along X-axis with a unique reference number. The size of each bubble represents sample size. Data were further grouped and color-coded by the treatment received prior to CDK4/6i treatment. Complete list of included studies and reported OS are presented in **Table 4**.
Abbreviations: #L = # of line of therapy; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CT = chemotherapy; ET = endocrine therapy; OS = overall survival (months); Ref # = reference number.

Fig. 9 Median Survival on Post-CDK4/6i Treatments by Line of Therapy

Median PFS (A) and median OS (B) of post-CDK4/6i treatments grouped by the therapy line in which subsequent therapy was received. Each subsequent treatment is presented along X-axis with a unique reference number. The size of each bubble represents sample size. Data were further grouped and color-coded by the subsequent treatment received. Complete lists of included studies and reported PFS and OS are presented in **Table 3** and **Table 4**, respectively.
Abbreviations: #L = # of line of therapy; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CT = chemotherapy; ET = endocrine therapy; NR = not reported; OS = overall survival (months); PFS = progression-free survival (months); Ref # = reference number.

Online Resource 1: Search Strategy and PRISMA

Original Search

The Ovid MEDLINE databases (Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily) were searched on October 15th, 2021. The date range of the search was from 1946 to October 14th, 2021. The detailed search strategies used to search the Ovid MEDLINE databases are shown in the tables below. The search strategy for narrative and systematic reviews, including search terms and number of studies identified with each search term, are shown in **Table S1**. The search strategy and number of results for clinical studies are shown in **Table S2**. The last row in each table represents the final number of studies included for screening.

Clinical trial registries and Google Scholar were searched separately in October and November 2021 using the search strategies shown in **Table S3**. Clinical trial registry search results were limited to trials that started on or after January 1st, 2015 up to the search date (October 15th, 2021), and in patients aged 18 and older.

Table S1: Reviews Search Strategy

#	Searches	Results
1	exp Breast Neoplasms/	313330
2	exp Breast Carcinoma In Situ/	10763
3	((breast* or mamma or mammaries or mammary) adj3 (adenocarcinoma* or adeno-carcinoma* or cancer* or carcinoma* or tumour* or tumor* or malignan* or neoplasm*)).tw,kw,kf.	381488
4	((ductal or intraductal or intra-ductal) adj (carcinoma? or hyperplasia?)).tw,kw,kf.	17240
5	(lobul* carcinoma? adj2 "in situ").tw,kw,kf.	1113
6	(paget* and (areola? or breast* or mammaries or mammary or nipple?)).tw,kw,kf.	1396
7	(DCIS or LCIS).tw,kw,kf.	5724
8	or/1-7 [BREAST CANCER]	445598
9	(abemaciclib* or bemaciclib* or "ly 2835210" or "ly 2835219" or ly2835210 or ly283521 or verzenio$2 or verzenios$2 or 1231929-97-7 or 60UAB198HK).tw,kw,kf,rn.	443
10	(lerociclib* or "g1t 38" or g1t38 or 1628256-23-4 or WBH8AY6ENB).tw,kw,kf,rn.	3
11	(palbociclib* or ibrance$2 or "pd 0332991" or "pd 332991" or pd332991 or "pf 00080665" or pf00080665 or 571190-30-2 or G9ZF61LE7G).tw,kw,kf,rn.	1318
12	(ribociclib* or kisqali$2 or "lee 011" or "lee 011a" or "lee 011bba" or "lee 11" or "lee 11a" or "lee 11bba" or lee011 or lee011a or lee011bba or lee11 or lee11a or lee11bba or 1211441-98-3 or TK8ERE8P56).tw,kw,kf,rn.	501
13	aceliciclib*.tw,kw,kf.	0
14	"CS-3002".tw,kw,kf.	0
15	("ON-123300" or ON123300 or 1357470-29-1 or QJ8RO3296G).tw,kw,kf,rn.	5
16	"QHRD-110".tw,kw,kf.	0
17	"TY-302".tw,kw,kf.	0
18	"VS2-370".tw,kw,kf.	0
19	Cyclin-Dependent Kinase 4/ai [antagonists & inhibitors]	777
20	Cyclin-Dependent Kinase 6/ai [antagonists & inhibitors]	611
21	("CDK 4/6 inhibitor?" or "CDK4/6 inhibitor?" or "CDK 4/6i" or "CDK4/6i").tw,kw,kf.	1383
22	("cyclin dependent kinase 4/6" adj3 inhibitor?).tw,kw,kf.	252
23	((CDK4 or CDK-4 or CDK6 or CDK-6) adj3 inhibitor?).tw,kw,kf.	1898

#	Searches	Results
24	(("cell division protein kinase 4" or "cell division protein kinase 6") adj3 inhibitor?).tw,kw,kf.	0
25	(("cyclin dependent kinase 4" or "cyclin dependent kinase 6") adj3 inhibitor?).tw,kw,kf.	422
26	or/9-25 [CDK 4/6i]	2972
27	8 and 26 [BREAST CANCER - CDK 4/6i]	1523
28	(exp Child/ or exp Infant/) not (exp Adults/ or Adolescent/)	1340199
29	27 not 28 [CHILD-, INFANT-ONLY REMOVED]	1523
30	exp Animals/ not Humans/	4897921
31	29 not 30 [ANIMAL-ONLY REMOVED]	1505
32	(comment or editorial or news or newspaper article).pt.	1542176
33	(letter not (letter and randomized controlled trial)).pt.	1149422
34	31 not (32 or 33) [OPINION PIECES REMOVED]	1388
35	Systematic Review.pt.	171192
36	exp Systematic Reviews as Topic/	6696
37	Meta Analysis.pt.	143567
38	exp Meta-Analysis as Topic/	23141
39	(meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw,kf.	221466
40	(systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or mapping review? or rapid review* or "review of reviews" or scoping review? or umbrella review? or technology assessment* or HTA or HTAs).tw,kw,kf.	286091
41	exp Technology Assessment, Biomedical/	11570
42	(cochrane or health technology assessment or evidence report or systematic reviews).jw.	20900
43	(network adj (MA or MAs)).tw,kw,kf.	15
44	(NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kw,kf.	8039
45	indirect* compar*.tw,kw,kf.	2318
46	(indirect treatment* adj1 compar*).tw,kw,kf.	352
47	(mixed treatment* adj1 compar*).tw,kw,kf.	504
48	(multiple treatment* adj1 compar*).tw,kw,kf.	205
49	(multi-treatment* adj1 compar*).tw,kw,kf.	1
50	simultaneous* compar*.tw,kw,kf.	1175
51	mixed comparison?.tw,kw,kf.	38
52	review.pt.	2874873
53	narrative review?.tw,kw,kf.	16786
54	or/35-53 [REVIEWS]	3118122
55	34 and 54 [BREAST CANCER - CDK 4/6i - REVIEWS]	445
56	limit 55 to yr="2018-current"	310

Table S2: Clinical Studies Search Strategy

#	Searches	Results
1	exp Breast Neoplasms/	313330
2	exp Breast Carcinoma In Situ/	10763
3	((breast* or mamma or mammaries or mammary) adj3 (adenocarcinoma* or adeno-carcinoma* or cancer* or carcinoma* or tumour* or tumor* or malignan* or neoplasm*)).tw,kw,kf.	381488
4	((ductal or intraductal or intra-ductal) adj (carcinoma? or hyperplasia?)).tw,kw,kf.	17240
5	(lobul* carcinoma? adj2 "in situ").tw,kw,kf.	1113

#	Searches	Results
6	(paget* and (areola? or breast* or mammaries or mammary or nipple?)).tw,kw,kf.	1396
7	(DCIS or LCIS).tw,kw,kf.	5724
8	or/1-7 [BREAST CANCER]	445598
9	(abemaciclib* or bemaciclib* or "ly 2835210" or "ly 2835219" or ly2835210 or ly283521 or verzenio$2 or verzenios$2 or 1231929-97-7 or 60UAB198HK).tw,kw,kf,rn.	443
10	(lerociclib* or "g1t 38" or g1t38 or 1628256-23-4 or WBH8AY6ENB).tw,kw,kf,rn.	3
11	(palbociclib* or ibrance$2 or "pd 0332991" or "pd 332991" or pd332991 or "pf 00080665" or pf00080665 or 571190-30-2 or G9ZF61LE7G).tw,kw,kf,rn.	1318
12	(ribociclib* or kisqali$2 or "lee 011" or "lee 011a" or "lee 011bba" or "lee 11" or "lee 11a" or "lee 11bba" or lee011 or lee011a or lee011bba or lee11 or lee11a or lee11bba or 1211441-98-3 or TK8ERE8P56).tw,kw,kf,rn.	501
13	auceliciclib*.tw,kw,kf.	0
14	"CS-3002".tw,kw,kf.	0
15	("ON-123300" or ON123300 or 1357470-29-1 or QJ8RO3296G).tw,kw,kf,rn.	5
16	"QHRD-110".tw,kw,kf.	0
17	"TY-302".tw,kw,kf.	0
18	"VS2-370".tw,kw,kf.	0
19	Cyclin-Dependent Kinase 4/ai [antagonists & inhibitors]	777
20	Cyclin-Dependent Kinase 6/ai [antagonists & inhibitors]	611
21	("CDK 4/6 inhibitor?" or "CDK4/6 inhibitor?" or "CDK 4/6i" or "CDK4/6i").tw,kw,kf.	1383
22	("cyclin dependent kinase 4/6" adj3 inhibitor?).tw,kw,kf.	252
23	((CDK4 or CDK-4 or CDK6 or CDK-6) adj3 inhibitor?).tw,kw,kf.	1898
24	(("cell division protein kinase 4" or "cell division protein kinase 6") adj3 inhibitor?).tw,kw,kf.	0
25	(("cyclin dependent kinase 4" or "cyclin dependent kinase 6") adj3 inhibitor?).tw,kw,kf.	422
26	or/9-25 [CDK 4/6i]	2972
27	8 and 26 [BREAST CANCER - CDK 4/6i]	1523
28	(exp Child/ or exp Infant/) not (exp Adults/ or Adolescent/)	1340199
29	27 not 28 [CHILD-, INFANT-ONLY REMOVED]	1523
30	exp Animals/ not Humans/	4897921
31	29 not 30 [ANIMAL-ONLY REMOVED]	1505
32	(comment or editorial or news or newspaper article).pt.	1542176
33	(letter not (letter and randomized controlled trial)).pt.	1149422
34	31 not (32 or 33) [OPINION PIECES REMOVED]	1388
35	clinical trials as topic.sh.	197738
36	(randomized controlled trial or controlled clinical trial).pt.	635770
37	(randomized or randomly or placebo or trial or groups).ab.	3105949
38	drug therapy.fs.	2385661
39	or/35-38 [RANDOMIZED STUDIES – MEDLINE, sensitivity-maximizing version – Cochrane Handbook, 2019]	5213278
40	(pragmatic clinical trial or equivalence trial).pt.	2784
41	exp "Controlled Clinical Trials as Topic"/	158253
42	(randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kw,kf.	1084682
43	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw,kf.	183817
44	or/40-43 [ADDITIONAL TERMS TO SUPPLEMENT COCHRANE HSSS]	1165984
45	39 or 44 [RCT FILTER]	5292748
46	34 and 45 [RCTS]	860
47	controlled clinical trial.pt.	94453
48	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/	100016
49	(control* adj2 trial).tw,kw,kf.	181270
50	Non-Randomized Controlled Trials as Topic/	989
51	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kw,kf.	63502
52	(nRCT or non-RCT).tw,kw,kf.	393
53	Controlled Before-After Studies/	657
54	(control* adj3 ("before and after" or "before after")).tw,kw,kf.	4737
55	Interrupted Time Series Analysis/	1410
56	time series.tw,kw,kf.	37099
57	(pre- adj5 post-).tw,kw,kf.	109608
58	(pretest adj5 posttest).tw,kw,kf.	6690

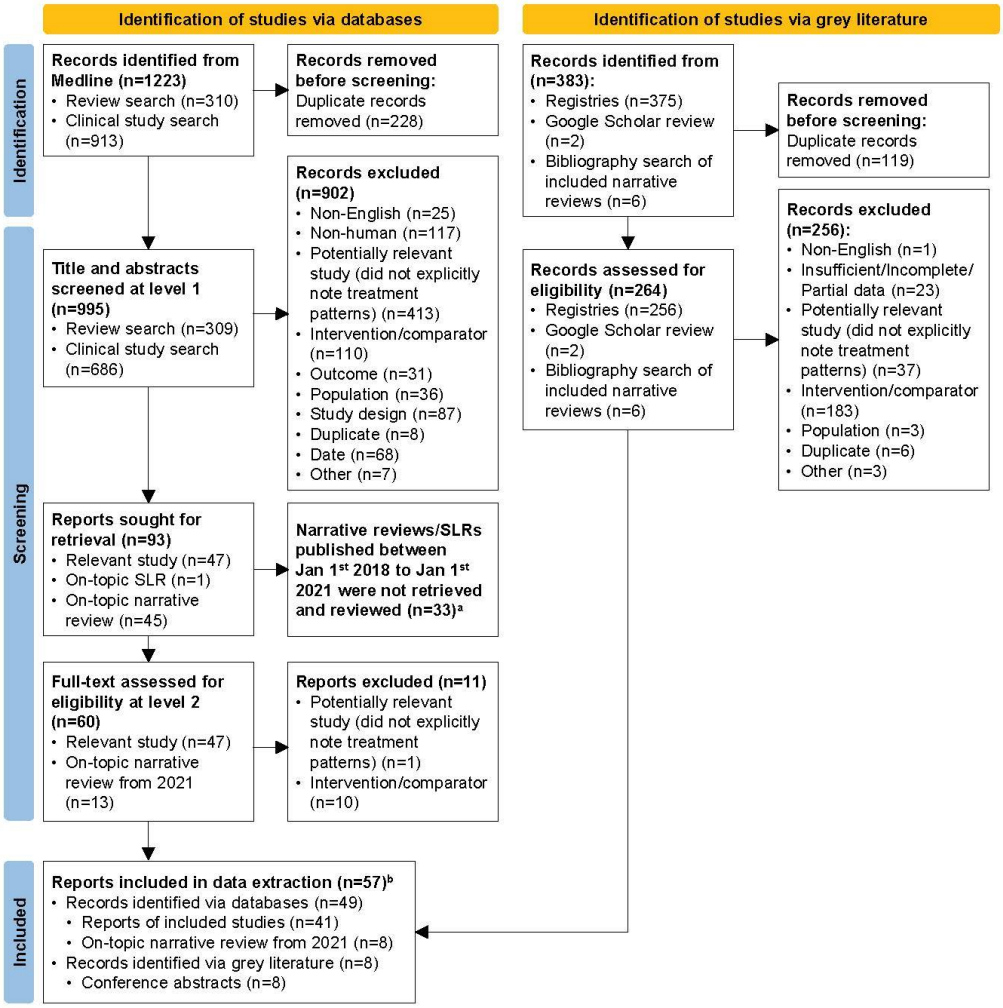
#	Searches	Results
59	(pre-test adj5 post-test).tw,kw,kf.	3184
60	Historically Controlled Study/	212
61	(control* adj2 study).tw,kw,kf.	189344
62	Control Groups/	1775
63	(control* adj2 group?).tw,kw,kf.	553159
64	trial.ti.	249218
65	or/47-64 [nRCT FILTER]	1228795
66	34 and 65 [nRCTs]	72
67	exp Cohort Studies/	2224003
68	cohort?.tw,kw,kf.	701175
69	Retrospective Studies/	950998
70	(longitudinal or prospective or retrospective).tw,kw,kf.	1445649
71	((followup or follow-up) adj (study or studies)).tw,kw,kf.	54616
72	Observational study.pt.	110855
73	(observation$2 adj (study or studies)).tw,kw,kf.	131989
74	((population or population-based) adj (study or studies or analys#s)).tw,kw,kf.	25870
75	((multidimensional or multi-dimensional) adj (study or studies)).tw,kw,kf.	126
76	Comparative Study.pt.	1900598
77	((comparative or comparison) adj (study or studies)).tw,kw,kf.	122813
78	exp Case-Control Studies/	1233904
79	((case-control* or case-based or case-comparison or case-compeer or case-referrent or case-referent) adj3 (study or studies)).tw,kw,kf.	126292
80	Cross-Sectional Studies/	391086
81	(crosssection* or cross-section*).tw,kw,kf.	460162
82	or/67-81 [OBSERVATIONAL STUDY FILTER]	5250955
83	34 and 82 [OBSERVATIONAL STUDIES]	233
84	"Clinical Trial, Phase II"/	35987
85	((phase 2 or phase II) adj2 (study or studies or trial? or design?)).tw,kw,kf.	43798
86	("single arm" adj2 (study or studies or trial? or design?)).tw,kw,kf.	4866
87	or/84-86 [SINGLE-ARM STUDY FILTER]	63264
88	34 and 87 [SINGLE-ARM STUDIES]	75
89	(real world or RWE or pragmatic design? or pragmatic stud$3 or pragmatic trial?).tw,kw,kf.	57199
90	34 and 89 [RWE]	73
91	46 or 66 or 83 or 88 or 90 [ALL STUDIES]	940
92	limit 91 to yr="2015-current"	913

Table S3: Grey Literature Search Strategy

Database	Search Terms/Strategy	Results
Clinicaltrials.gov	Breast cancer and CDK4/6	98
	Breast cancer and treatment pattern	107
WHO	Breast cancer and CDK4/6	84
	Breast cancer and treatment pattern	36
EudraCT	Breast cancer and CDK4/6	39
	Breast cancer and treatment pattern	11
Google Scholar	Breast cancer and CDK4/6 inhibitor and treatment sequence	50[a]
	CDK4/6 and treatment pattern	50[a]
	CDK4/6 and treatment sequence	50[a]
	Breast cancer and treatment pattern	50[a]
Narrative Review Bibliography	Studies relevant to treatment patterns	20

[a] Top 50 hits in each independent search were reviewed.

Figure A.1: PRISMA Study Selection Flow Diagram of Original Search



[a] Screening was further limited to Jan 1st, 2021, due to the large number of reviews identified.
[b] 57 records representing 53 unique studies (8 narrative reviews and 45 clinical studies).

Updated Search

An updated search for reviews and clinical studies combined was conducted in the Ovid MEDLINE databases (Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily) on October 19th, 2022. The date range of the search was from 1946 to October 18th, 2022. The detailed search strategy used to search the Ovid MEDLINE databases are shown in the tables below. The search strategy for narrative and systematic reviews, including search terms and number of studies identified with each search term, are shown in **Table S4**. The last row in each table represents the final number of studies included for screening.

Clinical trial registries and Google Scholar were searched separately in October and November 2022 using the search strategies shown in **Table S5**Table S3. Clinical trial registry search results were limited to trials that started on or after January 1st, 2015 up to the search dates, and in patients aged 18 and older.

Table S4: Updated Reviews and Clinical Studies Search Strategy

#	Searches	Results
1	exp Breast Neoplasms/	332485
2	exp Breast Carcinoma In Situ/	11184
3	((breast* or mamma or mammaries or mammary) adj3 (adenocarcinoma* or adeno-carcinoma* or cancer* or carcinoma* or tumour* or tumor* or malignan* or neoplasm*)).tw,kw,kf.	405813
4	((ductal or intraductal or intra-ductal) adj (carcinoma? or hyperplasia?)).tw,kw,kf.	18149
5	(lobul* carcinoma? adj2 "in situ").tw,kw,kf.	1151
6	(paget* and (areola? or breast* or mammaries or mammary or nipple?)).tw,kw,kf.	1458
7	(DCIS or LCIS).tw,kw,kf.	6034
8	or/1-7 [BREAST CANCER]	471688
9	(abemaciclib* or bemaciclib* or "ly 2835210" or "ly 2835219" or ly2835210 or ly283521 or verzenio$2 or verzenios$2 or 1231929-97-7 or 60UAB198HK).tw,kw,kf,rn.	607
10	(lerociclib* or "g1t 38" or g1t38 or 1628256-23-4 or WBH8AY6ENB).tw,kw,kf,rn.	3
11	(palbociclib* or ibrance$2 or "pd 0332991" or "pd 332991" or pd332991 or "pf 00080665" or pf00080665 or 571190-30-2 or G9ZF61LE7G).tw,kw,kf,rn.	1610
12	(ribociclib* or kisqali$2 or "lee 011" or "lee 011a" or "lee 011bba" or "lee 11" or "lee 11a" or "lee 11bba" or lee011 or lee011a or lee011bba or lee11 or lee11a or lee11bba or 1211441-98-3 or TK8ERE8P56).tw,kw,kf,rn.	622
13	auceliciclib*.tw,kw,kf.	0
14	"CS-3002".tw,kw,kf.	0
15	("ON-123300" or ON123300 or 1357470-29-1 or QJ8RO3296G).tw,kw,kf,rn.	6
16	"QHRD-110".tw,kw,kf.	0
17	"TY-302".tw,kw,kf.	0
18	"VS2-370".tw,kw,kf.	0
19	Cyclin-Dependent Kinase 4/ai [antagonists & inhibitors]	887
20	Cyclin-Dependent Kinase 6/ai [antagonists & inhibitors]	719
21	("CDK 4/6 inhibitor?" or "CDK4/6 inhibitor?" or "CDK 4/6i" or "CDK4/6i").tw,kw,kf.	1741
22	("cyclin dependent kinase 4/6" adj3 inhibitor?).tw,kw,kf.	353
23	((CDK4 or CDK-4 or CDK6 or CDK-6) adj3 inhibitor?).tw,kw,kf.	2296
24	(("cell division protein kinase 4" or "cell division protein kinase 6") adj3 inhibitor?).tw,kw,kf.	0
25	(("cyclin dependent kinase 4" or "cyclin dependent kinase 6") adj3 inhibitor?).tw,kw,kf.	535
26	or/9-25 [CDK 4/6i]	3643
27	8 and 26 [BREAST CANCER - CDK 4/6i]	1974
28	(exp Child/ or exp Infant/) not (exp Adults/ or Adolescent/)	1413635

#	Searches	Results
29	27 not 28 [CHILD-, INFANT-ONLY REMOVED]	1974
30	exp Animals/ not Humans/	5056817
31	29 not 30 [ANIMAL-ONLY REMOVED]	1952
32	(comment or editorial or news or newspaper article).pt.	1624173
33	(letter not (letter and randomized controlled trial)).pt.	1190648
34	31 not (32 or 33) [OPINION PIECES REMOVED]	1818
35	clinical trials as topic.sh.	200473
36	(randomized controlled trial or controlled clinical trial).pt.	669336
37	(randomized or randomly or placebo or trial or groups).ab.	3332573
38	drug therapy.fs.	2539917
39	or/35-38 [RANDOMIZED STUDIES – MEDLINE, sensitivity-maximizing version – Cochrane Handbook, 2019]	5559716
40	(pragmatic clinical trial or equivalence trial).pt.	3175
41	exp "Controlled Clinical Trials as Topic"/	167839
42	(randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kw,kf.	1163500
43	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw,kf.	192377
44	or/40-43 [ADDITIONAL TERMS TO SUPPLEMENT COCHRANE HSSS]	1246151
45	39 or 44 [RCT FILTER]	5644204
46	34 and 45 [RCTS]	1219
47	controlled clinical trial.pt.	95077
48	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/	100674
49	(control* adj2 trial).tw,kw,kf.	199342
50	Non-Randomized Controlled Trials as Topic/	1049
51	(nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kw,kf.	69127
52	(nRCT or non-RCT).tw,kw,kf.	461
53	Controlled Before-After Studies/	703
54	(control* adj3 ("before and after" or "before after")).tw,kw,kf.	5072
55	Interrupted Time Series Analysis/	1703
56	time series.tw,kw,kf.	42270
57	(pre- adj5 post-).tw,kw,kf.	121591
58	(pretest adj5 posttest).tw,kw,kf.	7301
59	(pre-test adj5 post-test).tw,kw,kf.	3633
60	Historically Controlled Study/	222
61	(control* adj2 study).tw,kw,kf.	201960
62	Control Groups/	1863
63	(control* adj2 group?).tw,kw,kf.	595060
64	trial.ti.	272253
65	or/47-64 [nRCT FILTER]	1321239
66	34 and 65 [nRCTs]	112
67	exp Cohort Studies/	2406952
68	cohort?.tw,kw,kf.	794631
69	Retrospective Studies/	1067110
70	(longitudinal or prospective or retrospective).tw,kw,kf.	1586454
71	((followup or follow-up) adj (study or studies)).tw,kw,kf.	57271
72	Observational study.pt.	133610
73	(observation$2 adj (study or studies)).tw,kw,kf.	150977
74	((population or population-based) adj (study or studies or analys#s)).tw,kw,kf.	26999
75	((multidimensional or multi-dimensional) adj (study or studies)).tw,kw,kf.	144
76	Comparative Study.pt.	1911693
77	((comparative or comparison) adj (study or studies)).tw,kw,kf.	129700

#	Searches	Results
78	exp Case-Control Studies/	1362410
79	((case-control* or case-based or case-comparison or case-compeer or case-referrent or case-referent) adj3 (study or studies)).tw,kw,kf.	135328
80	Cross-Sectional Studies/	443455
81	(crosssection* or cross-section*).tw,kw,kf.	518461
82	or/67-81 [OBSERVATIONAL STUDY FILTER]	5564360
83	34 and 82 [OBSERVATIONAL STUDIES]	338
84	"Clinical Trial, Phase II"/	38758
85	((phase 2 or phase II) adj2 (study or studies or trial? or design?)).tw,kw,kf.	46316
86	("single arm" adj2 (study or studies or trial? or design?)).tw,kw,kf.	5848
87	or/84-86 [SINGLE-ARM STUDY FILTER]	67765
88	34 and 87 [SINGLE-ARM STUDIES]	98
89	(real world or RWE or pragmatic design? or pragmatic stud$3 or pragmatic trial?).tw,kw,kf.	71029
90	34 and 89 [RWE]	133
91	46 or 66 or 83 or 88 or 90 [ALL STUDIES]	1310
92	limit 91 to yr="2015-current"	1283
93	92 and ((202110* not ("20211001" or "20211002" or "20211003" or "20211004" or 20211005 20211006 or "20211007" or "20211008" or "20211009" or "20211010" or "20211011" or "20211012" or "20211013" or "20211014")) or 202111* or 202112* or 2022*).dt. [Update results - 14 Oct 2021 - Current]	294
94	exp Breast Neoplasms/	332485
95	exp Breast Carcinoma In Situ/	11184
96	((breast* or mamma or mammaries or mammary) adj3 (adenocarcinoma* or adeno-carcinoma* or cancer* or carcinoma* or tumour* or tumor* or malignan* or neoplasm*)).tw,kw,kf.	405813
97	((ductal or intraductal or intra-ductal) adj (carcinoma? or hyperplasia?)).tw,kw,kf.	18149
98	(lobul* carcinoma? adj2 "in situ").tw,kw,kf.	1151
99	(paget* and (areola? or breast* or mammaries or mammary or nipple?)).tw,kw,kf.	1458
100	(DCIS or LCIS).tw,kw,kf.	6034
101	or/94-100 [BREAST CANCER]	471688
102	(abemaciclib* or bemaciclib* or "ly 2835210" or "ly 2835219" or ly2835210 or ly283521 or verzenio$2 or verzenios$2 or 1231929-97-7 or 60UAB198HK).tw,kw,kf,rn.	607
103	(lerociclib* or "g1t 38" or g1t38 or 1628256-23-4 or WBH8AY6ENB).tw,kw,kf,rn.	3
104	(palbociclib* or ibrance$2 or "pd 0332991" or "pd 332991" or pd332991 or "pf 00080665" or pf00080665 or 571190-30-2 or G9ZF61LE7G).tw,kw,kf,rn.	1610
105	(ribociclib* or kisqali$2 or "lee 011" or "lee 011a" or "lee 011bba" or "lee 11" or "lee 11a" or "lee 11bba" or lee011 or lee011a or lee011bba or lee11 or lee11a or lee11bba or 1211441-98-3 or TK8ERE8P56).tw,kw,kf,rn.	622
106	auceliciclib*.tw,kw,kf.	0
107	"CS-3002".tw,kw,kf.	0
108	("ON-123300" or ON123300 or 1357470-29-1 or QJ8RO3296G).tw,kw,kf,rn.	6
109	"QHRD-110".tw,kw,kf.	0
110	"TY-302".tw,kw,kf.	0
111	"VS2-370".tw,kw,kf.	0
112	Cyclin-Dependent Kinase 4/ai [antagonists & inhibitors]	887
113	Cyclin-Dependent Kinase 6/ai [antagonists & inhibitors]	719
114	("CDK 4/6 inhibitor?" or "CDK4/6 inhibitor?" or "CDK 4/6i" or "CDK4/6i").tw,kw,kf.	1741
115	("cyclin dependent kinase 4/6" adj3 inhibitor?).tw,kw,kf.	353
116	((CDK4 or CDK-4 or CDK6 or CDK-6) adj3 inhibitor?).tw,kw,kf.	2296
117	(("cell division protein kinase 4" or "cell division protein kinase 6") adj3 inhibitor?).tw,kw,kf.	0
118	(("cyclin dependent kinase 4" or "cyclin dependent kinase 6") adj3 inhibitor?).tw,kw,kf.	535
119	or/102-118 [CDK 4/6i]	3643

#	Searches	Results
120	101 and 119 [BREAST CANCER - CDK 4/6i]	1974
121	(exp Child/ or exp Infant/) not (exp Adults/ or Adolescent/)	1413635
122	120 not 121 [CHILD-, INFANT-ONLY REMOVED]	1974
123	exp Animals/ not Humans/	5056817
124	122 not 123 [ANIMAL-ONLY REMOVED]	1952
125	(comment or editorial or news or newspaper article).pt.	1624173
126	(letter not (letter and randomized controlled trial)).pt.	1190648
127	124 not (125 or 126) [OPINION PIECES REMOVED]	1818
128	Systematic Review.pt.	210008
129	exp Systematic Reviews as Topic/	9322
130	Meta Analysis.pt.	169310
131	exp Meta-Analysis as Topic/	25853
132	(meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw,kf.	256440
133	(systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or mapping review? or rapid review* or "review of reviews" or scoping review? or umbrella review? or technology assessment* or HTA or HTAs).tw,kw,kf.	336972
134	exp Technology Assessment, Biomedical/	12007
135	(cochrane or health technology assessment or evidence report or systematic reviews).jw.	21742
136	(network adj (MA or MAs)).tw,kw,kf.	17
137	(NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kw,kf.	8904
138	indirect* compar*.tw,kw,kf.	2619
139	(indirect treatment* adj1 compar*).tw,kw,kf.	430
140	(mixed treatment* adj1 compar*).tw,kw,kf.	518
141	(multiple treatment* adj1 compar*).tw,kw,kf.	220
142	(multi-treatment* adj1 compar*).tw,kw,kf.	3
143	simultaneous* compar*.tw,kw,kf.	1256
144	mixed comparison?.tw,kw,kf.	43
145	review.pt.	3060425
146	narrative review?.tw,kw,kf.	22478
147	or/128-146 [REVIEWS]	3339132
148	127 and 147 [BREAST CANCER - CDK 4/6i - REVIEWS]	557
149	limit 148 to yr="2018-current"	422
150	149 and ((202110* not ("20211001" or "20211002" or "20211003" or "20211004" or 20211005 20211006 or "20211007" or "20211008" or "20211009" or "20211010" or "20211011" or "20211012" or "20211013" or "20211014")) or 202111* or 202112* or 2022*).dt. [Update results - 14 Oct 2021 - Current]	97
151	**93 or 150 [COMBINED TRIALS & REVIEWS RESULTS - Update - 14 Oct 2021 - Current - MEDLINE]**	**330**

Table S5: Updated Grey Literature Search Strategy

Database	Search Terms/Strategy	Results
Clinicaltrials.gov	Breast cancer and CDK4/6	142
	Breast cancer and treatment pattern	146
WHO	Breast cancer and CDK4/6	10
	Breast cancer and treatment pattern	1
EudraCT	Breast cancer and CDK4/6	46
	Breast cancer and treatment pattern	12
Google Scholar	Breast cancer and CDK4/6 inhibitor and treatment sequence	50[a]
	CDK4/6 and treatment pattern	50[a]
	CDK4/6 and treatment sequence	50[a]
	Breast cancer and treatment pattern	50[a]
Narrative Review Bibliography	Studies relevant to treatment patterns	6

[a] Top 50 hits in each independent search were reviewed.

Online Resource 2: List of Studies Included or Excluded for Full-text Review

The complete list of studies included at the level of full-text review is provided in **Table S6**.

Table S7 provides a list of the 53 studies excluded during the full-text review stage organized by exclusion reason. Of the 135 studies that were screened through the full-text review, 10 studies were excluded due to irrelevant intervention or comparator; seven studies were excluded because while it was a potentially relevant study, the study did not explicitly note treatment patterns; one study was excluded for irrelevant outcomes, and two studies were excluded due to study design. Finally, 33 narrative or systematic reviews published between Jan 1st 2018 to Jan 1st 2021 were excluded due to the publication date.

Table S6: Studies Included for Full-text Review

Author, Year	Trial Name/ID	Title
Full-Text Publications		
Reviews		
Hui, 2021 [102]	N/A	CDK4/6 inhibitor plus endocrine therapy for hormone receptor-positive, HER2-negative metastatic breast cancer: The new standard of care
Kearney, 2021 [103]	N/A	Clinical trial data and emerging immunotherapeutic strategies: hormone receptor-positive, HER2- negative breast cancer
Li, 2021 [104]	N/A	Advances in Therapy for Hormone Receptor (HR)-Positive, Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Advanced Breast Cancer Patients Who Have Experienced Progression After Treatment with CDK4/6 Inhibitors
Loibl, 2021 [23]	N/A	Breast cancer
Mavratzas, 2021 [105]	N/A	Treatment of Luminal Metastatic Breast Cancer beyond CDK4/6 Inhibition: Is There a Standard of Care in Clinical Practice?
Migliaccio, 2021 [106]	N/A	CDK4/6 inhibitors: A focus on biomarkers of response and post-treatment therapeutic strategies in hormone receptor-positive HER2-negative breast cancer
Nagaraj, 2021 [107]	N/A	Clinical Challenges in the Management of Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: A Literature Review
Xu, 2021 [108]	N/A	Intrinsic and acquired resistance to CDK4/6 inhibitors and potential overcoming strategies
Cogliati, 2022 [109]	N/A	How to Treat HR+/HER2- Metastatic Breast Cancer Patients after CDK4/6 Inhibitors: An Unfinished Story
Munzone, 2021 [110]	N/A	Systematic review and meta-analysis of post-progression outcomes in ER+/HER2- metastatic breast cancer after CDK4/6 inhibitors within randomized clinical trials
Clinical Trials		
Bardia, 2021a [93]	NCT02338349	Phase I Study of Elacestrant (RAD1901), a Novel Selective Estrogen Receptor Degrader, in ER-Positive, HER2-Negative Advanced Breast Cancer

Author, Year	Trial Name/ID	Title
Bardia, 2021b [41]	TRINITI-1	Phase I/II Trial of Exemestane, Ribociclib, and Everolimus in Women with HR+/HER2- Advanced Breast Cancer after Progression on CDK4/6 Inhibitors (TRINITI-1)
Dudek, 2020 [55]	NCT03201913	Phase 1 study of TTC-352 in patients with metastatic breast cancer progressing on endocrine and CDK4/6 inhibitor therapy
Masuda, 2021 [49]	PALOMA-2, PALOMA-3	Analysis of subsequent therapy in Japanese patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer who received palbociclib plus endocrine therapy in PALOMA-2 and -3
Neven, 2021 [68]	MONARCH 2	MONARCH 2: Subgroup Analysis of Patients Receiving Abemaciclib Plus Fulvestrant as First-Line and Second-Line Therapy for HR+, HER2--Advanced Breast Cancer
Rossi, 2019 [59]	TREnd	Clinical outcomes after palbociclib with or without endocrine therapy in postmenopausal women with hormone receptor positive and HER2-negative metastatic breast cancer enrolled in the TREnd trial
Albanell, 2022 [88]	BioPER	Palbociclib Rechallenge for Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor-Negative Advanced Breast Cancer: Findings from the Phase II BioPER Trial
Bidard, 2022 [52]	EMERALD	Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial
Garcia-Saenz, 2022 [111]	NA	Sapanisertib plus Fulvestrant in Postmenopausal Women with Estrogen Receptor-Positive/HER2-Negative Advanced Breast Cancer after Progression on Aromatase Inhibitor
Lim, 2022 [97]	NA	Phase Ib/II Dose Expansion Study of Lenvatinib Combined with Letrozole in Postmenopausal Women with Hormone Receptor-Positive Breast Cancer
Martin, 2022a [90]	PEARL	Overall survival with palbociclib plus endocrine therapy versus capecitabine in postmenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer in the PEARL study
Zhang, 2022 [29]	LORDSHIPS	Dalpiciclib Combined With Pyrotinib and Letrozole in Women With HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer (LORDSHIPS): A Phase Ib Study
Prospective Observational Studies		
Davie, 2021 [30]	N/A	Real-world clinical profile, treatment patterns and patient-reported outcomes in a subset of HR+/HER2- advanced breast cancer patients with poor prognostic factors: data from an international study
Fountzilas, 2020 [47][a]	N/A	Real-world clinical outcome and toxicity data and economic aspects in patients with advanced breast cancer treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors combined with endocrine therapy: the experience of the Hellenic Cooperative Oncology Group
Palumbo, 2021 [69]	N/A	Patterns of treatment and outcome of palbociclib plus endocrine therapy in hormone receptor-positive/HER2 receptor-negative metastatic breast cancer: a real-world multicentre Italian study
Petracci, 2020 [48]	RENATA	RENATA study-Latin American prospective experience: clinical outcome of patients treated with palbociclib in hormone receptor-positive metastatic breast cancer-real-world use
Schneeweiss, 2020 [67]	PRAEGNANT	Initial experience with CDK4/6 inhibitor-based therapies compared to antihormone monotherapies in routine clinical use in patients with hormone receptor positive, HER2 negative breast cancer - Data from the PRAEGNANT research network for the first 2 years of drug availability in Germany
Engler, 2022 [34]	PRAEGNANT	Implementation of CDK4/6 Inhibitors and its Influence on the Treatment Landscape of Advanced Breast Cancer Patients - Data from the Real-World Registry PRAEGNANT
Gharib, 2022 [76]	NA	Palbociclib and letrozole in hormone-receptor positive advanced breast cancer: Predictive response and prognostic factors

Author, Year	Trial Name/ID	Title
Shen, 2022 [83]	NA	Treatment patterns, effectiveness, and patient-reported outcomes of palbociclib therapy in Chinese patients with advanced breast cancer: A multicenter ambispective real-world study
Retrospective Observational Studies		
Agrawal, 2021 [63]	N/A	Multicentric real world evidence with palbociclib in hormone positive HER2 negative metastatic breast cancer in Indian population
Basile, 2021 [36]	N/A	First- and second-line treatment strategies for hormone-receptor (HR)-positive HER2-negative metastatic breast cancer: A real-world study
Battisti, 2019 [86]	N/A	Palbociclib and endocrine therapy in heavily pretreated hormone receptor-positive HER2-negative advanced breast cancer: the UK Compassionate Access Programme experience
Boer, 2021 [61]	N/A	Demographic Characteristics and Treatment Patterns Among Patients Receiving Palbociclib for HR+/HER2- Advanced Breast Cancer: A Nationwide Real-World Experience
Brufsky, 2019 [70]	N/A	Treatment Patterns and Outcomes Associated with Palbociclib Plus Letrozole for Postmenopausal Women With HR+/HER2- Advanced Breast Cancer Enrolled in an Expanded Access Program
Carter, 2021 [112]	N/A	Real-world treatment patterns and outcomes of abemaciclib for the treatment of HR+, HER2- metastatic breast cancer
Collins, 2021 [91]	N/A	A Real-World Evidence Study of CDK4/6 Inhibitor Treatment Patterns and Outcomes in Metastatic Breast Cancer by Germline BRCA Mutation Status
Cook, 2021 [94]	N/A	Everolimus Plus Exemestane Treatment in Patients with Metastatic Hormone Receptor-Positive Breast Cancer Previously Treated with CDK4/6 Inhibitor Therapy
Cui, 2021 [32]	N/A	Predicting optimal treatment regimens for patients with HR+/HER2- breast cancer using machine learning based on electronic health records
Dhakal, 2020 [95]	N/A	Outcome of Everolimus-Based Therapy in Hormone-Receptor-Positive Metastatic Breast Cancer Patients After Progression on Palbociclib
Goldschmidt, 2018 [35]	N/A	Current Treatment Patterns Among Postmenopausal Women with HR+/HER2- Metastatic Breast Cancer in US Community Oncology Practices: An Observational Study
Gong, 2018 [113]	N/A	A single institution experience with palbociclib toxicity requiring dose modifications
Jeong, 2021 [37]	N/A	Comparison of the Effectiveness and Clinical Outcome of Everolimus Followed by CDK4/6 Inhibitors with the Opposite Treatment Sequence in Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer
Kessler, 2020 [89]	N/A	Efficacy and safety of cyclin dependent kinases 4/6 inhibitors in the treatment of metastatic breast cancer: a real-world experience
Li, 2021 [99]	N/A	A multicenter analysis of treatment patterns and clinical outcomes of subsequent therapies after progression on palbociclib in HR+/HER2- metastatic breast cancer
Lin, 2021 [71]	N/A	Treatment patterns and clinical outcomes of palbociclib-based therapy received in US community oncology practices
Liu, 2020 [64]	N/A	Clinical Outcomes of 130 Patients with Hormone Receptor-Positive and Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer Treated with Palbociclib plus Endocrine Therapy and Subsequent Therapy: A Real-World Single-Center Retrospective Study in China
Meegdes, 2021 [31]	SONABRE	The implementation of CDK 4/6 inhibitors and its impact on treatment choices in HR+/HER2- advanced breast cancer patients: A study of the Dutch SONABRE Registry
Mougalian, 2019 [54]	N/A	Observational study of clinical outcomes of eribulin mesylate in metastatic breast cancer after cyclin-dependent kinase 4/6 inhibitor therapy

Author, Year	Trial Name/ID	Title
Norman, 2021 [114]	N/A	Incidence and Severity of Myelosuppression with Palbociclib After Palliative Bone Radiation in Advanced Breast Cancer: A Single Center Experience and Review of Literature
Pizzuti, 2019 [115]	N/A	Palbociclib plus endocrine therapy in HER2 negative, hormonal receptor-positive, advanced breast cancer: A real-world experience
Princic, 2019 [38]	N/A	Predictors of systemic therapy sequences following a CDK 4/6 inhibitor-based regimen in post-menopausal women with hormone receptor positive, HEGFR-2 negative metastatic breast cancer
Rath, 2021 [65]	N/A	Efficacy and safety of palbociclib and ribociclib in patients with estrogen and/or progesterone receptor positive, HER2 receptor negative metastatic breast cancer in routine clinical practice
Rozenblit, 2021 [100]	N/A	Patterns of treatment with everolimus exemestane in hormone receptor-positive HER2-negative metastatic breast cancer in the era of targeted therapy
Taylor-Stokes, 2019 [116]	IRIS	Treatment patterns and clinical outcomes among patients receiving palbociclib in combination with an aromatase inhibitor or fulvestrant for HR+/HER2-negative advanced/metastatic breast cancer in real-world settings in the US: Results from the IRIS study
Varella, 2019 [72]	N/A	Real-world clinical outcomes and toxicity in metastatic breast cancer patients treated with palbociclib and endocrine therapy
Waller, 2019 [117]	IRIS	Real-World Treatment Patterns and Clinical Outcomes in Patients Receiving Palbociclib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced or Metastatic Breast Cancer in Argentina: The IRIS Study
Wander, 2021 [42]	N/A	Clinical Outcomes with Abemaciclib After Prior CDK4/6 Inhibitor Progression in Breast Cancer: A Multicenter Experience
Xi, 2019 [51]	N/A	Retrospective Analysis of Treatment Patterns and Effectiveness of Palbociclib and Subsequent Regimens in Metastatic Breast Cancer
Zhang, 2021 [66]	N/A	The efficacy and safety of palbociclib combined with endocrine therapy in patients with hormone receptor-positive HER2-negative advanced breast cancer: a multi-center retrospective analysis
Choong, 2022 [73]	NA	Clinical management of metastatic hormone receptor-positive, HER2-negative breast cancer (MBC) after CDK 4/6 inhibitors: a retrospective single-institution study
Endo, 2022 [74]	NA	Time to Chemotherapy for Patients With Estrogen Receptor-Positive Breast Cancer and Cyclin-Dependent Kinase 4 and 6 Inhibitor Use
Fernandez-Cuerva, 2022 [75]	NA	Effectiveness and Safety of Palbociclib plus Endocrine Therapy in Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer: Real-World Results
Gao, 2021 [92]	NA	Overall survival in patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer treated with a cyclin-dependent kinase 4/6 inhibitor plus fulvestrant: a US Food and Drug Administration pooled analysis
Ha, 2022 [78]	NA	Palbociclib plus endocrine therapy significantly enhances overall survival of HR+/HER2- metastatic breast cancer patients compared to endocrine therapy alone in the second-line setting: A large institutional study
Hayama, 2022 [57]	NA	Treatment Strategy for Patients with HR-Positive HER2-Negative Metastatic Breast Cancer That Progressed on CDK4/6 Inhibitors
Kitano, 2022 [53]	NA	Everolimus for Treating Hormone Receptor-positive Metastatic Breast Cancer Previously Treated With Cyclin-dependent Kinase 4/6 Inhibitors
Li, 2021 [80]	NA	Real-world effectiveness and sensitivity of palbociclib plus endocrine therapy in HR+/HER2- patients with metastatic breast cancer

Author, Year	Trial Name/ID	Title
Marineau, 2022 [118]	NA	Cyclin-dependent kinase 4/6 inhibitor treatment use in women treated for advanced breast cancer: Integrating ASCO/NCODA patient-centered standards in a community pharmacy
Martin, 2022b [87]	NA	Systemic Therapies Following Progression on First-line CDK4/6-inhibitor Treatment: Analysis of Real-world Data
Mo, 2022a [79]	NA	Treatment patterns and clinical outcomes in patients with metastatic breast cancer treated with palbociclib-based therapies: real-world data in the Han population
Mo, 2022b [98]	NA	Real-World Outcomes of Everolimus and Exemestane for the Treatment of Metastatic Hormone Receptor-Positive Breast Cancer in Patients Previously Treated With CDK4/6 Inhibitors
Mycock, 2022 [85]	IRIS	Real-world treatment patterns and clinical outcomes in patients receiving palbociclib combinations for HR+/HER2- advanced/metastatic breast cancer in Japan: Results from the IRIS study
Novick, 2022 [119]	NA	Real world evidence study on treatment patterns and health resource utilization in patients with HR+/HER2-locally advanced or metastatic breast cancer in Korea
Sawaki, 2022 [33]	NA	Real-world treatment patterns of palbociclib and blood count monitoring in patients with advanced breast cancer in Japan
Seki, 2022 [56]	NA	Subsequent-abemaciclib Treatment After Disease Progression on Palbociclib in Patients With ER-positive HER2-negative Metastatic Breast Cancer
Smyth, 2022 [120]	NA	Real-World Patient Characteristics, Utilization Patterns, and Outcomes of US Patients with HR+, HER2- Metastatic Breast Cancer Treated with Abemaciclib
Whitaker, 2022 [40]	NA	Racial inequities in second-line treatment and overall survival among patients with metastatic breast cancer
Yildirim, 2022 [84]	NA	Clinical outcomes of cyclin-dependent kinase 4-6 (CDK 4-6) inhibitors in patients with male breast cancer: A multicenter study
Zhong, 2022 [39]	NA	Efficacy and safety of palbociclib plus endocrine therapy for patients with HR+/HER2- advanced breast cancer in real-world clinical practice
Zhou, 2022 [96]	NA	Clinical outcomes of tucidinostat-based therapy after prior CDK4/6 inhibitor progression in hormone receptor-positive heavily pretreated metastatic breast cancer
Trial Records		
Retrospective Observational Studies		
ClinicalTrials.gov [121]	NA	Description of Treatment Patterns and Description and Comparison of Healthcare Resource Utilization and Costs of Women With Metastatic HR+/HER2- Breast Cancer Treated With CDK4/6 Inhibitors
ClinicalTrials.gov [122]	NA	Treatment Patterns And Clinical Outcomes Among Patients in Latin America Receiving First Line Palbociclib Combinations For HR+/HER2- Advanced/Metastatic Breast Cancer In Real World Settings.
ClinicalTrials.gov [123]	NA	A Study to Describe the Breast Cancer Patient Population, Treatment, and Results in Indian Patients Receiving Combinations of the Medicines Called Palbociclib for Advanced Breast Cancer
Abstracts		
Clinical Trials		
Bardia, 2019 [124]	TRINITI-1	Triplet therapy (continuous ribociclib, everolimus, exemestane) in HR+/HER2− advanced breast cancer post progression on a CDK4/6 inhibitor (TRINITI-1): Efficacy, safety, and biomarker results.
Prospective Observational Studies		
Marschner, 2022 [81]	OPAL	Second-line therapies of patients with early progression under CDK4/6-inhibitor in first-line – data from the registry platform OPAL

Author, Year	Trial Name/ID	Title
Retrospective Observational Studies		
Agrawal, 2020 [125]	N/A	Real world evidence of palbociclib use in metastatic hormone positive HER negative metastatic breast cancer in Indian population
dos Anjos, 2019 [46]	N/A	A large retrospective analysis of CDK 4/6 inhibitor retreatment in ER+ metastatic breast cancer (MBC).
Eziokwu, 2019 [45]	N/A	Real-world evidence evaluating continuation of CDK4/6 inhibitors beyond first progression in hormone receptor-positive (HR+) metastatic breast cancer.
Giridhar, 2019 [58]	N/A	Abstract P6-18-09: Clinical management of metastatic breast cancer (MBC) after CDK 4/6 inhibitors: A retrospective single-institution study
McLaurin, 2019 [126]	N/A	A real-world evidence study of CDK4/6 inhibitor treatment patterns and outcomes in metastatic breast cancer by gBRCA mutation status.
Tamragouri, 2019 [44]	N/A	Abemaciclib with or without fulvestrant for the treatment of hormone receptor-positive and HER2-negative metastatic breast cancer with disease progression following prior treatment with palbociclib.
Wander, 2019 [43]	N/A	A multicenter analysis of abemaciclib after progression on palbociclib in patients (pts) with hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC).
Check, 2022 [127]	NA	Treatment patterns and health care resource use of patients with metastatic breast cancer with HER2-low expression: A cancer registry-linked insurance claims study
Gousis, 2022 [77]	NA	Beyond First Line CDK4/6 Inhibitors (CDK4/6i) and Aromatase Inhibitors (AI) in Patients with Oestrogen Receptor Positive Metastatic Breast Cancer (ER+ MBC): The Guy's Cancer Centre Experience
Parola, 2022 [128]	NA	CDK4/6 inhibitors in hormone receptor-positive, HER2-negative, locally advanced breast cancer (LABC): Biological and clinical activity, and post-surgical approaches
Sampedro-Gimeno, 2021 [82]	NA	Observational real world data with palbociclib associated to hormone therapy for advanced breast carcinoma

[a] Prospective-retrospective observational study.

Abbreviations: ASCO = American Society of Clinical Oncology; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; EBCC = European Breast Cancer Conference; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; MBC = metastatic breast cancer; N/A = not applicable; SABC = San Antonio Breast Cancer Symposium.

Table S7: Studies Excluded for Full-text Review

Reason for Exclusion/Reference
Intervention/comparator (n = 10)
Wang B, Li R, Wu S, Liu X, Ren J, Li J, et al. Breast Cancer Resistance to Cyclin-Dependent Kinases 4/6 Inhibitors: Intricacy of the Molecular Mechanisms. Front Oncol. 2021;11:651541. doi: https://dx.doi.org/10.3389/fonc.2021.651541.
Braal CL, Jongbloed EM, Wilting SM, Mathijssen RHJ, Koolen SLW, Jager A. Inhibiting CDK4/6 in Breast Cancer with Palbociclib, Ribociclib, and Abemaciclib: Similarities and Differences. Drugs. 2021;81(3):317-31. doi: https://dx.doi.org/10.1007/s40265-020-01461-2.
Tolba MF, Elghazaly H, Bousoik E, Elmazar MMA, Tolaney SM. Novel combinatorial strategies for boosting the efficacy of immune checkpoint inhibitors in advanced breast cancers. Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico. 2021;23(10):1979-94. doi: https://dx.doi.org/10.1007/s12094-021-02613-w.

Reason for Exclusion/Reference
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Online Resource 3: Detailed Characteristics of Reviews

Table S8: Summary of Review Characteristics

Reference	Topic	Unique References [a]	Patient Population	Treatment Patterns Discussed
Hui, 2021 [102]	Recent efficacy findings from key phase III clinical trials of CDK4/6i + ET in patients with HR+/HER2 mBC	11	• HR+/HER2- mBC • Progressed on CDK4/6i	• ET -> Abemaciclib + AI • AI -> Palbociclib + ET • CDK4/6i -> Alpelisib + Fulvestrant • CDK4/6i -> Ribociclib + EVE + EXE • CDK4/6i -> Targeted Therapy (CDK4/6i-based, PI3Ki-based)
Kearney, 2021 [103]	Current and emerging combination strategies for treatment of HR+/HER2- BC	1	• HR+/HER2- mBC	• CDK4/6i -> CDK4/6i-based
Li, 2021 [104]	Recent and future treatment strategies post-CDK4/6i	24	• HR+/HER2- aBC • Progressed on CDK4/6i	• CDK4/6i -> CDK4/6i • CDK4/6i -> PI3Ki • CDK4/6i -> mTORi • CDK4/6i -> PARPi • CDK4/6i -> Chemotherapy • CDK4/6i -> Other (eg, CDK7i, BCL2i) • CDK4/6i -> ET-based
Loibl, 2021 [23]	Biology and treatment management pathways for patients with eBC and mBC	4	• eBC • mBC (ER+/-, HER2+/-, TNBC)	• CDK4/6i + AI/Fulvestrant -> Alpelisib + Fulvestrant • ET -> Different ET + CDK4/6i • CDK4/6i + AI/Fulvestrant -> ET + EVE • CDK4/6i + AI/Fulvestrant -> Different AI • CDK4/6i + AI/Fulvestrant -> Talazoparib • CDK4/6i + AI/Fulvestrant -> Fulvestrant • CDK4/6i + AI -> Different AI • CDK4/6i -> Targeted Therapy (CDK4/6i-based, mTORi-based, PI3Ki-based; PARPi-based) • CDK4/6i -> ET-based • CDK4/6i + AI/Fulvestrant -> Tamoxifen • CDK4/6i + AI/Fulvestrant -> Olaparib

Reference	Topic	Unique References [a]	Patient Population	Treatment Patterns Discussed
Mavratzas, 2021 [105]	Recent potential therapeutic strategies after progression on CDK4/6i	32	• HR+/HER2- mBC • Progressed on CDK4/6i	• CDK4/6i -> Palbociclib + EVE + EXE • CDK4/6i -> Venetoclax +/- Fulvestrant • Palbociclib -> Abemaciclib +/- ET • CDK4/6i -> continued CDK4/6i • Palbociclib -> CT • CDK4/6i -> Alpelisib + Letrozole/Fulvestrant • Palbociclib + ET -> Palbociclib + different ET • CDK4/6i -> Ribociclib + EVE + EXE • AI +/- CDK4/6i -> Alpelisib + Fulvestrant • CDK4/6i -> Targeted Therapy (CDK4/6i-based, AKTi-based, PI3Ki-based, BCL2i-based) • CDK4/6i -> ET-based
Migliaccio, 2021 [106]	Recent potential therapeutic strategies after progression on CDK4/6i	28	• HR+/HER2- mBC • Progressed on CDK4/6i	• Palbociclib -> ET monotherapy • CDK4/6i -> EVE + EXE • CDK4/6i + AI -> Alpelisib + Fulvestrant • Palbociclib + Letrozole -> Palbociclib + Fulvestrant • Palbociclib + Letrozole -> CT + EXE + EVE -> Palbociclib + Fulvestrant • Palbociclib/Ribociclib -> Abemaciclib (+/- ET) • CDK4/6i -> Ribociclib + EVE + EXE • CDK4/6i -> Targeted Therapy (CDK4/6i-based, mTORi-based, PI3Ki-based, AKTi-based)
Nagaraj, 2021 [107]	Recent progress in optimizing ET and the development of targeted agents in the management of mBC	15	• HR+/HER2- mBC • Progressed on CDK4/6i	• AI +/- CDK4/6i -> Alpelisib + Fulvestrant • CDK4/6i -> Targeted Therapy (CDK4/6i-based, mTORi-based) • CDK4/6i -> ET-based
Xu, 2021 [108]	Treatment combination strategies to extend the use of CDK4/6i in various tumour types	1	• HR+/HER2- mBC	• ET -> Ribociclib + Fulvestrant
Cogliati, 2022 [109]	Analyze significant results in post-CDK4/6i setting trials	20	• HR+/HER2- mBC • Progressed on CDK4/6i	• CDK4/6i -> CT • CDK4/6i -> ET, • CDK4/6i -> EVE + EXE • CDK4/6i -> CDK4/6i • CDK4/6i -> anti-VEGF + CT • CDK4/6i -> PIK3CA inhibitors • CDK4/6i -> BCL-2 inhibitors • CDK4/6i -> Immunotherapy

Reference	Topic	Unique References [a]	Patient Population	Treatment Patterns Discussed
Munzone, 2021 [110]	Assessment of benefit of CDK4/6i on PFS2 and on time to chemotherapy	8	• HR+HER2- aBC/mBC	• CDK4/6i -> ET • CDK4/6i -> CT • CDK4/6i -> mTORi, • CDK4/6i -> CDK4/6i • CDK4/6i -> Eribulin

[a] Included ongoing trials evaluating subsequent treatments after progression on CDK4/6i.
Abbreviations: aBC = advanced breast cancer; AI = aromatase inhibitor; CDK = cyclin dependent kinase; CT = chemotherapy; eBC = early breast cancer; ET = endocrine therapy; EVE = everolimus; EXE = exemestane; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; mBC = metastatic breast cancer; mPFS = median progression-free survival; mTORi = mammalian target of rapamycin inhibitor; Bcl2i = B-cell lymphoma 2 inhibitor; N = number/sample size; OS = overall survival; PARP = poly adenosine diphosphate-ribose polymerase; PI3K = phosphoinositide 3 kinase; TNBC = triple negative breast cancer; VEGF = vascular endothelial growth factor.

Online Resource 4: Detailed Characteristics of Clinical Studies

Table S9: CDK4/6i Clinical Studies: Patient Population and Treatment Characteristics

Reference	Study Design	Patient Population	Patient (N)	CDK4/6i LoT	CDK4/6i Regimen Received	Prior Treatment Received
Agrawal, 2021 [63]	Retrospective Observational	HR+/HER2- mBC	115	1L	Palbociclib + AI	N/A
			73	2L	Palbociclib + Fulvestrant	CT[a]
Bardia, 2021b [41]	Clinical Trial	HR+/HER2- aBC/mBC	95	2L+	EXE + ribociclib + EVE	CT, ET, CDK4/6i
Basile, 2021 [36]	Retrospective Observational	HR+/HER2- mBC	40	2L	CDK4/6i + ET	ET
Battisti, 2019 [86]	Retrospective Observational	HR+/HER2- aBC	43	1L-3L	Palbociclib + ET	CT
			52	1L-3L	Palbociclib + ET	ET
			75	4L+	Palbociclib + ET	CT
			66	4L+	Palbociclib + ET	ET
Boer, 2021 [61]	Retrospective Observational	HR+/HER2- aBC	399	1L+	Palbociclib + AI	CT, ET
			563	1L+	Palbociclib + Fulvestrant	CT, ET
Brufsky, 2019 [70]	Retrospective Observational	HR+/HER2- mBC	14	1L	Palbociclib + Letrozole	N/A
			18	2L	Palbociclib + Letrozole	CT, ET[a]
			94	3L+	Palbociclib + Letrozole	CT, ET[a]
Collins, 2021 [91]	Retrospective Observational	HR+/HER2- mBC, gBRCAm	36	1L	Palbociclib +/- ET	N/A

Reference	Study Design	Patient Population	Patient (N)	CDK4/6i LoT	CDK4/6i Regimen Received	Prior Treatment Received
		HR+/HER2- mBC, gBRCAwt	293	1L	Palbociclib +/- ET	N/A
		HR+/HER2- mBC, gBRCAwt/unknown	1160	1L	Palbociclib +/- ET	N/A
		HR+/HER2- mBC, gBRCAm	27	2L	Palbociclib +/- ET	ET[b]
		HR+/HER2- mBC, gBRCAwt	253	2L	Palbociclib +/- ET	ET[b]
		HR+/HER2- mBC, gBRCAwt/unknown	922	2L	Palbociclib +/- ET	ET[b]
		HR+/HER2- mBC, gBRCAm	22	3L+	Palbociclib +/- ET	CT, ET, EVE + EXE[c]
		HR+/HER2- mBC, gBRCAwt	228	3L+	Palbociclib +/- ET	CT, ET, EVE + EXE[c]
		HR+/HER2- mBC, gBRCAwt/unknown	801	3L+	Palbociclib +/- ET	CT, ET, EVE + EXE[c]
Cui, 2021 [32]	Machine Learning Analysis	HR+/HER2- mBC	3965	1L	CDK4/6i (palbociclib, abemaciclib, ribociclib) +/- ET	N/A
			2455	2L	CDK4/6i (palbociclib, abemaciclib, ribociclib) +/- ET	CT, ET
Davie, 2021 [30]	Prospective Observational	HR+/HER2- aBC	2259	1L+	CT, ET, CDK4/6i + ET, ET + targeted therapies	CT, ET, CDK4/6i + ET, ET + targeted therapies
dos Anjos, 2019 [46]	Retrospective Observational	ER+ mBC	135	2L+	CDK4/6i	CDK4/6i
Eziokwu, 2019 [45]	Retrospective Observational	HR+/HER2- mBC	30	2L	CDK4/6i (palbociclib, abemaciclib) + ET	Palbociclib + letrozole, fulvestrant, or other AI
Fountzilas, 2020 [47]	Prospective-Retrospective Observational	HR+/HER2- aBC/mBC	149	1L	Palbociclib or ribociclib	N/A
			94	2L	Palbociclib or ribociclib	CT, ET
			117	3L+	Palbociclib or ribociclib	CT, ET
Giridhar, 2019 [58]	Retrospective Observational	ER+ mBC	81	1L	Palbociclib + ET	N/A
			55	2L	Palbociclib + ET	NR
Goldschmidt, 2018 [35]	Retrospective Observational	HR+/HER2- mBC	210	1L-2L	CDK4/6i	NR
Gong, 2018 [113]	Retrospective Observational	HR+/HER2- aBC/mBC	100	1L+	Palbociclib + ET	CT, ET
Jeong, 2021 [37]	Retrospective Observational	HR+/HER2- mBC	33	2L+	Palbociclib or abemaciclib + fulvestrant	EVE + EXE
Kessler, 2020 [89]	Retrospective Observational	aBC/mBC	68	2L-3L	CDK4/6i	CT
			20	4L+	CDK4/6i	CT

Reference	Study Design	Patient Population	Patient (N)	CDK4/6i LoT	CDK4/6i Regimen Received	Prior Treatment Received
Lin, 2021 [71]	Retrospective Observational	HR+/HER2- aBC/mBC	233	1L	Palbociclib + AI	N/A
			48	1L-2L	Palbociclib + Fulvestrant	ET
Liu, 2020 [64]	Retrospective Observational	HR+/HER2- mBC	42	1L	Palbociclib + ET	N/A
			88	2L+	Palbociclib + ET	CT, ET, EVE[a]
			19	4L+	Palbociclib + ET	CT, ET, EVE[a]
Masuda, 2021 [49]	Clinical Trial	ER+/HER- aBC	32	1L+	Palbociclib + letrozole	NR
			27	1L+	Palbociclib + Fulvestrant	NR
McLaurin, 2019 [126]	Retrospective Observational	HR+/HER2- mBC	2968	1L+	CDK4/6i	NR
Meegdes, 2021 [31]	Retrospective Observational	HR+/HER2- aBC	214	1L	CDK4/6i + ET	N/A
			71	2L	CDK4/6i + ET	NR
Neven, 2021 [68]	Clinical Trial	HR+/HER2- aBC	265	1L	Abemaciclib + fulvestrant	N/A
			170	2L	Abemaciclib + fulvestrant	ET
Palumbo, 2021 [69]	Retrospective Observational	HR+/HER2- mBC	61	1L	Palbociclib + ET	N/A
			32	1L	Palbociclib + letrozole	N/A
			29	1L	Palbociclib + fulvestrant	N/A
			51	2L	Palbociclib + ET	CT, ET[a, d]
			28	2L	Palbociclib + letrozole	CT, ET[a, d]
			23	2L	Palbociclib + fulvestrant	CT, ET[a, d]
			70	3L+	Palbociclib + ET	CT, ET[a, d]
			30	3L+	Palbociclib + letrozole	CT, ET[a, d]
			40	3L+	Palbociclib + fulvestrant	CT, ET[a, d]
Petracci, 2020 [48]	Prospective Observational	HR+/HER2- aBC	63	1L	Palbociclib + ET	N/A
			44	2L+	Palbociclib + ET	CT, ET[a]
Pizzuti, 2019 [115]	Retrospective Observational	HR+/HER2- aBC	158	1L	Palbociclib + ET	N/A
			106	2L	Palbociclib + ET	CT, ET
			159	3L+	Palbociclib + ET	CT, ET
Rath, 2021 [65]	Retrospective Observational	HR+/HER2- mBC[e]	22	1L	Palbociclib or ribociclib + ET	N/A
			79	2L+	Palbociclib or ribociclib + ET	CT, ET
Schneeweiss, 2020 [67]	Clinical Trial	HR+/HER2- aBC	864	1L	CDK4/6i + ET	N/A
			512	2L	CDK4/6i + ET	CT, ET[f]

Reference	Study Design	Patient Population	Patient (N)	CDK4/6i LoT	CDK4/6i Regimen Received	Prior Treatment Received
			188	3L	CDK4/6i + ET	CT, ET[f]
Tamragouri, 2019 [44]	Retrospective Observational	HR+/HER2- mBC	21	2L+	Abemaciclib monotherapy, or in combination with fulvestrant	Palbociclib + AI or fulvestrant
Taylor-Stokes, 2019 [116]	Retrospective Observational	HR+/HER2- aBC/mBC	106	1L	1L Palbociclib + Fulvestrant	N/A
			186	2L+	2L+ Palbociclib + Fulvestrant	NR
			162	2L	2L Palbociclib + Fulvestrant	NR
			22	3L	3L Palbociclib + Fulvestrant	NR
Varella, 2019 [72]	Retrospective Observational	HR+ aBC/mBC	57	1L	Palbociclib + letrozole	N/A
			34	1L	Palbociclib + fulvestrant	N/A
			39	2L	Palbociclib + fulvestrant	CT[a]
			31	2L	Palbociclib + letrozole	NR
			32	3L+	Palbociclib + fulvestrant	CT[a]
			85	3L+	Palbociclib + letrozole	NR
Waller, 2019 [117]	Retrospective Observational	HR+/HER2- aBC/mBC	105	1-3L	Palbociclib + letrozole	NR
			8	1L	1L Palbociclib + fulvestrant	N/A
			49	2L+	2L+ Palbociclib + fulvestrant	NR
Wander, 2019 [43]	Retrospective Observational	HR+/HER2- mBC	58	2L+	Abemaciclib +/- ET	Palbociclib
Wander, 2021 [42]	Retrospective Observational	HR+/HER2- mBC	70	2L	Abemaciclib + antiestrogen	Palbociclib
			17	2L	Abemaciclib	Palbociclib
			87	2L	Abemaciclib +/- antiestrogen	Palbociclib
Xi, 2019 [51]	Retrospective Observational	mBC	42	1L	Palbociclib + HT	N/A
			50	2L	Palbociclib + HT	NR
			108	3L+	Palbociclib + HT	NR
Zhang, 2021 [66]	Retrospective Observational	HR+/HER2- aBC	88	1L	Palbociclib + ET	N/A
			39	2L	Palbociclib + ET	CT, ET[g]
			24	3L	Palbociclib + ET	CT, ET[g]
Albanell, 2022 [88]	Clinical Trial	HR+/HER2- aBC	32	2L+	Palbociclib + ET	Palbociclib + ET
Check, 2022 [127]	Retrospective Observational	HER2-low mBC	635	1L-2L	ET/CT/CDK4/6i+ET	ET/CT/CDK4/6i+ET
Choong, 2022 [73]	Retrospective Observational	HR+/HER2- mBC	91	1L	Palbociclib + Letrozole/Fulvestrant	NA

Reference	Study Design	Patient Population	Patient (N)	CDK4/6i LoT	CDK4/6i Regimen Received	Prior Treatment Received
			45	2L	Palbociclib + Letrozole/Fulvestrant	CT, ET
Endo, 2022 [74]	Retrospective Observational	HR+/HER2- aBC	41	1L	CDK4/6i + ET	NA
			33	2L	CDK4/6i + ET	CT, ET
Engler, 2022 [34]	Prospective Registry	HR+/HER2- aBC	474	1L	CDK4/6i + Anti-hormone therapy	NA
Gao, 2021 [92]	Retrospective pooled analysis	HR+/HER2- aBC/mBC	1305	1L-2L	CDK4/6i + Fulvestrant	NR
Gharib, 2022 [76]	Prospective Retrospective Observational	HR+/HER2- aBC	30	1L	Palbociclib + Letrozole	NA
			30	2L+	Palbociclib + Letrozole	NR
Ha, 2022 [78]	Retrospective Observational	HR+/HER2- aBC	708	1L	CDK4/6i + AI	NA
			380	2L	CDK4/6i + Fulvestrant	AI
Li, 2021 [80]	Retrospective Observational	HR+/HER2- aBC	54	1L	Palbociclib + Letrozole/Fulvestrant	NA
				2L	Palbociclib + Letrozole/Fulvestrant	CT, ET
				3L+	Palbociclib + Letrozole/Fulvestrant	CT, ET
Marineau, 2022 [118]	Retrospective Observational	HR+/HER2- mBC	65	1L-2L+	Abemaciclib/Palbociclib + ET	NR
Martin, 2022a [90]	Clinical Trial	HR+HER2- mBC	601	1L-4L+	Palbociclib + ET	NR
Mo, 2022a [79]	Retrospective Observational	HR+/HER2- mBC	186	1L	Palbociclib + ET	NR
				2L-3L	Palbociclib + ET	NR
				4L-5L	Palbociclib + ET	NR
				6L+	Palbociclib + ET	NR
Mycock, 2022 [85]	Retrospective Observational	HR+/HER2- aBC/mBC	170	2L+	Palbociclib + AI/Fulvestrant	CT/ET/Targeted
ClinicalTrials.gov [121]	Retrospective Observational	HR+/HER2- mBC	4320	1L+	CDK4/6i (Palbociclib, Abemaciclib, Ribociclib)	CT, ET, or other
Novick, 2022 [119]	Retrospective Observational	HR+/HER2- aBC/mBC	22	1L	Palbociclib + Letrozole	NR
Sampedro-Gimeno, 2021 [82]	Retrospective Observational	aBC/mBC	73	1L	Palbociclib + ET	NR
				2L	Palbociclib + ET	NR
Sawaki, 2022 [33]	Retrospective Observational	HR+/HER2- aBC	357	1L	1L Palbociclib + Fulvestrant	NA
					1L Palbociclib + Letrozole	NA
					1L Palbociclib + Exemestane	NA

Reference	Study Design	Patient Population	Patient (N)	CDK4/6i LoT	CDK4/6i Regimen Received	Prior Treatment Received
					1L Palbociclib + Anastrozole	NA
					1L Palbociclib + Tamoxifen	NA
					1L Palbociclib + Torimifen	NA
					1L Palbociclib + Other	NA
			336	2L	2L Palbociclib + Fulvestrant	CT, ET
					2L Palbociclib + Letrozole	CT, ET
					2L Palbociclib + Exemestane	CT, ET
					2L Palbociclib + Anastrozole	CT, ET
					2L Palbociclib + Tamoxifen	CT, ET
					2L Palbociclib + Torimifen	CT, ET
					2L Palbociclib + Other	CT, ET
			150	3L	3L Palbociclib + Fulvestrant	CT, ET
					3L Palbociclib + Letrozole	CT, ET
					3L Palbociclib + Exemestane	CT, ET
					3L Palbociclib + Anastrozole	CT, ET
					3L Palbociclib + Tamoxifen	CT, ET
					3L Palbociclib + Other	CT, ET
Shen, 2022 [83]	Ambispective Observational	HR+/HER2- aBC	190	1L	Palbociclib + Letrozole/Anastrozole	CT, ET
					Palbociclib + Exemestane	CT, ET
					Palbociclib + Fulvestrant	CT, ET
				2L	Palbociclib + Letrozole/Anastrozole	CT, ET
					Palbociclib + Exemestane	CT, ET
					Palbociclib + Fulvestrant	CT, ET
				3L	Palbociclib + Letrozole/Anastrozole	CT, ET
					Palbociclib + Exemestane	CT, ET
					Palbociclib + Fulvestrant	CT, ET
Smyth, 2022 [120]	Retrospective Observational	HR+/HER2- mBC	115	2L	Abemaciclib-based	Palbociclib or Ribociclib-based
Whitaker, 2022 [40]	Retrospective Observational	HR+/HER2- mBC	2,408	2L	CDK4/6i	CDK4/6i/ET/CT

Reference	Study Design	Patient Population	Patient (N)	CDK4/6i LoT	CDK4/6i Regimen Received	Prior Treatment Received
Yildirim, 2022 [84]	Retrospective Observational	HR+/HER2- mBC	12	1L	CDK4/6i + GnRH + fulvestrant/AI	NA
			13	2L+	CDK4/6i + GnRH + fulvestrant/AI	NR
Zhang, 2022 [29]	Clinical Trial	HR+/HER2+ mBC	7	1L	Dalpiciclib + pyrotinib + letrozole	CT/ET/Targeted
			8	2L	Dalpiciclib + pyrotinib + letrozole	CT/ET/Targeted
Zhong, 2022 [39]	Retrospective Observational	HR+/HER2- aBC	34	1L	Palbociclib + ET	CT/ET
			14	2L	Palbociclib + ET	CT/ET
			15	3L+	Palbociclib + ET	CT/ET

[a] Study only reported % of patients who received this prior treatment. Prior treatment received for remaining patients were not reported.
[b] Top agents included letrozole, anastrozole, fulvestrant, tamoxifen.
[c] Top agents included fulvestrant, EVE + EXE, letrozole, capecitabine, anastrozole, and paclitaxel.
[d] CT included taxane, capecitabine, vinorelbine, eribulin, and other; ET included AI, EVE, and fulvestrant.
[e] ER+ and/or PR+.
[f] ET included fulvestrant-based, tamoxifen-based, or AI monotherapy; CT type not reported.
[g] CT included anthracyclines, taxanes, anthracyclines + taxanes, fluorouracil + adriamycin + cyclophosphamide, capecitabine/fluorouracil/thiotepa/cisplatin + vinorelbine; ET included SERMs, AI, SERMs followed by AI.
Abbreviations: #L = # of lines of therapy; aBC = advanced breast cancer; AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CT = chemotherapy; ET = endocrine therapy; EVE = everolimus; EXE = exemestane; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; LOT = line of therapy; mBC = metastatic breast cancer; N = sample size; N/A = not applicable; NR = not reported; OS = overall survival.

Table S10: CDK4/6i Clinical Studies: Treatment Patterns

Reference	Patient Population	Patient (N)	Treatment Sequence	Number of Patients Receiving Sequence (%)	Median OS (months)	Median PFS (months)
Basile 2021 [36]	HR+/HER2- luminal mBC; received first and second lines	717	ET + CDK4/6i -> ET	19 (2.65%)	Not reached	NR
			ET + CDK4/6i -> CT	29 (4.04%)	20.35	NR
			ET -> ET + CDK4/6i	40 (5.58%)	61.38	NR
			ET -> ET or CT	254 (35.43%)	24.49	NR
			CT -> ET or CT	194 (27.06%)	23.57	NR
			No therapy	51 (7.11%)	N/A	N/A
			Missing	130 (18.13%)	N/A	N/A
Goldschmidt 2018 [35]	HR+/HER2- mBC; postmenopausal female;	147	CDK4/6i + AI -> EVE + AI	13 (8.8%)	NR	NR
			CDK4/6i + AI -> CT	13 (8.8%)		

Reference	Patient Population	Patient (N)	Treatment Sequence	Number of Patients Receiving Sequence (%)	Median OS (months)	Median PFS (months)
	at least two lines of therapy		CDK4/6i + AI -> Fulvestrant	8 (5.4%)		
			CDK4/6i + fulvestrant -> EVE + AI	4 (2.7%)		
			AI -> CDK4/6i + fulvestrant	20 (13.6%)		
			AI -> Fulvestrant	7 (4.8%)		
			AI -> CDK4/6i + AI	5 (3.4%)		
			CT -> CDK4/6i + AI	15 (10.3%)		
			CT -> CT	9 (6.3%)		
			CT -> CDK4/6i + fulvestrant	6 (4.2%)		
			CT -> fulvestrant	3 (2.0%)		
			CT -> AI	3 (2.0%)		
			Fulvestrant -> CDK4/6i + AI	4 (2.7%)		
			EVE + AI -> CDK4/6i + fulvestrant	5 (3.4%)		
			Fulvestrant -> CT	5 (3.4%)		
			NR	27 (18.4%)		
Jeong 2021 [37]	HR+/HER2- mBC; treated with both CDK4/6i-based and everolimus-based regimens	88	CDK4/6i -> EVE + EXE	51 (58%[a])	46.8	24.8
			EVE + EXE -> CDK4/6i	37 (42%[a])	38.9	21.8

[a] Percentage was calculated based on reported sample size.
Abbreviations: AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CT = chemotherapy; ET = endocrine therapy; EVE = everolimus; EXE = exemestane; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; mBC = metastatic breast cancer; N/A = not applicable; NR = not reported.

Table S11: CDK4/6i Clinical Studies: Prognostic Factors Associated with Reported Outcomes

Reference	Patient Population	Patient (N)	CDK4/6i Regimen	Outcome	Associated Prognostic Factor
Agrawal, 2021 [63]	HR+/HER2- mBC; received prior palbociclib	188	Palbociclib + AI or fulvestrant	3-year PFS rate	Line of HT
					Disease stage at presentation
					Prior chemotherapy before Palbociclib in the neoadjuvant/adjuvant setting
Basile, 2021 [36]		717	CT, ET alone, ET + CDK4/6i	PFS	ET naive
				PFS	De novo metastatic disease

Reference	Patient Population	Patient (N)	CDK4/6i Regimen	Outcome	Associated Prognostic Factor
	HR+/HER2- luminal mBC; received first and second lines			PFS, OS	Metastatic sites: Bone only vs. no visceral vs. visceral
				PFS, OS	Number of metastatic sites and lesions
				PFS, OS	ECOG PS
				PFS, OS	First-line therapy choice (ET + CDK4/6i vs. ET alone vs. CT)
				OS	Treatment strategy (presented in Table S10)
				OS	Ki-67 on primary tumor (<14% vs. ≥ 14%)
Battisti, 2019 [86]	HR+/HER2- aBC; commenced palbociclib within program between 2015-Sep 2017	118	Palbociclib	Median PFS, 6-month PFS rate, median OS, 18-month OS rate	Metastatic sites: Bone only vs. non-bone only
				Median PFS, OS, 18-month OS rate	Metastatic sites: Visceral only vs. non-visceral only
				Median OS, 18-month OS rate	Prior lines of CT
Kessler, 2020 [89]	mBC or unresectable aBC	88	CDK4/6i	PFS, OS	Prior lines of CT for mBC
Liu, 2020 [64]	HR+/HER2- mBC; female	130	Palbociclib	Tumor response	Number of metastatic sites
				Tumor response	Prior CT for mBC (yes vs. no)
				Tumor response	Sensitivity to prior ET
				Tumor response	Line of palbociclib therapy
				DCR	ET choice to palbociclib
Norman, 2021 [114]	HR+/HER2- aBC; female	247	CDK4/6i with or without bone radiation	Absolute neutrophil count prior to palbociclib	With or without bone radiation prior to CDK4/6i
				Absolute lymphocyte count prior to palbociclib and during cycle 1	With or without bone radiation prior to CDK4/6i
				Lymphopenia grade	With or without bone radiation prior to CDK4/6i
				Platelets prior to palbociclib	With or without bone radiation prior to CDK4/6i
Palumbo, 2021 [69]	HR+/HER2- mBC; pre- and postmenopausal women	182	Palbociclib + letrozole	PFS	Disease-free interval from adjuvant treatment (≤ 24 months vs. > 24 months)
				PFS, OS	Visceral involvement (yes vs. no)
				PFS, OS	Line of palbociclib therapy
Pizzuti, 2019 [115]	HR+/HER2- aBC/mBC	423	Palbociclib	1-year PFS rate, 1-year OS rate	Line of palbociclib therapy
				1-year PFS rate	Visceral involvement (yes vs. no)

Reference	Patient Population	Patient (N)	CDK4/6i Regimen	Outcome	Associated Prognostic Factor
				1-year PFS rate, 1-year OS rate	EVE pretreatment (yes vs. no)
Princic, 2019 [38]	HR+/HER2- mBC; postmenopausal female; after progression on a CDK4/6i-based treatment line	525	Mixed treatment (EVE, CDK4/6i, ET alone, or CT)	Subsequent systemic therapy type following a CDK4/6i-based line	Age
					Recurrent and with ET prior to metastasis diagnosis vs. de novo
					Metastatic sites: Bone only vs. visceral
					Prior CDK4/6i duration (> 6 vs. ≤ 6 months)
					Prior CDK4/6i treatment partner (AI vs. fulvestrant)
					Baseline BC-related costs
					Prior CT (yes vs. no)
Rath, 2021 [65]	ER and/or PR+/HER2- mBC	101	CDK4/6i	PFS, OS	ECOG PS at CDK4/6i initiation
				PFS, OS	Dose reduction type
				PFS, OS	CDK4/6i partner drug choice
				PFS, OS	Number of prior line of therapy
				PFS, OS	Previous lines of HT
				PFS	Previous lines of CT
				PFS	Metastatic sites: Bone only vs. visceral
				PFS, OS	Prior CT (yes vs. no)
Wander, 2021 [42]	HR+ mBC; received prior palbociclib	87	Abemaciclib +/- antiestrogen agents	PFS	Sequence of CDK4/6i (palbociclib followed by abemaciclib)
Zhang, 2021 [66]	Women with HR+/HER2- aBC	151	Palbociclib + ET	PFS	ECOG PS
					Disease-free survival (≤ 24 months vs. > 24 months)
					Line of palbociclib therapy
					Sensitivity to prior ET
					Initial palbociclib dose (125 mg vs. 100 mg)
Gharib, 2022 [76]	Women with previously treated or untreated HR+/HER2- BC	60	Palbociclib + Letrozole	Response to Palbociclib + Letrozole	Age
					Liver metastases
					Response at initial evaluation
					Best response
Li, 2021 [80]	HR+/HER2- aBC who received at least one cycle of palbociclib	54	Palbociclib + ET	Palbociclib sensitivity	Ki67 in metastatic tumours
					Progesterone in metastatic tumours
		1210		rwPFS	Continuation of CDK4/6i

Reference	Patient Population	Patient (N)	CDK4/6i Regimen	Outcome	Associated Prognostic Factor
Martin, 2022b [87]	HR+/HER2- mBC who received CDK4/6i in first line		CT, ET, everolimus, alpelisib, PARPi, clinical trial, CDK4/6i	rwOS	Continuation of CDK4/6i
					Subsequent Everolimus
Sampedro-Gimeno, 2021 [82]	Patients with mBC or aBC previously treated with Palbociclib + ET	73	Palbociclib + ET	PFS	Performance status
Whitaker, 2022 [40]	HR+/HER2- mBC	2,408	CDK4/6i	OS	CDK4/6i in 1L
Yildirim, 2022 [84]	Men with HR+/HER2- mBC treated with any CDK4/6i	25	CDK4/6i + GnRH + fulvestrant/AI	PFS	Line of treatment
					Presence of liver metastases
Zhong, 2022 [39]	HR+HER2- aBC	64	Palbociclib + ET	Survival benefit	No prior chemotherapy
					1 or less lines of prior ET
					No primary resistance to ET
					Fewer visceral metastases sites
					No liver metastasis
					Received Palbociclib 1L or 2L
					Ki67 level (independent)
					Molecular typing (independent)
					Sensitivity to ET (independent)
					Number of visceral metastases (independent)
					Line of Palbociclib + ET (independent)
Zhou, 2022 [96]	HR+/HER2- breast cancer patients treated with tucidinostat and progression on prior CDK4/6i	44	Tucidinostat post-CDK4/6i	Benefit from Tucidinostat + ET	1 metastatic site
					Sequential tucidinostat after CDK4/6i progression

Abbreviations: AI = aromatase inhibitor; BC = breast cancer; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CT = chemotherapy; DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ET = endocrine therapy; EVE = everolimus; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; HT = hormone therapy; mBC = metastatic breast cancer; mOS = median overall survival; mPFS = median progression-free survival; OS = overall survival; PFS = progression-free survival.

Table S12: Post-CDK4/6i Clinical Studies: Patient Population and Treatment Characteristics

Reference	Study Design	Patient Population	Patient (N)	Subsequent LoT	Subsequent Therapy Composition
Bardia, 2021a [93]	Phase I clinical trial	ER+/HER2- aBC or mBC	26	2L+	Elacestrant (ET)
Bardia, 2021b [41]	Phase I/II clinical trial (TRINITI-1)	HR+/HER2- aBC/mBC	96	2L+	EXE + Ribociclib + EVE
Basile, 2021 [36]	Retrospective observational study	HR+/HER2- mBC	29	2L	CT
			19	2L	ET
Boer, 2021 [61]	Retrospective observational study	aBC	962	2L+	CT, ET
Brufsky, 2019 [70]	Retrospective observational study	HR+/HER2- aBC/mBC	126	2L+	CT, ET, CT + ET
Cook, 2021 [94]	Retrospective observational study	HR+ mBC	17	2L+	EVE + EXE
Dhakal, 2020 [95]	Retrospective observational study	HR+/HER2- mBC	41	2L+	EVE
Dos Anjos, 2019 [46]	Retrospective observational study	ER+/HER2- mBC	135	3L+	ET, CDK4/6i + ET
Dudek, 2020 [55]	Phase I clinical trial	ER+ mBC	15	3L+	TTC-352 (ET)
Eziokwu, 2019 [45]	Retrospective observational study	HR+/HER2- mBC	30	2L+	CDK4/6i + ET
Fountzilas, 2020 [47]	Retrospective/prospective observational study	HR+/HER2- aBC/mBC	149	2L	CT, ET, CDK4/6i + ET
Giridhar, 2019 [58]	Retrospective observational study	ER+ mBC	37	2L	CT, ET, EVE + EXE
			24	3L	CT, ET, EVE + EXE
Jeong, 2021 [37]	Retrospective observational study	HR+/HER2- mBC	51	2L+	EVE + EXE
Li, 2021 [99]	Retrospective observational study	HR+/HER2- mBC	200	2L+	CT, ET
Liu, 2020 [64]	Retrospective observational study	HR+/HER2- mBC	37	2L+	CT
			19	2L+	ET
Masuda, 2021 [49]	Phase III clinical trial (PALOMA-2)	ER+/HER2- aBC	46	2L-3L	CT, ET, investigational drug
	Phase III clinical trial (PALOMA-3)	HR+/HER2- aBC	35	2L-3L	CT, ET, investigational drug
Mougalian, 2019 [54]	Retrospective observational study	HR+/HER2- mBC	121	2L	Eribulin (CT)
			111	3L	Eribulin (CT)
			28	≥4L	Eribulin (CT)

Reference	Study Design	Patient Population	Patient (N)	Subsequent LoT	Subsequent Therapy Composition
Petracci, 2020 [48]	Prospective observational study (RENATA)	HR+/HER2- aBC	50	2L+	CT, ET, palliative care, investigational drug
Princic, 2019 [38]	Retrospective observational study	HR+/HER2- mBC	208	2L	CT, ET, CDK4/6i-based, EVE-based
			317	3L-5L	CT, ET, CDK4/6i-based, EVE-based
Rath, 2021 [65]	Retrospective observational study	HR+/HER2- mBC	77	2L+	CT, ET, CT + ET, best supportive care
Rossi, 2019 [59]	Phase II clinical trial (TREnd)	HR+/HER2- mBC	105	3L+	CT, ET, targeted therapy
Rozenblit, 2021 [100]	Retrospective observational study	HR+/HER2- mBC	273	2L	EVE + EXE
			245	3L	EVE + EXE
Tamragouri, 2019 [44]	Retrospective observational study	HR+/HER2- mBC	21	2L+	Abemaciclib
Wander, 2019 [43]	Retrospective observational study	HR+/HER2- mBC	58	2L+	Abemaciclib
Wander, 2021 [42]	Retrospective observational study	HR+/HER2- mBC	87	2L+	Abemaciclib
Xi, 2019 [51]	Retrospective observational study	HR+/HER2- mBC	7	2L	CT
			14	3L	CT
			49	4L+	CT
			7	2L	ET, ET + targeted agents
			9	3L	ET, ET + targeted agents
			16	4L+	ET, ET + targeted agents
Bidard, 2022 [52]	Phase III Clinical Trial (EMERALD)	ER+/HER2- aBC	239	2L/3L	Elacestrant (ET)
			238	2L/3L	Standard of Care (ET)
Garcia-Saenz, 2022 [111]	Phase II Clinical Trial	ER+/HER2- aBC/mBC	16	2L+	Fulvestrant + Sapanisertib 30mg
			16	2L+	Fulvestrant + Sapanisertib 4mg
Gousis, 2022 [77]	Retrospective observational study	ER+/HER2- mBC	22	2L	CT
			12	2L	ET
Hayama, 2022 [57]	Retrospective observational study	HR+/HER2- aBC/mBC	34	2L-5L+	Everolimus + Exemestane
			20	2L-5L+	ET
			32	2L-5L+	CT
Kitano, 2022 [53]	Retrospective observational study	HR+/HER2- mBC	13	NR	Everolimus
Lim, 2022 [97]	Phase Ib/II Clinical Trial	HR+/HER2-	25	NR	Letrozole + Lenvatinib

Reference	Study Design	Patient Population	Patient (N)	Subsequent LoT	Subsequent Therapy Composition
Marschner, 2022 [81]	Prospective Registry	HR+/HER2- aBC	113	2L	CT, ET, CDK4/6i, PARPi
Martin, 2022b [87]	Retrospective observational study	HR+/HER2- mBC	23	2L	AI-based therapy
			302	2L	CDK4/6i-based therapy
			249	2L	Chemotherapy
			84	2L	Fulvestrant-based therapy
			99	2L	mTORi
			82	2L	Other (targeted, clinical trial, etc.)
Mo, 2022b [98]	Retrospective observational study	HR+/HER2- invasive BC	79	2L-5L+	Everolimus + Exemestane
ClinicalTrials.gov [123]	Retrospective observational study	HR+/HER2- aBC/mBC	150	2L+	CDK4/6i + Fulvestrant or ET
ClinicalTrials.gov [122]	Retrospective observational study	HR+/HER2- aBC/mBC	847	2L+	Mixed treatment
Parola, 2022 [128]	Retrospective observational study	HR+/HER2- locally advanced BC	59	1L+	ET
Seki, 2022 [56]	Retrospective observational study	ER+/HER2- mBC	37	2L+	CT
Zhong, 2022 [39]	Retrospective observational study	HR/HER2- aBC	10	2L-3L+	CT
			4	2L-3L+	ET
Zhou, 2022 [96]	Retrospective observational study	HR+/HER2- mBC	44	2L or 3L	Tucidinostat
				4L+	Tucidinostat

Abbreviations: #L = # of lines of therapy; aBC = advanced breast cancer; AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CT = chemotherapy; ET = endocrine therapy; EVE = evrolimus; EXE = exemestane; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; LOT = line of therapy; mBC = metastatic breast cancer; N = sample size; N/A = not applicable; NR = not reported; OS = overall survival.

Online Resource 5: Ongoing Clinical Studies of Post-CDK4/6i Treatments

Table S13: Ongoing Clinical Studies of Post-CDK4/6i Treatments

Study Name	NCT #	Country	Study Design/ Phase	Patient Population	Interventions	Comparator
Phase I – I/II						
N/A	NCT04247126	US	Single-arm Open-label, Phase I	HR+/HER2- aBC/mBC with progression on CDK4/6i + ET	SY-5609 + fulvestrant	N/A
N/A	NCT04134884	US	Single-arm Open-label, Phase I	HR+/HER2- TNBC/mBC with progression on CDK4/6i (subgroup of trial)	ASTX727 + talazoparib	N/A
TAKTIC	NCT03959891	US	Non-randomized Open-label, Phase I	HR+/HER2- aBC/mBC with progression on CDK4/6i + ET	Ipatasertib + fulvestrant Ipatasertib + letrozole Ipatasertib + palbociclib + fulvestrant	N/A
ASPIRE	NCT03854903	US	Single-arm Open-label, Phase I	HR+/HER2- aBC/mBC with progression on CDK4/6i + AI	Palbociclib + bosutinib + fulvestrant	N/A
N/A	NCT04606446	US, Japan	Non-randomized Open-label, Phase I	ER+/HER2- aBC/mBC with progression on CDK4/6i + ET	PF-07248144 PF-07248144 + fulvestrant PF-07248144 + letrozole + palbociclib	N/A
N/A	NCT02779751	Global	Non-randomized Open-label, Phase I	HR+/HER2- aBC/mBC	Pembrolizumab + abemaciclib Pembrolizumab + abemaciclib + anastrazole	N/A
N/A	NCT03519178	Global	Single-arm Open-label, Phase I/II	HR+/HER2- aBC/mBC with progression on CDK4/6i + ET (subgroup of trial)	PF-06873600 + ET	N/A
N/A	NCT03363893	US, UK	Randomized Open-label, Phase I/II	HR+/HER2- aBC/mBC with progression on CDK4/6i + AI (subgroup of trial)	CT7001 + fulvestrant	Placebo
MORPHEUS HR + BC	NCT03280563	US, South Korea, Israel	Randomized Open-label, Phase Ib/II	HR+/HER2- mBC	Atezolizumab + entinostat Atezolizumab + fulvestrant	Fulvestrant

Study Name	NCT #	Country	Study Design/ Phase	Patient Population	Interventions	Comparator
					Atezolizumab + ipatasertib	
					Atezolizumab + ipatasertib + fulvestrant	
					Atezolizumab + bevacizumab + ET	
					Atezolizumab + abemaciclib + fulvestrant	
N/A	NCT05181033	Singapore	Phase Ib/II trial	ER+/HER2- mBC who progressed on 1L CDK4/6i + ET	Lenvatinib+Letrozole	Fulvestrant
N/A	NCT05586841	China	Phase Ib trial	HR+HER2- aBC after failure of CDK4/6i	Dalpiciclib + Chidamide	N/A
N/A	NCT05251714	USA	Non-randomized dose confirming trial	ER+ HER2- advanced BC after disease progression on prior CDK4/6i + ET	CFI-402257	N/A
Phase II						
PACE	NCT03147287	US	Randomized Open-Label, Phase II	HR+/HER2- mBC with progression on CDK4/6i + ET	Palbociclib + fulvestrant	Fulvestrant
					Palbociclib + fulvestrant + avelumab	
BYLieve	NCT03056755	Global	Non-randomized Open-label, Phase II	HR+/HER2- aBC	Alpelisib + fulvestrant	N/A
					Alpelisib + letrozole	
N/A	NCT04318223	Italy	Single-arm Open-label, Phase II	HR+/HER2- aBC/mBC with progression on CDK4/6i + AI/tamoxifen +/- LHRHa	Palbociclib + fulvestrant	N/A
SMILE	NCT04738292	US	Single-arm Open-label, Phase II	HR+/HER2- aBC/mBC with progression on CDK4/6i + AI	Onapristone + fulvestrant	N/A
TATEN	NCT04251169	Spain	Single-arm Open-label, Phase II	HR+/HER2- aBC/mBC with progression on CDK4/6i	Pembrolizumab + paclitaxel	N/A
MAINTAIN	NCT02632045	US	Randomized Double-blind, Phase II	HR+/HER2- mBC with progression on CDK4/6i + AI	Ribociclib + fulvestrant	Placebo + fulvestrant
N/A	NCT04553133	US	Single-arm Open-label, Phase II	HR+/HER2- aBC/mBC with progression on CDK4/6i + ET (subgroup of trial)	PF-07104091 + palbociclib + fulvestrant	N/A
N/A	NCT02738866	US	Single-arm Open-label, Phase II	HR+/HER2- aBC/mBC with progression on palbociclib + AI	Palbociclib + fulvestrant	N/A

Study Name	NCT #	Country	Study Design/ Phase	Patient Population	Interventions	Comparator
CAPTURE	ACTRN12619001117101	Australia, New Zealand	Randomized Open-label, Phase II	ER+/HER2- aBC/mBC with progression on CDK4/6i + AI	Alpelisib + fulvestrant	Capecitabine
N/A	NCT05411380	China	Phase II Single-arm	HR+/HER2- post-menopausal mBC after failure on CDK4/6i	Tucidinostat	N/A
N/A	NCT05536128	Korea	Phase II Single-arm	HR+/HER2- mBC or inoperable BC with progression after CDK4/6i or ET	Fulvestrant + Olaparib	N/A
N/A	NCT05079360	USA	Phase II Single-arm	ER+ HER2- MBC after disease progression on CDK4/6i + NSAI + Fulvestrant	Sabizabulin	Active Control
N/A	NCT05594095	China	Phase II Randomized trial	Patients with HR+ HER2- aBC who have previously used CDK4/6i	Mixed treatment post-CDK4/6i	N/A
N/A	NCT05159778	USA	Phase II Single-arm	Patients with ER/PR+/ HER2- mBC who have progressed through prior hormone therapy with at least one CDK4/6i, and a maximum of 2 subsequent chemotherapy treatments	Imprime PGG + Pembrolizumab	N/A
SEQUEL-BREAST	NCT05392608	Netherlands	Phase II Single-arm	HR+ HER2- aBC with PIK3CA mutated tumors, with progressive disease on fulvestrant and previous treatment with CDK4/6i in 1L or 2L	Alpelisib	N/A
Phase III						
SOLAR-1	NCT02437318	Global	Randomized Double-blind, Phase III	HR+/HER2- aBC with progression on AI (subgroup with prior progression on CDK4/6i)	Alpelisib + fulvestrant	Placebo + fulvestrant
EMERALD	NCT03778931	Global	Randomized Open-label, Phase III	ER+/HER2- aBC/mBC with progression on CDK4/6i + ET/AI	Elacestrant	Standard of care: fulvestrant, anastrozole, letrozole, or exemestane
FINER	NCT04650581	Canada	Randomized Double-blind, Phase III	ER+/HER2- aBC with progression on CDK4/6i + AI	Ipatasertib + fulvestrant	Placebo + fulvestrant

Study Name	NCT #	Country	Study Design/ Phase	Patient Population	Interventions	Comparator
TROPiCS-02	NCT03901339	Global	Randomized Open-label, Phase III	HR+/HER2- mBC with progression on CDK4/6i	Sacituzumab govitecan	Treatment of physician's choice: eribulin, capecitabine, gemcitabine, or vinorelbine
SONIA	NCT03425838	Netherlands	Randomized Open-label, Phase III	HR+/HER2- aBC	1L CDK4/6i + AI (letrozole/anastrozole) -> 2L Fulvestrant	1L AI letrozole/ anastrozole) -> CDK4/6i + fulvestrant
evERA	NCT05306340	USA	Randomized Open-label, Phase III	Patients with ER+/HER2- local aBC or mBC who have had previous treatment with CDK4/6is and ET	Giredestrant + Everolimus	Exemestane + Everolimus
postMONARCH	NCT05169567	Global	Randomized, double-blind, placebo-controlled Phase III	Patients with HR+/HER2- BC that progressed or recurred after previous CDK4/6i + ET	Abemaciclib + Fulvestrant	Placebo + Fulvestrant
VIKTORIA-1	NCT05501886	Global	Randomized Open-label, Phase III	HR+ HER2- aBC previously treated with CDK4/6i + NSAI	Gedatolisib + Fulvestrant + Palbociclib	Gedatolisib + Fulvestrant
Observational						
PROSPERITY	NCT04943497	Russia	Prospective observational	HR+/HER2- aBC/mBC and initiated treatment with ribociclib, alpelisib, ET or combination therapy	Non-interventional	N/A
Treasure	NCT04916509	Qatar	Retrospective observational	HR+/HER2- aBC/mBC and initiated treatment with palbociclib	Non-interventional	N/A
PRECIOUS	NCT04937660	Africa, Middle East	Prospective observational	HR+/HER2- aBC/mBC	Non-interventional	N/A
N/A	NCT04460911	US	Retrospective observational	HR+/HER2- mBC and receiving palbociclib + fulvestrant or fulvestrant monotherapy	Non-interventional	N/A
SIRI	NCT04654208	Sweden	Retrospective observational	HR+/HER2- mBC and at least one filled prescription of palbociclib in the Swedish Prescribed Drug Register	Non-interventional	N/A
HERMIONE-13	NCT05173103	Italy	Retrospective observational	HR+/HER2- aBC treated in second line after failure of CDK4/6i + AI/Fulvestrant	Non-interventional	N/A

Study Name	NCT #	Country	Study Design/ Phase	Patient Population	Interventions	Comparator
N/A	NCT05276713	China	Retrospective observational	HR+ mBC previously treated with CDK4/6i	Non-interventional	N/A
N/A	NCT05153187	Japan	Retrospective observational	Japanese patients with HR+/HER2- BC initiating palbociclib	Non-interventional	N/A
N/A	NCT05505175	Brazil	Retrospective observational	Adult female patients with HR+/HER2 non-metastatic breast cancer who progressed to locally aBC/mBC receiving palbociclib combination regimens	Non-interventional	N/A
N/A	NCT05452798	Denmark	Retrospective observational	Patients with HR+/HER2- locally advanced or metastatic breast cancer treated with palbociclib	Non-interventional	N/A
N/A	NCT05399329	Japan	Retrospective observational	Japanese patients with HR+/HER2- aBC who have received palbociclib + ET in 1L or 2L	Non-interventional	N/A
N/A	NCT05132101	South Korea	Retrospective observational	BC patients who were prescribed with palbociclib in combination with AI for at least 1 cycle	Non-interventional	N/A
EUCHARIS	NCT05043506	Europe	Retrospective observational	Patients with HR+/HER2- aBC who initiated 1L treatment with palbociclib + AI or AI monotherapy	Non-interventional	N/A

Abbreviations: aBC = advanced breast cancer; AI = aromatase inhibitor; BC = breast cancer; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; ER = estrogen receptor; ET = endocrine therapy; EU = Europe; EVE = everolimus; EXE = exemestane; FDG-PET = fluorodeoxyglucose positron emission tomography; FES-PET = fluoroestradiol positron emission tomography; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; mBC = metastatic breast cancer; N/A = not applicable; RCT = randomized controlled trial; UK = United Kingdom; US = United States.