PALBOCICLIB IN HR-POSITIVE, HER2-NEGATIVE ADVANCED/METASTATIC BREAST CANCER: A SYSTEMATIC SCOPING REVIEW OF REAL-WORLD EVIDENCE FROM COUNTRIES OUTSIDE OF WESTERN REGIONS AND UNDERREPRESENTED IN CLINICAL TRIALS

Supplementary Material

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Supplementary Methods

PubMed search terms

("Treatment Outcome"[MH] OR "Evidence-Based Medicine"[MH] OR "Retrospective Studies"[MH] OR "Time Factors"[MH] OR "Case-Control Studies"[MH] OR "Observational Studies as Topic"[MH] OR "Cohort Studies"[MH] OR "Longitudinal Studies"[MH] OR "Cross-Sectional Studies"[MH] OR "Product Surveillance, Postmarketing"[MH] OR "naturalistic inquiry"[All Fields] OR "pragmatic clinical trial"[All Fields] OR "naturalistic study"[All Fields] OR "registry study"[All Fields] OR "real*world"[All Fields] OR "RWD"[All Fields] OR "RWE"[All Fields] OR "real*life"[All Fields] OR "real*patient"[All Fields] OR "real*practice"[All Fields] OR "real*clinical"[All Fields] OR "real*population"[All Fields] OR "actual*world"[All Fields] OR "actual*life"[All Fields] OR "actual*patient"[All Fields] OR "actual*practice"[All Fields] OR "actual*clinical"[All Fields] OR "actual*population"[All Fields]) AND ("palbociclib"[Supplementary Concept] OR "palbociclib"[All Fields] OR "ibrance"[All Fields] OR "iburance"[All Fields] OR "parvociclib"[All Fields] OR "PD*0332991"[All Fields] OR "PD*332991"[All Fields] OR "PD*991"[All Fields] OR "PF*332991"[All Fields] OR "TQB*3616"[All Fields]) AND ("Breast Neoplasms"[MH] OR "mammary carcinoma"[All Fields] OR "breast neoplasm"[All Fields] OR "breast tumor"[All Fields] OR "breast tumour"[All Fields] OR "breast carcinoma"[All Fields])

Embase search terms

('retrospective study'/exp OR 'evidence based medicine'/exp OR ‘case control study’/exp OR ‘observational study’/exp OR ‘cohort analysis’/exp OR ‘longitudinal study’/exp OR ‘cross-sectional study’/exp OR ‘postmarketing surveillance’/exp OR ‘naturalistic inquiry’/exp OR ‘pragmatic trial’/exp OR 'naturalistic study' OR ‘registry

study’ OR 'real world' OR 'real-world' OR 'RWD' OR 'RWE' OR 'real life' OR 'real patient' OR 'real practice' OR 'real clinical' OR 'real population' OR 'actual world' OR 'actual life' OR 'actual patient' OR 'actual practice' OR 'actual clinical' OR 'actual population') AND ('palbociclib’/syn OR ‘palbociclib’ OR ‘ibrance’ OR ‘iburance’ OR ‘parvociclib’ OR ‘PD*0332991’ OR ‘PD*332991’ OR ‘PD*991’ OR ‘PF*332991’ OR ‘TQB*3616’) AND (Breast cancer: 'breast cancer'/syn OR 'mammary carcinoma' OR 'breast neoplasm' OR 'breast tumor' OR 'breast carcinoma') [embase]/lim AND [english]/lim

Supplementary Table S1. Eligibility criteria.

PICO components	Inclusion criteria	Exclusion criteria
P - Population	Adult (men and women) patients diagnosed with HR-positive, HER2-negative advanced or metastatic breast cancer from Non-Western countries excluding China, Japan and Korea. Cross-country studies of underrepresented Non-Western countries with Western countries or China, Japan and Korea will be included.	Patients who are (i) not adults or (ii) not diagnosed with HR-positive, HER2-negative advanced/ metastatic breast cancer or (iii) are exclusively from North America (US and Canada), Europe, Australia, New Zealand, China, Japan and Korea.
I - Intervention	Patients treated with palbociclib, either in combination with an aromatase inhibitor as initial therapy or with fulvestrant in patients with disease progression following endocrine therapy.	Studies where palbociclib is used without an aromatase inhibitor or fulvestrant, or is not mentioned as one of the interventional CDK4/6 inhibitors.

C - Comparison	Comparisons of palbociclib against another treatment, placebo, or no treatment, or its descriptive studies. Studies detailing effects of palbociclib as part of the broader class effect of CDK4/6 inhibitors to be included.	No comparison or description of the effects of palbociclib, unless the effects of palbociclib are detailed as part of the broader class effect of CDK4/6 inhibitors.
O - Outcomes	Phase 4 studies (including PCTs) reporting on any of the real-world outcomes such as effectiveness (including patient-reported outcomes), safety/ tolerability, or quality of life.	Phase 1-3 studies, RCTs, study protocols, pre-clinical or in-vitro results, case studies/ series, review articles, opinion pieces, or commentaries.

CDK4/6, cyclin-dependent kinase 4/6; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PCT, pragmatic clinical trial; RCT, randomized clinical trial.

Supplementary Table S2. Characteristics of the publications included in the present analysis.

	Emerging Asia (n=14)	Latin America (n=14)	Middle East (n=5)	Russia (n=1)	Türkiye (n=12)	Overall (n=46)
Publication type, n (%)						
Congress abstract or poster	8 (57.1)	7 (50.0)	3 (60.0)	1 (100.0)	4 (33.3)	23 (50.0)
Full-text publication	6 (42.9)	6 (42.9)	2 (40.0)	–	8 (66.7)	22 (47.8)
Erratum	–	1 (7.1)	–	–	–	1 (2.2)
Publication date, n (%)						
2017	1 (7.1)	–	–	–	–	1 (2.2)
2018	1 (7.1)	1 (7.1)	–	–	–	2 (4.3)
2019	–	3 (21.4)	1 (20.0)	–	–	4 (8.7)
2020	1 (7.1)	4 (28.6)	1 (20.0)	–	1 (8.3)	7 (15.2)
2021	6 (42.9)	–	1 (20.0)	1 (100.0)	–	8 (17.4)
2022	4 (28.6)	4 (28.6)	1 (20.0)	–	5 (41.7)	14 (30.4)
2023	1 (7.1)	2 (14.3)	1 (20.0)	–	6 (50.0)	10 (21.7)

Supplementary Table S3. Publications reporting clinical outcomes by publication type.

	Congress abstracts or posters (n=23)	Full-text publications (n=22)	Errata (n=1)	Total (n=46)
Outcomes reported, n (%)				
Clinical	23 (100.0)	20 (90.9)	1 (100.0)	44 (95.7)
PRO	–	1 (4.5)	–	1 (2.2)
Clinical and PRO	–	1 (4.5)	–	1 (2.2)
Follow-up, n (%)				
Reported	7 (30.4)	13 (59.1)	–	20 (43.5)
Not reported	16 (69.6)	9 (40.9)	1 (100.0)	26 (56.5)
Any effectiveness outcome, n (%)				
Reported	23 (100.0)	21 (95.5)	1 (100.0)	45 (97.8)
Not reported	–	1 (4.5)	–	1 (2.2)
PFS, n (%)				
Reported	11 (47.8)	17 (77.3)	–	28 (60.9)
Not reported	12 (52.2)	5 (22.7)	1 (100.0)	18 (39.1)
OS, n (%)				

Reported	4 (17.4)	8 (36.4)	–	12 (26.1)
Not reported	19 (82.6)	14 (63.6)	1 (100.0)	34 (73.9)
Any safety outcome, n (%)				
Reported	14 (60.9)	18 (81.8)	–	32 (69.6)
Not reported	9 (39.1)	4 (18.2)	1 (100.0)	14 (30.4)
Incidence of dose modifications, n (%)				
Reported	8 (34.8)	13 (59.1)	–	21 (45.7)
Not reported	15 (65.2)	9 (40.9)	1 (100.0)	25 (54.3)
Incidence of treatment discontinuation, n (%)				
Reported	6 (26.1)	8 (36.4)	–	14 (30.4)
Not reported	17 (73.9)	14 (63.6)	1 (100.0)	32 (69.6)
Incidence of grade ≥3 neutropenia, n (%)				
Reported	7 (30.4)	9 (40.9)	–	16 (34.8)
Not reported	16 (69.6)	13 (59.1)	1 (100.0)	30 (65.2)

CDK4/6, cyclin-dependent kinase 4/6; NC, not calculated; PRO, patient-reported outcomes; SD, standard deviation.

Supplementary Table S4. Effectiveness outcomes reported with individual CDK4/6 inhibitors in conference abstracts and posters.

Reference	Region	Patient population	Treatment	Subgroup	Median PFS (95% CI), months	Median OS (95% CI), months	ORR, %
1st line							
Gad (2023) [1]	Middle East	Pre-menopausal women; post-menopausal women; men	CDK4/6i + ET	1st line (n=NS)	19.0	50.3	–
Gogia (2021) [2]	Emerging Asia	Pre-menopausal women; post-menopausal women	CDK4/6i + ET	Overall (n=120)	18.0 (4.0 to 36.0)[a]	–	77.5
Kahraman (2023b) [3]	Türkiye	Women, menopausal status NS; men	CDK4/6i + ET	Overall (n=448)	29.4 (16.3 to 42.6)	NR	–
			CDK4/6i + ET	HER2 IHC 0 (n=295)	27.7 (11.2 to 44.2)	–	–
			CDK4/6i + ET	HER2 IHC 1+ (n=117)	NR	–	–
			CDK4/6i + ET	HER2 IHC 2+ (n=36)	NR	–	–
Nasr (2019) [4], Nasr (2020) [5]	Middle East	NS	P + L	Overall (n=NS)	26.0 (2.6)	–	–
Nasr (2021) [6]	Middle East	Pre-menopausal women; post-menopausal women	P + AI	Overall (n=NS)	30.3 (2.3)	116.1[b] (7.2)	
Rauthan (2018) [7]	Emerging Asia	NS	P + L	With data (n=12)	–	–	41.7
Rauthan (2020) [8]	Emerging Asia	NS	P + ET	1st line (n=83)	NR	–	71.0
			P + ET	*De novo* metastatic	NR	–	–

				(n=46)			
			P + ET	Post-adjuvant relapse (n=37)	18.0	–	–
			P + ET	Bone metastases (n=38)	NR	–	–
			P + ET	Visceral metastases (n=45)	28.0	–	–
≥2nd line							
Artac (2022) [9]	Türkiye	NS	CDK4/6i + ET	BMI 18.5 to 24.9 kg/m^2 (n=NS)	9.3 (5.3–13.4)[c]	–	23.0
			CDK4/6i + ET	BMI 25 to 29.9 kg/m^2 (n=NS)	11.1 (9.7–12.6)[c]	–	43.3
			CDK4/6i + ET	BMI ≥30 kg/m^2 (n=NS)	NR	–	32.8
Gad (2023) [1]	Middle East	Pre-menopausal women; post-menopausal women; men	CDK4/6i + ET	2nd line (n=NS)	15.0 (NS)	51.6 (NS)	–
			CDK4/6i + ET	≥3rd line (n=NS)	5.0 (NS)	33.1 (NS)	–
Matiz (2022) [10]	Latin America	Pre-menopausal women; post-menopausal women	P + F	Overall (n=69)	NR	–	–
Rauthan (2020) [8]	Emerging Asia	NS	P + ET	2nd line (n=50)	14.0	–	52.0
			P + ET	Bone metastases (n=15)	14.0	–	–
			P + ET	Visceral metastases (n=35)	13.0	–	–

All lines or line NS							
Bao (2021) [11]	Emerging Asia	NS	CDK4/6i + ET	HER2-low (n=82)	8.9 (6.5 to 11.3)	–	–
			CDK4/6i + ET	HER2 IHC 0 (n=24)	18.8 (9.4 to 28.2)	–	–
Çağlayan (2022) [12]	Türkiye	NS	CDK4/6i + ET	BMI 18.5 to 24.9 kg/m^2 (n=42)	NR	–	–
			CDK4/6i + ET	BMI 25 to 29.9 kg/m^2 (n=65)	NR	–	–
			CDK4/6i + ET	BMI ≥30 kg/m^2 (n=72)	NR	–	–
Frolova (2021) [13]	Russia	NS	P + ET	Overall (n=105)	6.0 (1.0 to 28.0)[a]	–	–
Gad (2023) [1]	Middle East	Pre-menopausal women; post-menopausal women; men	CDK4/6i + ET	Overall (n=164)	14.2 (9.8 to 18.7)	51.6 (35.8 to 67.5)	42.0
Keskinkilic (2023b) [14]	Türkiye	NS	CDK4/6i + ET	Overall (n=149)	26.1[d] (22.0 to 30.2)	34.3[d] (31.4 to 37.2)	–
			CDK4/6i + ET	HR >50% (n=NS)	26.2[d] (NS)	34.6[d] (NS)	–
			CDK4/6i + ET	HR ≤50% (n=NS)	20.3[d] (NS)	24.9[d] (NS)	–
Lapuchesky (2022) [15]	Latin America	NS	CDK4/6i + ET	HER2-low (n=64)	19.0 (13.9 to 24.1)	–	–
			CDK4/6i + ET	HER2 IHC 0 (n=122)	15.6 (11.1 to 20.0)	–	–
Mainella (2019) [16]	Latin America	Pre-menopausal women; post-menopausal women	P + ET	Overall (n=48)	–	–	39.6
Mainella (2020)	Latin	Pre-menopausal women; post-	P + ET	Overall (n=54)	–	–	38.9

[17]	America	menopausal women					
Pavithran (2021) [18]	Emerging Asia	NS	CDK4/6i + ET	*PIK3CA* mutation (n=17)	18.0[e] (NS)	41.7[e] (NS)	0
			CDK4/6i + ET	*PIK3CA* wild type (n=19)	32.2[e] (NS)	45.0[e] (NS)	26.0
Vaid (2022) [19]	Emerging Asia	NS	P + ET	With data (n=100)	–	–	17.0

[a]The nature of the error estimate was not specified.

[b]9.67 years in the original. The OS reported in Nasr (2021) is notably higher that in other studies and may be an error. Caution is advised when interpreting this value.

[c]The nature of the central measure and error estimate was not specified.

[d]Mean.

[e]The nature of the central measure was not specified.

AI, aromatase inhibitor; BMI, body mass index; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ET, endocrine therapy; F, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; L, letrozole; NA, not applicable; NR, not reached; NS, not specified; OS, overall survival; PFS, progression-free survival; SD, standard deviation.

Supplementary Table S5. Safety outcomes in abstracts and posters.

Reference	Region	Treatment/subgroup	Incidence of AEs, %		Incidence of neutropenia, %			Incidence of infection, %	Change in treatment, %		
			Any-grade	Grade ≥3	Any grade	Grade ≥3	Febrile		Inter-ruption	Dose modifi-cation	Cessation
Çağlayan (2022) [12]	Türkiye	CDK4/6i + ET/ BMI 18.5 to 24.9 kg/m^2 (n=42)	–	42.9	–	–	–	–	–	–	–
		CDK4/6i + ET/ BMI 25 to 29.9 kg/m^2 (n=65)	–	30.8	–	–	–	–	–	–	–
		CDK4/6i + ET/ BMI ≥30 kg/m^2 (n=72)	–	30.6	–	–	–	–	–	–	–
Chiu (2017) [20]	Emerging Asia	P + ET (n=50)[a]	–	–	–	43.0	0	–	–	31.0	–
Frolova (2021) [13]	Russia	P + ET (n=105)	–	–	–	–	–	–	–	13.7	4.1
Gad (2023) [1]	Middle East	CDK4/6i + ET (n=164)	–	–	–	56.0	–	–	–	–	7.3
Gogia (2021) [2]	Emerging Asia	CDK4/6i + ET (n=120)	–	–	–	15.0	0	–	20.0	10.0	8.3

Huang (2023) [21]	Emerging Asia	P + ET (n=102)	–	–	>95.0	74.5	–	–	–	–	–
Mainella (2019) [16]	Latin America	P + ET (n=48)	–	–	52.0	31.3	0	–	48.0	12.5	4.2
Mainella (2020) [17]	Latin America	P + ET (n=54)	–	–	–	60.0	–	–	50.0	13.0	5.6
Matiz (2022) [10]	Latin America	P + F (n=69)	–	–	–	–	–	–	15.9	33.3	20.3
Rauthan (2018) [7]	Emerging Asia	P + ET (n=16)	–	–	81.2	15.4	0	–	37.5	12.5	–
Rauthan (2020) [8]	Emerging Asia	P + ET (n=133)	–	–	75.2	23.0	–	–	30.0	8.2	–
Rodriguez (2020) [22]	Latin America	CDK4/6i + ET (65)	67.7	21.5	63.0	–	–	–	–	26.2	–
Vaid (2022) [19]	Emerging Asia	P + ET (n=102)	39.22	–	12.7	–	–	–	–	–	–

[a]Patients who started palbociclib 125 mg/day.

A, abemaciclib; AE, adverse event; BMI, body mass index; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; F, fulvestrant; NS, not specified; P, palbociclib; R, ribociclib.

Supplementary Table S6. Studies included in the present analysis.

Study No.	Reference	Publication type	Cross-country collaborative study	Target countries	Target region	Non-target countries	Patient population	Palbociclib-specific	Therapy line	Study duration, years	Participating centres in target countries, n	Palbociclib, n	CDK4/6 inhibitors, n
1	Agrawal (2021) [23]	Full-text	No	India	Emerging Asia	NA	Pre-menopausal women; post-menopausal women	Yes	1L; ≥2L	3.2	2	188	NA
2	Al-Foheidi (2022) [24]	Full-text	No	Saudi Arabia	Middle East	NA	Pre-menopausal women; post-menopausal women	Yes	≥2L	4.9	2	97	NA
3	Artac (2022) [9]	Abstract/poster	No	Türkiye	Türkiye	NA	NS	No	≥2L	2.9	3	NS	115
4	Bao (2021) [11]	Abstract/poster	No	Hong Kong	Emerging Asia	NA	NS	No	1L; ≥2L	3.3	1	90	106
5	Bruno (2022) [25]	Full-text	No	Argentina	Latin America	NA	Pre-menopausal women; post-menopausal women	No	1L; ≥2L	4.7	1	188	217
6	Çağlayan (2022) [12]	Abstract/poster	No	Türkiye	Türkiye	NA	NS	No	NS	3.9	3	NS	179
7	Çağlayan (2023) [26]	Full-text	No	Türkiye	Türkiye	NA	NS	No	≥2L	3.9	3	50	86
8	Chiu (2017) [20]	Abstract/poster	No	Hong Kong	Emerging Asia	NA	Post-menopausal women	Yes	1L; ≥2L	NS	NS	54	NA
9	Darden (2019) [27]	Full-text	Yes	Argentina	Latin America	Canada, Denmark, Germany, Netherlands, USA	NS	Yes	NS	NS	NS	51	NA
10	Demir (2020) [28]	Full-text	No	Türkiye	Türkiye	NA	Pre-menopausal women; post-menopausal women	Yes	≥2L	4.2	NS	43	NA

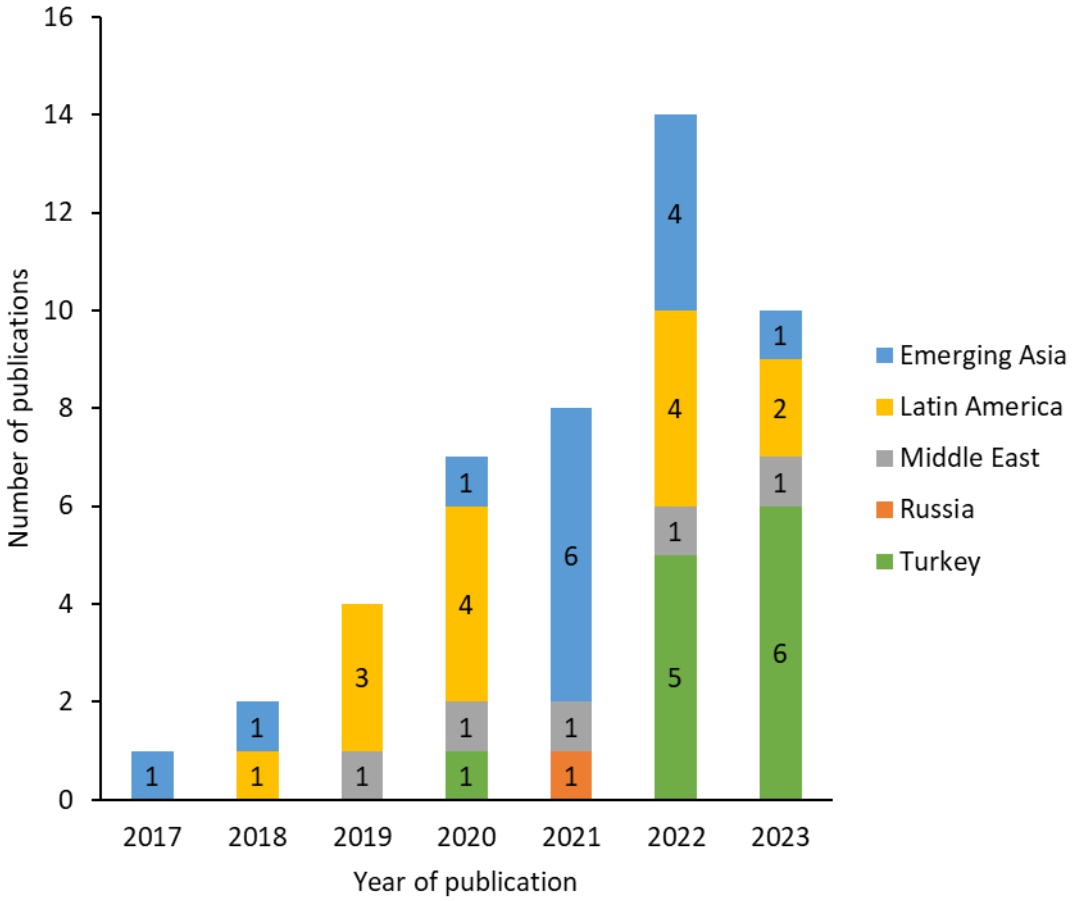
11	Dülgar (2022) [29]	Full-text	No	Türkiye	Türkiye	NA	Pre-menopausal women; post-menopausal women; men	No	1L; ≥2L	NS	3	44	80
12	Eser (2022) [30]	Full-text	No	Türkiye	Türkiye	NA	Pre-menopausal women; post-menopausal women	No	1L; ≥2L	NS	NS	105	217
13	Frolova (2021) [13]	Abstract/poster	No	Russia	Russia	NA	NS	Yes	1L; ≥2L	4.0	NS	105	NA
14	Gad (2023) [1]	Abstract/poster	No	Saudi Arabia	Middle East	NA	Pre-menopausal women; post-menopausal women; men	No	1L; ≥2L	4.2	1	NS	164
15	Ganguly (2022) [31]	Full-text	No	India	Emerging Asia	NA	Pre-menopausal women; post-menopausal women	No	1L; ≥2L	5.0	1	108	144
16	Gogia (2021) [2]	Abstract/poster	No	India	Emerging Asia	NA	Pre-menopausal women; post-menopausal women	No	1L	3.9	1	91	120
17	Huang (2023) [21]	Abstract/poster	No	Taiwan	Emerging Asia	NA	Pre-menopausal women; post-menopausal women	Yes	1L; ≥2L	NS	1	102	NA
18	Kahraman (2023) [32]	Full-text	No	Türkiye	Türkiye	NA	Pre-menopausal women; post-menopausal women; men	No	1L	4.4	46	272	600
19	Kahraman (2023) [3]	Abstract/poster	No	Türkiye	Türkiye	NA	Women, menopausal status NS; men	No	1L	6.0	NS	NS	448
20	Keskinkilic (2023) [33]	Full-text	No	Türkiye	Türkiye	NA	Pre-menopausal women; post-menopausal women; men	No	1L; ≥2L	2.4	1	58	106
21	Keskinkilic (2023) [14]	Abstract/poster	No	Türkiye	Türkiye	NA	NS	No	1L; ≥2L	2.9	1	NS	149
22	Lakkavalli (2021) [34]	Full-text	No	India	Emerging Asia	NA	NS	Yes	1L	1.9	1	26	NA
23	Lapuchesky (2022) [15]	Abstract/poster	No	Argentina	Latin America	NA	NS	No	1L; ≥2L	4.8	1	161	186
24	Loi (2022) [35]	Full-text	Yes	India	Emerging Asia	Australia	Post-menopausal women	Yes	1L; ≥2L	1.8	NS	100	NA

25	Low (2022) [36]	Full-text	No	Singapore	Emerging Asia	NA	Pre-menopausal women; post-menopausal women; Men	No	1L; ≥2L	6.0	5	435	456
26	Mainella (2020) [17]	Abstract/poster	No	Argentina	Latin America	NA	Pre-menopausal women; post-menopausal women	Yes	NS	4.2	NS	54	NA
27	Mainella (2019) [16]	Abstract/poster	No	Argentina	Latin America	NA	Pre-menopausal women; post-menopausal women	Yes	NS	3.3	NS	48	NA
28	Matiz (2022) [10]	Abstract/poster	No	Colombia	Latin America	NA	Pre-menopausal women; post-menopausal women	Yes	≥2L	1.5	11	69	NA
29	Nasr (2021) [6]	Abstract/poster	No	Lebanon	Middle East	NA	Pre-menopausal women; post-menopausal women	Yes	NS	3.4	NS	95	NA
30	Nasr (2019) [4] Nasr (2020) [5]	Abstract/poster Abstract/poster	No	Lebanon	Middle East	NA	NS	Yes	NS	17.0	NS	44	NA
31	Odabas (2023) [37]	Full-text	No	Türkiye	Türkiye	NA	Post-menopausal women	No	1L; ≥2L	1.9	NS	120	220
32	Pavithran (2021) [18]	Abstract/poster	No	India	Emerging Asia	NA	NS	No	NS	NS	NS	21	36
33	Petracci (2020) [38] Petracci (2020) [39]	Full-text Erratum	No	Argentina	Latin America	NA	Pre-menopausal women; post-menopausal women; Men	Yes	1L; ≥2L	3.8	2	128	NA
34	Queiroz (2023) [40]	Full-text	No	Brazil	Latin America	NA	NS	No	1L; ≥2L	5.4	3	79	142
35	Rath (2021) [41]	Full-text	No	India	Emerging Asia	NA	Pre-menopausal women; post-menopausal women	No	1L; ≥2L	4.5	1	91	101
36	Rauthan (2020) [8]	Abstract/poster	No	India	Emerging Asia	NA	NS	Yes	1L; ≥2L	2.8	5	133	NA
37	Rauthan (2018) [7]	Abstract/poster	No	India	Emerging Asia	NA	NS	Yes	1L	0.3	1	16	NA
38	Rodriguez (2020) [22]	Abstract/poster	No	Mexico	Latin America	NA	NS	No	1L; ≥2L	2.5	2	62	65

39	Samame (2023) [42]	Abstract/poster	Yes	Peru, Argentina	Latin America	Spain	Pre-menopausal women	Yes	1L	NS	3	45	NA
40	Vaid (2022) [19]	Abstract/poster	No	India	Emerging Asia	NA	NS	Yes	1L; ≥2L	4.0	1	102	NA
41	Mycock (2022) [43] Taylor-Stokes (2018) [44] Waller (2019) [45]	Full-text Abstract/poster Full-text	Yes	Argentina	Latin America	Belgium, Canada, France, Germany, Italy, Japan, Netherlands, Portugal, Spain, Switzerland, UK, USA		Yes	1L; ≥2L	1.9	NS	162	NA
42	Yıldırım (2022) [46]	Full-text	No	Türkiye	Türkiye	NA	Men	No	1L; ≥2L	4.0	14	16	25

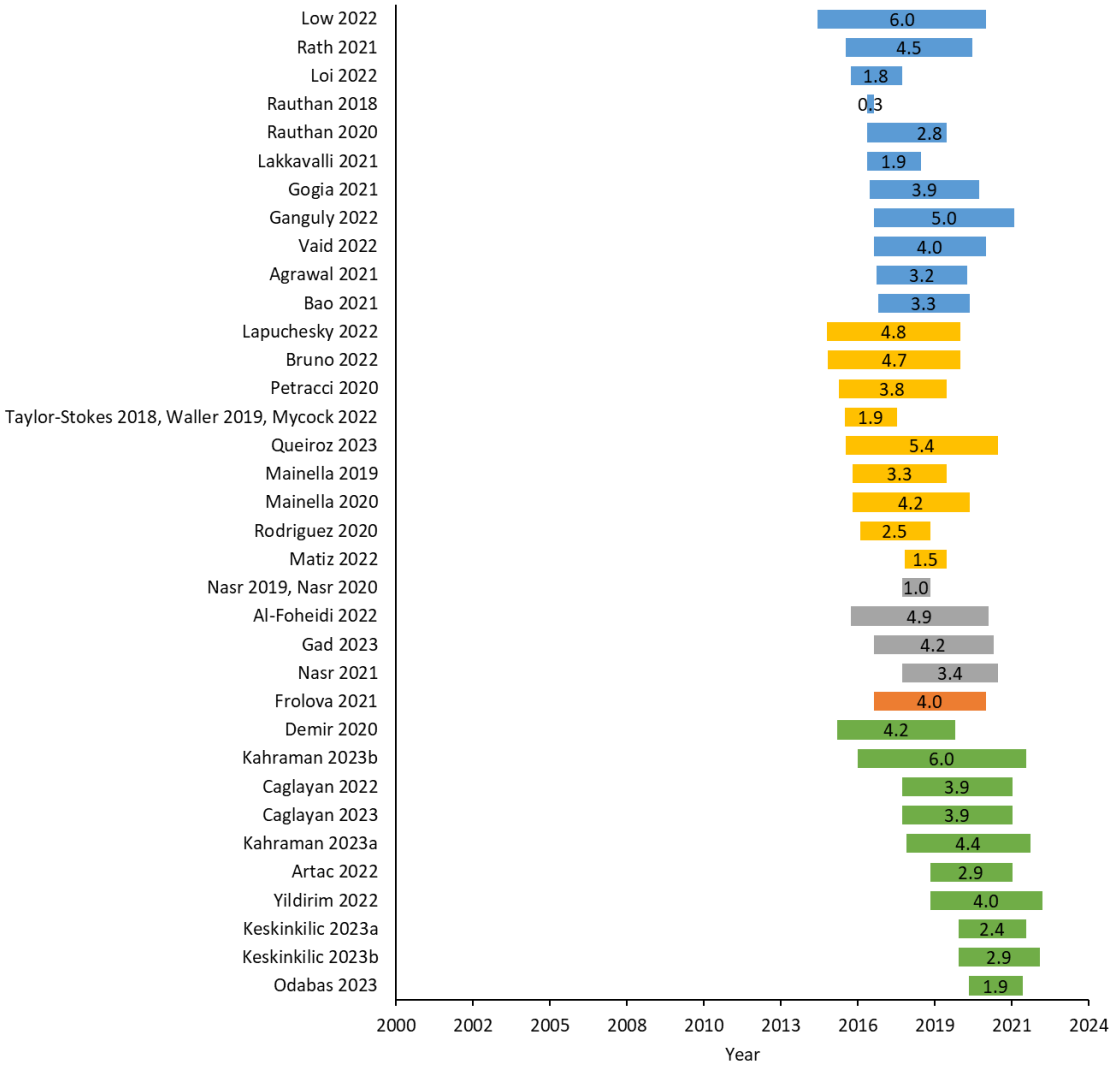
1L, first-line; ≥2L, second-line and beyond; NA, not applicable; NS, not specified.

Supplementary Figure S1. Publications included in the analysis by year (n=46).



This review included records published between 2017 and 2023. The number of publications increased in each full year. From 2017 to 2022, the annual growth rate in the number of records was 69.5%. Based on this rate, 23.7 records were expected to be published in 2023. As of August 2023, 10 records have been published. The largest proportion of publications from countries of Emerging Asia was released in 2021 (42.9%), while no publications from the Middle East or Türkiye date from that year. In addition, the only publication from Russia was released in 2021. The majority of publications from Türkiye were released in 2022 (41.7%) or 2023 (50.0%).

Supplementary Figure S2. Duration of studies in years (n=35).



The majority of studies for which duration information was available (n=35, 83.3%) were between 2.9 and 4.5 years long. The cumulative duration of the included studies was 123.1 years. Study duration was not reported for 7 studies (16.7%), including one cross-sectional study [27].

The stated duration of the shortest study was 0.3 years, however, it is possible that the authors intended this to be the period when patients were diagnosed or prescribed treatment, as they also provided the median duration of treatment, which was 11

months [7].

A study conducted in Lebanon and reported in two abstracts by Nasr and colleagues had the longest stated duration (from 2002 to 2018) [4, 5]. However, because the start of this study precedes the approval of palbociclib and because the overall quality of reporting in these two abstracts was poor, this duration was judged to be unrealistic, and instead, the duration of this study was equated to its reported follow-up duration of 1.0 year.

References

1. Gad AM, AlSayed A, AlShibani A, Twegieri T, Suleman K, Ajarim D. Clinical outcome and toxicity profile of Cyclindependent kinase 4/6 inhibitors in combination with hormonal treatment in management of metastatic breast cancer patients: A Middle-East Real World Experience. Cancer Research. 2023;83(5).

2. Gogia A, Arora S, Choudhary P, Kumar R, Thulkar S, Deo SVS, et al. Real-world Indian scenario of CDK4/6 inhibitors (palbociclib and ribociclib) with endocrine therapy in upfront hormone positive metastatic breast cancer. Journal of Clinical Oncology. 2021;39(15 SUPPL).

3. Kahraman S, Seyyar M, Sahin E, Cabuk D, Gumusay O, Basaran G, et al. Impact of HER2 expression levels on survival in patients with hormone receptor positive and HER2 negative advanced breast cancer and treated with ribociclib and palbociclib in combination with endocrine therapy: A real-life data, Turkish Oncology Group study. ESMO open. 2023b;8(1).

4. Nasr F, Ghoche A, Diab S, Nasr L. REAL-WORLD SURVIVAL DATA OF PALBOCICLIB IN ADVANCED AND METASTATIC BREAST CANCER: A MULTICENTER EXPERIENCE IN LEBANON. Breast. 2019;48:S53.

5. Nasr L, Ghoche A, Diab S, Nasr F. Real-world survival data of palbociclib in advanced and metastatic breast cancer: A multicenter experience in Lebanon. Journal of Clinical Oncology. 2020;38(15).

6. Nasr F, Diab S, Ghoche AA, Yehia I, Nasr L. PO61 PALBOCICLIB REAL WORLD DATA IN ADVANCED AND METASTATIC BREAST CANCER TREATED: A MULTICENTER EXPERIENCE IN LEBANON. Breast. 2021;59:S48.

7. Rauthan A, Patil P, Somashekhar SP, Zaveri S. Real-World single centre experience with Palbociclib as first line treatment in Indian patients with metastatic breast cancer. Journal of Clinical Oncology. 2018;36(15).

8. Rauthan A, Patil P, Somashekhar SP, Jacob LA, Lokanatha D, Kumar K, et al. Palbociclib in hormone positive metastatic breast cancer: A real world multicenter Indian experience. Journal of Clinical Oncology. 2020;38(15).

9. Artac M, Cağlayan D, Koçak MZ, Geredeli C, Tatli AM, Sezgin Goksu S, et al. The impact of body mass index (BMI) on the progression-free survival of CDK4/6 inhibitors in metastatic breast cancer patients (MBC). Annals of Oncology. 2022;33:S644-S5.

10. Matiz GA, Alarcon BA, Reyes Sanchez JM, Moran D, Bruges R, Lombana M, et al. CO107 Progression-Free Survival in Patients with Advanced or Metastatic, Hormone Receptor Positive, HER2-Negative Breast Cancer Treated with Palbociclib in Combination with Fulvestrant: A Real-World Study. Value in Health. 2022;25(7):S324.

11. Bao KKH, Sutanto L, Tse SSW, Man Cheung K, Chan JCH. The Association of ERBB2 -Low Expression with the Efficacy of Cyclin-Dependent Kinase 4/6 Inhibitor in Hormone Receptor-Positive, ERBB2 -Negative Metastatic Breast Cancer. JAMA network open. 2021;4(11).

12. Çağlayan D, Kocak MZ, Geredeli C, Tatli AM, Eryõlmaz MK, Göksu SS, et al. The effect of BMI on the outcomes of CDK 4/6 inhibitor therapy in HR-positive metastatic breast cancer patients. Journal of Clinical Oncology. 2022;40(16).

13. Frolova M, Karaseva V, Tjulandin S. PO59 REAL CLINICAL PRACTICE OF LUMINAL HER2-NEGATIVE METASTATIC BREAST CANCER TREATMENT PATTERNS WITH PALBOCICLIB IN COMBINATION WITH ENDOCRINE THERAPY IN RUSSIAN FEDERATION. Breast. 2021;59:S47-S8.

14. Keskinkilic M, Semiz HS, Yavuzsen T, Oztop I. The effect of hormone receptor positive percentage on treatment response and prognosis in HR+ HER2- metastatic breast cancer receiving CDK 4/6 inhibitor + endocrine treatment. ESMO open. 2023b;8(1).

15. Lapuchesky LS, Bortz M, Waisberg F, Enrico DH, Bruno LI, Ostinelli CA, et al. CDK4/6 inhibitors outcomes in patients with advanced breast cancer based on HER2- low expression. Journal of Clinical Oncology. 2022;40(16).

16. Mainella A, Vigo S, Marmissolle F, Price P, Sansano M, Luján ML, et al. Palbociclib in the treatment of metastatic breast cancer. institutional experience. International Journal of Gynecological Cancer. 2019;29:A624.

17. Mainella A, Marmissolle F, Vigo S, Price P, Sansano M, Lujan ML, et al. Palbociclib in the daily clinical use: Real experience in metastatic breast cancer in our institution. International Journal of Gynecological Cancer. 2020;30(SUPPL 3):A98-A9.

18. Pavithran K, Jayamohanan H, Jose WM, Soman S, Vijaykumar DK, Ariyannur PS. PI3K mutation is associated with reduced sensitivity to CDK4/6 inhibitors in metastatic breast cancer. Annals of Oncology. 2021;32:S471.

19. Vaid AK, Sharma D, Wadhwa J, Sharma N, Mishra S, Gautam D, et al. Efficacy and safety of palbociclib in treatment of HR-positive advanced breast cancer patients: A single center real-world experience. Journal of Clinical Oncology. 2022;40(16).

20. Chiu J, Leung R, Sze H, Teo P, Choi P, Lam TC, et al. Real world data on use of palbociclib in hormone-receptor (ER) positive HER2 negative metastatic breast cancer (MBC) among Asian patients. Annals of Oncology. 2017;28:x33-x4.

21. Huang KJ, Kuo TH, Chao TC, Liu CY, Tsai YF, Huang CC, et al. High Incidence of Palbociclib Related Neutropenia in Asian Patients Associated with Genetic Polymorphisms. Cancer Research. 2023;83(5).

22. Rodriguez B, Zepeda LL, Noguez-Ramos A, Juarez DV, Limas CPC, Porras GOR, et al. Real-world clinical outcomes in patients receiving cyclindependent kinase 4/6 inhibitors (iCDK 4/6) for hormone receptorpositive, human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer in Mexico. Journal of Clinical Oncology. 2020;38(15).

23. Agrawal C, Goyal P, Agarwal A, Tripathi R, Dodagoudar C, Baghmar S, et al. Multicentric real world evidence with palbociclib in hormone positive HER2 negative metastatic breast cancer in Indian population. Scientific reports. 2021;11(1):16236.

24. Al-Foheidi MH, Albeshri AM, Moamenkahan SN, Abdullah AM, Abualola MS, Alharbi MH, et al. Combination of palbociclib with adjuvant endocrine therapy for treatment of hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer: An experience at two cancer centers in Saudi Arabia. Molecular and Clinical Oncology. 2022;17(1).

25. Bruno L, Ostinelli A, Waisberg F, Enrico D, Ponce C, Rivero S, et al. Cyclin-Dependent Kinase 4/6 Inhibitor Outcomes in Patients With Advanced Breast Cancer Carrying Germline Pathogenic Variants in DNA Repair–Related Genes. JCO Precis Oncol. 2022;6.

26. Çağlayan D, Koçak MZ, Geredeli Ç, Tatlı AM, Göksu SS, Eryılmaz MK, et al. The effect of concomitant use of proton pump inhibitors with CDK 4/6 inhibitors on survival in metastatic breast cancer. European Journal of Clinical Pharmacology. 2023;79(2):243-8.

27. Darden C, Mitra D, McSorley D, Davis K, Band J, Iyer S. Treatment satisfaction in women receiving palbociclib combination therapies for advanced/metastatic breast cancer. Future Oncology. 2019;15(2):141-50.

28. Demir A, Mandel NM, Paydas S, Demir G, Er Ö, Turhal NS, et al. Efficacy of Palbociclib and Endocrine Treatment in Heavily Pretreated Hormone Receptor-positive/HER2-negative Advanced Breast Cancer: Retrospective Multicenter Trial. Balkan medical journal. 2020;37(2):104-7.

29. Dülgar Ö, Ferik S, Ay S, Bayram E, Şakalar T. Sleep Quality Analysis in Metastatic Breast Cancer Patients Receiving Cyclin-Dependent Kinase 4-6 Inhibitor. Journal of Oncological Science. 2022;8(3):113-8.

30. Eser K, Önder AH, Sezer E, Çil T, İnal A, Öztürk B, et al. Proton pump inhibitors may reduce the efficacy of ribociclib and palbociclib in metastatic breast cancer patients based on an observational study. BMC cancer. 2022;22(1).

31. Ganguly S, Mukherjee N, Mandal S, Roy S, Agarwal S, Biswas B, et al. Efficacy of cyclin-dependent kinase 4/6 inhibitors in patients with metastatic hormone positive breast cancer: a single institutional study from India. ecancermedicalscience. 2022;16.

32. Kahraman S, Erul E, Seyyar M, Gumusay O, Bayram E, Demirel BC, et al. Treatment efficacy of ribociclib or palbociclib plus letrozole in hormone receptor-positive/HER2-negative metastatic breast cancer. Future oncology (London, England). 2023a;19(10):727-36.

33. Keskinkilic M, Semiz HS, Polat G, Arayici ME, Yavuzsen T, Oztop I. The prognostic indicator in breast cancer treated with CDK4/6 inhibitors: The prognostic nutritional index. Future Oncology. 2023a;19(7):517-29.

34. Lakkavalli RK, Pehalajani JK, Tirumala V, Babu GK, Loknatha D, Jacob LA, et al. Metastatic hormone receptor-positive breast cancer in CDK 4/6 era: An outcome audit. J Cancer Res Ther. 2021;17(4):994-7.

35. Loi S, Karapetis CS, McCarthy N, Oakman C, Redfern A, White M, et al. Palbociclib plus letrozole as treatment for postmenopausal women with hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer for whom letrozole therapy is deemed appropriate: An expanded access study in Australia and India. Asia-Pacific Journal of Clinical Oncology. 2022;18(6):560-9.

36. Low JL, Lim E, Bharwani L, Wong A, Wong K, Ow S, et al. Real-world outcomes from use of CDK4/6 inhibitors in the management of advanced/metastatic breast cancer in Asia. Therapeutic Advances in Medical Oncology. 2022;14.

37. Odabas H, Dogan A, Ozcelik M, Yildirim S, Ozkerim U, Turan N, et al. Does Proton Pump Inhibitors Decrease the Efficacy of Palbociclib and Ribociclib in Patients with Metastatic Breast Cancer? Medicina (Kaunas, Lithuania). 2023;59(3).

38. Petracci F, Abuin GG, Pini A, Chacón M. RENATA study-Latin American prospective experience: Clinical outcome of patients treated with palbociclib in hormone receptor-positive metastatic breast cancer-real-world use. ecancermedicalscience. 2020;14.

39. Petracci F, Abuin GG, Pini A, Chacón M. Erratum: RENATA study - Latin American prospective experience: Clinical outcome of patients treated with palbociclib in hormone receptor-positive metastatic breast cancer - Real-world use (ecancermedicalscience (2020) 14 (1058) DOI: 10.3332/ecancer.2020.1058). ecancermedicalscience. 2020;14.

40. Queiroz MM, Sacardo KP, Ribeiro MF, Gadotti LL, Saddi R, Oliveira LJC, et al. Real-world treatment outcomes in HR+ HER2- metastatic breast cancer patients treated with CDK4/6 inhibitors: Results from a reference center in Brazil. Cancer treatment and research communications. 2023;35:100683.

41. Rath S, Elamarthi P, Parab P, Gulia S, Nandhana R, Mokal S, et al. 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. PLoS ONE. 2021;16(7 July).

42. Samame JC, Costanzo MV, Gasol A, Ostinelli A, Rua O, Motta R, et al. RealWorld Data Analysis of Palbociclib plus endocrine therapy in first-line in ibero-american premenopausalwomen with Luminal Advanced Breast Cancer. Breast. 2023;68:S118.

43. Mycock K, Hanson KA, Taylor-Stokes G, Milligan G, Atkinson C, Mitra D, et al. Real-world Treatment Patterns and Clinical Outcomes Associated With Palbociclib Combination Therapy: A Multinational, Pooled Analysis From the Ibrance Real World Insights Study. Clin Ther. 2022;44(12):1588-601.

44. Taylor-Stokes G, Waller J, Mitra D, Gibson K, Milligan G, Iyer S. Real world treatment patterns and clinical outcomes associated with palbociclib combination therapy in Argentina: Results from the IRIS study. Journal of Clinical Oncology. 2018;36(15).

45. Waller J, Mitra D, Mycock K, Taylor-Stokes G, Milligan G, Zhan L, et al. 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. J Glob Oncol. 2019;5:Jgo1800239.

46. Yıldırım H, Mutlu E, Chalabiyev E, Özen M, Keskinkılıç M, Ön S, et al. Clinical outcomes of cyclin-dependent kinase 4-6 (CDK 4-6) inhibitors in patients with male breast cancer: A multicenter study. Breast. 2022;66:85-8.