Thieme

Palbociclib: Randomized Studies and Real-world Evidence as the Basis for Therapeutic Planning in Metastatic Breast Cancer

Palbociclib: randomisierte Studien und Real-World-Evidenz als Grundlage für die Therapieplanung beim metastasierten Mammakarzinom

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ABSTRACT

Endocrine-based combination therapy with an inhibitor of the cyclin-dependent kinases 4 and 6 (CDK4/6 inhibitors) is currently the first-line therapy of choice for patients with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2−), locally advanced or metastatic breast cancer (mBC). The efficacy and safety of the treatment with palbociclib, the first CDK4/6 inhibitor approved for this indication, have been confirmed in large randomized controlled clinical trials (RCTs) with strictly defined patient cohorts. Since then, many relevant questions about CDK4/6 inhibition with palbociclib for mBC have been investigated in RCTs and real-world studies. Based on this evidence, palbociclib is widely used in clinical practice since many years because of its efficacy and good tolerability.

The aim of this review is to summarize findings from RCTs and RWE considering clinically relevant aspects such as safety, tolerability, quality of life and efficacy with a focus on specific questions and patient characteristics. A critical discussion and review of the overall evidence for endocrine-based therapy with the CDK4/6 inhibitor palbociclib can contribute to support therapy decisions in daily clinical practice.

ZUSAMMENFASSUNG

Die endokrin basierte Kombinationstherapie mit einem Inhibitor der cyclinabhängigen Kinasen 4 und 6 (CDK4/6-Inhibitor) gilt heute als Erstlinientherapie der ersten Wahl für Patientinnen und Patienten mit hormonrezeptorpositivem (HR+) und humaner epidermaler Wachstumsfaktor-Rezeptor 2 (HER2)-negativem lokal fortgeschrittenem bzw. metastasiertem Mammakarzinom (mBC). Wirksamkeit und Sicherheit einer Behandlung mit Palbociclib, dem ersten in dieser Indikation zugelassenen CDK4/6-Inhibitor, wurden in großen randomisierten, kontrollierten klinischen Studien (RCTs) mit streng definierten Patientinnenkollektiven belegt. Seither wurden zahlreiche relevante Fragen zur CDK4/6-Inhibition mit Palbociclib beim mBC in RCTs und Real-World-Evidenz-Erhebungen untersucht. Auf dem Boden dieser Evidenz wird Palbociclib im klinischen Alltag aufgrund der Wirksamkeit und der guten Verträglichkeit seit vielen Jahren breit eingesetzt.

Ziel des vorliegenden Reviews ist es, Ergebnisse aus RCTs einerseits und RWE andererseits unter klinisch bedeutsamen Gesichtspunkten wie Sicherheit, Verträglichkeit, Lebensqualität und Wirksamkeit mit dem Blick auf spezifische Fragestellungen und Patientencharakteristika zusammenzufassen. Die kritische Diskussion und Übersicht zur Gesamtevidenz der endokrin basierten Therapie mit dem CDK4/6-Inhibitor Palbociclib soll dazu beitragen, Therapieentscheidungen im klinischen Alltag zu stützen.

Introduction

Following several new diagnostic and, especially, therapeutic developments, the prognosis of patients with locally advanced or metastatic breast cancer (mBC) has improved significantly in recent years. The disease is not curable in its metastatic stage and the therapeutic approach is therefore palliative. The primary objectives of a therapy for mBC are symptom control, delayed progression, prolongation of overall survival, and maintaining the patient's quality of life and autonomy [1, 2].

A combination of endocrine therapy (ET) and an inhibitor of the cyclin-dependent kinases 4 and 6 (CDK4/6 inhibitor) is currently the standard first-line treatment for the majority of patients with hormone receptor-positive (HR+)/human epidermal growth factor 2-negative (HER2−) mBC [3, 4]. In Germany, an aromatase inhibitor (AI) or fulvestrant is used as the endocrine combination partner [5, 6, 7]. Analyses of the German PRAEGNANT registry have shown that the use of CDK4/6 inhibitors plus ET to treat HR+/HER2− mBC quickly became the standard first-line therapy following the market launch of the first CDK4/6 inhibitor palbociclib in 2016. The percentage of chemotherapies and endocrine monotherapies has continually decreased ever since [8]. Among the available CDK4/6 inhibitors, the most extensive real-word evidence currently available is for palbociclib [9]. This review aims to present and summarize the evidence for the CDK4/6 inhibitor palbociclib.

Pivotal trials for CDK4/6 inhibitors to treat mBC

In Germany, three CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) in combination with ET are currently approved to treat HR+/HER2− mBC [5, 6, 7]. The data from the PALOMA-1, 2 and 3 studies were relevant for the approval of palbociclib [10, 11, 12]; for ribociclib, the relevant data were obtained from the MONALEESA-2, -3 and -7 studies [13, 14, 15]; and the data for abemaciclib were taken from the MONARCH 3 and 2 studies [16, 17]. The approval of CDK4/6 inhibitors was based on a significant prolongation of the primary endpoint "progression-free survival" (PFS) which was observed in all of these studies for the respective combination therapy when compared to ET monotherapy [10, 12, 13, 14, 15, 16, 17]. The range of side effects for the three CKD4/6 inhibitors differed across the registrational studies [5, 6, 7]. The first-line studies PALOMA-1 and 2 found no statistically significant OS benefit from the addition of a CDK4/6 inhibitor to ET [18, 19]. A clinically relevant but statistically not significant OS benefit of 6.9 months was observed in the PALOMA-3 study for palbociclib plus fulvestrant compared to fulvestrant monotherapy, and this was confirmed after a follow-up of 73 months [20, 21] (▶ **Table 1**).

Additional evidence from randomized trials with palbociclib

The PALOMA-1, 2 and 3 trials focused on efficacy, safety, tolerability, and quality of life and provided the rationale for the use of palbociclib to treat HR+/HER2− mBC [10, 11, 12]. Nevertheless, some questions have remained unanswered, and new ones have arisen, e.g., about the optimal endocrine combination partner for palbociclib.

This question was adressed in the phase-II study PARSIFAL (▶ **Table 2**). No differences were found with regards to efficacy and adverse events between the combination partners letrozole and fulvestrant [24]. In the combined analysis of both treatment arms, the PARSIFAL-Long trial reported a mean OS of 65.4 months (95 % CI: 57–72.0). These data coherently fit into the overall picture of OS data from other CDK4/6 inhibitor first-line studies [25, 50, 51]. The phase-III PADA-1 trial investigated whether early switch of the endocrine partner from letrozole to fulvestrant would be useful in patients with HR+/HER2− mBC and rising mutation of the estrogen receptor-1 gene (*ESR1*) [52]. After AI therapy, *ESR1* mutations were detected in about 40 % of cases, with certain alterations imparting AI resistance [53, 54]. In PADA-1, PFS doubled when therapy was switched from AI plus palbociclib to

▶**Table 1** Review of relevant clinical and real-world studies with palbociclib.

mPFS, HR (95% CI)	mOS, HR (95% CI)	Additional endpoints	Comments	Ref.
RCT				
PALOMA-1 (phase II, n = 84/81) efficacy, tolerability; PAL+LET vs. LET in 1 L; postmenop. women				
20.2 vs. 10.2 mos. HR 0.49 (0.32–0.75), p = 0.0004	37.5 vs. 34.5 mos. HR 0.90 (0.623–1.294), p = 0.281	ORR, CBR, DOR, safety, biomarkers, PROs	Time to first subsequent chemotherapy 26.7 vs. 17.7 mos. (mFU: 67.7 mos.)	[11, 18]
PALOMA-2 (phase III, n = 444/222) efficacy, tolerability; PAL+LET vs. LET in 1 L; postmenop. women				
24.8 vs. 14.5 mos. HR 0.58 (0.46–0.72), p < 0.001 *Update:* 27.6 vs. 14.5 mos. HR 0.56 (0.46–0.69), p < 0.0001	53.9 vs. 51.2 mos. HR 0.96 (0.78–1.18), p = 0.34	ORR, DOR, CBR, PROs, PK, safety, biomarkers	Pts. with endocrine resistance were included	[12, 19, 22]
PALOMA-3 (phase III, n = 347/174) efficacy, tolerability; PAL+FUL vs. FUL in ≥ 1 L; pre-/postmenop. women after progression/recurrence under ET				
9.5 vs. 4.6 mos. HR 0.46 (0.36–0.59), p < 0.0001 *Update:* 11.2 vs. 4.6 mos. HR 0.50 (0.40–0.62), p < 0.0001	*Final analysis:* 34.9 vs. 28.0 mos. HR 0.81 (0.64–1.03), p = 0.09 *Ad hoc analysis:* (mFU: 73.3 mos.) 34.8 vs. 28.0 mos. HR 0.81 (0.65–0.99)	ORR, DOR, CBR, biomarkers, proteins, RNA expression, safety, PROs, PK	Any number of previous endocrine therapies and one previous CT for aBC permitted (comparatively heavily pretreated cohort)	[10, 20, 21]
PALOMA-4 (phase III, n = 169/171) efficacy, tolerability; PAL +LET vs. LET in 1 L; postmenop. women				
21.5 vs. 13.9 mos. HR 0.68 (0.53–0.87), p = 0.001	immature/n. ach.	ORR, CBR, DOR, PK, PROs, safety	Asian population, median age: 54 Y	[23]
PARSIFAL/PARSIFAL-LONG (phase II, n = 243/243) superiority, PAL+FUL vs. PAL+LET in 1 L; pre-/postmenop. women				
27.9 vs. 32.8 mos. HR 1.13 (0.89–1.45), p = 0.321 PARSIFAL-LONG: 31.4 vs. 34.5 mos. HR 1.00 (0.78–1.29), p = 0.985	3-year OS: 79.4% vs. 77.1% HR 1.00 (0.68–1.48), p = 0.986 PARSIFAL-LONG: 68.5 vs. 61.9 mos. HR 0.94 (0.72–1.23), p = 0.635	ORR, DOR, CBR, TTP, TTR, safety	*de novo* metastasized and/or ET-sensitive; European study (also in GER); PARSIFAL-LONG: prolonged mFU: 59.7 mos. with 80.5% of pts. (n = 197/192) from PARSIFAL, prim. EP: prolongation of OS	[24, 25]
Young-PEARL (phase II, n = 92/86) efficacy, tolerability, PAL+EXE+GnRH vs. capecitabine in 1–3 L; premenop. women				
20.1 vs. 14.4 mos. HR 0.66 (0.44–0.99), p = 0.024	immature/n. ach.	OS, ORR, toxicity, CBR, biomarkers, QoL	86% TAM-resistant; stratification factor: CT for aBC and visceral metastases	[26]
SONIA (phase III, n = 524/526) efficacy, tolerability of CDK4/6i in 1 L vs. 2 L: FUL-mono after PAL-AI vs. CDK4/6i after AI-mono; pre-/peri-/postmenop. women				
PFS1: 24.7 vs. 16.1 mos., HR 0.59 (0.51–0.69), p < 0.0001 *PFS2:* 31.0 vs. 26.8 mos., HR 0.87 (0.74–1.03), p = 0.10	45.9 vs. 53.7 mos., HR 0.98 (0.80–1.20), p = 0.83	QoL; cost effectivity, ORR, ≥ grade 3 AEs, biomarkers	Dutch sequential study; 91% treated with PAL; prim. EP: PFS2; mFU 37.3 mos.; full publication still pending	[27]
PEARL (phase III, cohort 1 PAL+EXE n = 153/143, cohort 2 PAL+FUL n = 149/156) efficacy of PAL+ET vs. capecitabine in 1–4 L; postmenop. women				
Cohort 2: 7.5 vs. 10.0 mos. aHR 1.13 (0.85–1.50), p = 0.398; *Cohort 1 + 2, wtESR1:* 8.0 vs. 10.6 mos.; aHR 1.11 (0.87–1.41), p = 0.404	*Cohort 2:* 31.1 vs. 32.8 mos. aHR 1.10 (0.81–1.50) p = 0.550; *Cohort 1 + 2, wtESR1:* 37.2 vs. 34.8 mos.; aHR 1.06 (0.81–1.37), p = 0.683	ORR, CBR, DOR, safety, PROs	Resistant to AI (recurrence during/ within 12 mos. after adjuvant AI or progression during /within 1 mo. after AI for aBC); OS ITT: 32.6 vs. 30.9 mos., HR 1.00 (0.82–1.23), p = 0.995	[28, 29]
PATHWAY (phase III, n = 91/93) efficacy, tolerability; PAL+TAM vs. TAM in 1 L and 2 L; pre-/peri-/postmenop. women				
24.4 vs. 11.1 mos. HR 0.60 (0.43–0.85), p = 0.002	mOS n. ach. HR 0.73 (0.44–1.21), p-value n. r.	ORR, CBR, DOR, PK, safety, PROs	Asian population; adjuvant TAM permitted if TFI > 12 mos.; OS still immature	[30]

▶Table 1 continued

mPFS, HR (95% CI)	mOS, HR (95% CI)	Additional endpoints	Comments	Ref.
PADA-1 (phase III, n = 1017) efficacy of early switch in 1 L from PAL+AI to PAL+FUL if level of *ESR1mut* increases vs. continuation of PAL+AI				
Δ*mPFS* = 7.0 mos. HR 0.54 (0.38–0.75) Δ*mPFS2* = 15.4 mos. HR 0.37 (0.24–0.56)	immature/n. ach.	≥ grade 3 hematological AEs in total population, QoL, chemotherapy-free survival, OS	Step 1: PAL + AI n = 1017, Step 2: 172 with *ESR1mut* and without tumor progression, 1:1 switch to PAL+FUL vs. continued PAL+AI n = 88/84; endocrine AI partner switched to FUL after clinical progression showed limited efficacy (mPFS 3.5 mos.)	[31, 32]
PreCycle (phase IV, n = 499, ITT-PRO n = 271/141) effect of electronic PRO collection on QoL; PAL+ET: CANKADO-active vs. CANKADO-inform, 1 L and 2 L+				
21.4 mos. (19.4–23.7) vs. 18.7 mos. (15.1–23.5)	n. ach. vs. 42.6 mos.	TTD of the QoL, DQoL, cumulative incidence of SAEs	Patient-focused study; prim. EP mTTD of the QoL (HR 0.70 [0.51–0.96], p = 0.03); mFU QoL: CANKADO-active 20 mos., CANKADO-inform 18 mos.	[33, 34]
RWE				
P-REALITY (retrospective, n = 772/658) effectiveness of PAL+LET vs. LET 1 L; post- and premenop. women				
20.0 vs. 11.9 mos. aHR 0.58 (0.49–0.69), p < 0.0001 Shown here: adjusted (sIPTW)	n. ach. vs. 43.1 mos. aHR 0.66 (0.53–0.82), p = 0.0002 Shown here: adjusted (sIPTW)	n. r.	Flatiron database (USA), Adjustment: none, sIPTW and PSM. mFU after sIPTW: 24.2 vs. 23.3 mos.; prim. EP: PFS; sec. EP: OS	[35]
P-REALITY X (retrospective, n = 1324/1564) effectiveness of PAL+AI vs. AI 1 L; postmenop. women and men				
19.3 vs. 13.9 mos. aHR 0.70, (0.62–0.78) p < 0.0001 Shown here: adjusted (sIPTW)	49.1 vs. 43.2 mos. aHR 0.76 (0.65–0.87), p < 0.0001 Shown here: adjusted (sIPTW)	n. r.	Flatiron database (USA); adjustment: none, sIPTW and PSM. mFU after sIPTW: 23.9 vs. 24.5 mos.; prim. EP: OS; sec. EP: PFS	[36]
SEER analysis (retrospective, n = 169/461) effectiveness of CDK4/6i+ET vs. ET 1 L; postmenop. women ≥ 65 Y, *de novo* mBC				
n. r.	*1 L:* n. ach. vs. 34.8 mos. aHR 0.59 (0.42–0.82) Shown here: adjusted (Cox)	TTD, adherence	SEER Medicare database (USA), unadjusted and after multivariable Cox regression analysis (shown here). mFU: 30.0 vs. 24.0 mos.; also OS benefit for CDK4/6 inhibitor in 2 L (s. ▶**Table 4**); CDK4/6i+ET: ca. 90% PAL+ET	[37, 38]
MD Anderson analysis (retrospective, n = 708/708 [1 L] and n = 380/380 [2 L]) effectiveness of PAL+ET vs. ET 1 L+ 2 L				
1 L: 17,4 vs. 11.1 mos. aHR 0.71 (0.60–0.84), p = 0.0001 *2 L:* 10.0 vs. 5.0 mos. aHR 0.51 (0.41–0.64), p < 0.0001 Shown here: adjusted (PSM)	*1 L:* 44.3 vs. 40.2 mos. aHR 1 (0.80–1.23), p = 1 *2 L:* 32.3 vs. 24.6 mos. aHR 0.67 (0.52–0.87), p = 0.002 Shown here: adjusted (PSM)	n. r.	Single center; 1 L PAL+AI vs. AI; 2 L PAL+FUL vs. FUL (1.3% vs. 61.3% with 250 mg instead of 500 mg FUL); adjustment: none, PSM and sIPTW. mFU after PSM: 1 L: 30 vs. 119 mos., 2 L: 30 vs. 106 mos.; 1 L: different OS trends for PSM and sIPTW (HR 0.79 [0.67–0.93])	[39]
UK study (retrospective, n = 276) effectiveness, safety of PAL+AI 1 L; women ≥ 75 Y				
12 mos. PFS: 75.9% *24 mos. PFS:* 64.9%	*12 mos. OS:* 85.1% *24 mos. OS:* 74,0%	Safety, BRR, CBR, CR, PR, SD, PD	14 centers in the UK	[40]
IRIS (Europe) (retrospective) n = 982 (PAL+AI) and n = 741 (PAL+FUL) treatment patterns, effectiveness of PAL+AI and PAL+FUL; post-/peri-/premenop. women				
12 mos. PFS: PAL+AI: 88.1%; PAL+FUL: 79.8% *24 mos. PFS:* PAL+AI: 63.9%; PAL+FUL: 48.0%	*12 mos. OS:* PAL+AI 97.3%; PAL+FUL 97.5% *24 mos. OS:* PAL+AI: 90.1%; PAL+FUL 88.6%	CR, PR, SD, PD, ORR, CBR, OS rate, TTP	Also in GER; PAL+AI: mFU 10.5 mos., 925 1 L and 57 2 L+; PAL+FUL: mFU 8.0 mos. 379 1 L, 362 2 L+; analysis of pts. from Europe, other analyses available, e.g., for USA [41] and Canada [42]	[43]

▶**Table 1** continued

mPFS, HR (95% CI)	mOS, HR (95% CI)	Additional endpoints	Comments	Ref.
MADELINE (prospective, n = 139) PRO PAL+ET in 1–3 L; women ≥ 18 Y				
n. r.	n. r.	QoL (SF12, CES-D-10), pain and fatigue scores, mood survey, ability to function in daily life; AEs	PAL+AI (n = 85)/PAL+FUL (n = 54); patient-focused study; eCRF combined with PRO collection via mobile app; including PROs as a function of neutropenia	[44]
PERFORM (prospective NIS, n [planned] = 1900), n [IA2] = 624) effectiveness of PAL+ET in 1 L; women and men				
6 mos. PFS: 85.6% (82.5–88.2%); *12 mos. PFS:* 71.7% (67.1–75.7%); *18 mos. PFS:* 60.8% (53.7–75.9%)	immature/n. ach.	PFS, PFS2, OS, ORR, DOR, DCR, TFST, TTC, PROs	NIS from D, AT; IA2 with FU ≥ 6 mos.; collection of PROs continued after progression	[45, 46]
PalomAGE (prospective, cohort A n = 400; cohort B n = 407) effectiveness, safety, tolerability of PAL+AI/FUL, 1 L/≥ 1 L; women ≥ 70 Y				
Cohort A: 28.1 mos. *Cohort B:* 11.6 mos. (mTTF)	immature/n. ach.	Therapy discontinuation rates, TTF, geriatric assessment, QoL	Cohort A: ET-sensitive and 1 L; Cohort B: ET-resistant and/or ≥ 2 L; prim. EP: discontinuation rate after 18 mos. (cohort A, 41.9%) and 6 mos. (cohort B, 28.8%); PFS n. r.	[47, 48, 49]

1 L = first-line therapy; ≥ 1 L = first-line therapy or higher; 2 L+ = second-line therapy or higher; aBC = advanced breast cancer; AE = adverse event; aHR = adjusted HR; AI = aromatase inhibitor; AT = Austria; BRR = best radiological response; CBR = clinical benefit rate; CDK4/6i = CDK4/6 inhibitor; CI = confidence interval; CR = complete remission; CT = chemotherapy; DCR = disease control rate; DOR = duration of response; DQoL = decrease in quality of life; eCRF = electronic case report form; EP = endpoint; *ESR1mut* = estrogen receptor-1 gene mutation; ET = endocrine therapy; EXE = exemestane; FUL = fulvestrant; GER = Germany; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; IA = interim analysis; ITT = intention-to-treat population; LET = letrozole; mFU = median follow-up; mos. = month(s); mono = monotherapy; mOS = median overall survival; mPFS = median progression-free survival; n = number of patients in the study; mTTD = median time to treatment failure; n. ach. = not achieved; n. r. = not reported; NIS = non-interventional study; ORR = objective response rate; OS = overall survival; PAL = palbociclib; pts. = patients; PD = disease progression; PFS = progression-free survival; PK = pharmacokinetic analysis; PR = partial remission; PSM = propensity score matching; pre-/peri-/postmenop. = pre-/peri-/postmenopausal; PRO = patient-reported outcome; QoL = quality of life; SAE = serious adverse event; SD = stable disease; sIPTW = stabilized inverse probability of treatment weighting; TAM = tamoxifen; TFI = therapy-free interval; TFST = time to first subsequent therapy; TTC = time to first subsequent chemotherapy; TTF = time to treatment failure; TTP = time to progression; TTR = time to response; UK = United Kingdom; USA = United States of America; *wtESR1* = wild-type ESR1 gene; Y = years

fulvestrant plus palbociclib at the emergence of new *ESR1* mutations and prior to confirmed disease progression by imaging [31].

The open-label phase-III trial PEARL compared palbociclib plus exemestane or plus fulvestrant with chemotherapy with capecitabine in postmenopausal patients with HR+/HER2− mBC, who had previously been treated with an AI. The median PFS and OS was comparable in both arms (▶**Table 2**) [28, 29]. In the open-label phase-II trial Young-PEARL, palbociclib plus exemestane and a gonadotropin-releasing hormone (GnRH) analog significantly prolonged PFS in premenopausal patients compared to capecitabine (p = 0.002) [26]. PEARL and Young-PEARL demonstrated better tolerability and quality of life with lower therapy discontinuation rates (▶**Table 3**) emphasizing the use of endocrine-based therapy with a CDK4/6 inhibitor as the treatment standard compared to chemotherapy [28, 29, 26, 55, 56].

The phase-III study SONIA investigated whether the best use of CDK4/6 inhibitors for the treatment of HR+/HER2− mBC was as part of the first or the second line of therapy [27]. The participating patients (pre- and postmenopausal) received either a non-steroidal AI (NSAI) plus a CDK4/6 inhibitor followed by fulvestrant in the first and second line of therapy, or a NSAI followed by fulvestrant plus a CDK4/6 inhibitor (a GnRH analog in addition if they were premenopausal). PFS was significantly prolonged with a HR of 0.59 (p < 0.0001) if a CDK4/6 inhibitor was used in the first line of therapy. With a non-significant difference of 5.2 months (p = 0.10) in the PFS2 favoring the first-line use of a CDK4/6 inhibitor, the primary endpoint was not reached and there was no difference in OS either (p = 0.83) [27, 63].

Other RCTs with palbociclib investigated the combination of alternative endocrine partners (PATHWAY with tamoxifen), special patient populations (Asian female patients in the PALOMA-4 trial) or the use of a supporting eHealth application (PreCycle) (▶**Table 1**). Other clinically relevant questions were answered using data obtained from routine clinical care and are discussed below.

Real-world evidence on palbociclib as an important addition to RCTs – opportunities and limitations

RCTs are the gold standard for generating clinical evidence and for obtaining approval [64, 65, 66]. As the results obtained from RCTs

▶**Table 2** Overview of clinical studies focusing on endocrine pretreatment.

Study/clinical question		ITT	ET-sensitive	*de novo* mBC	ET-resistant	Comments	Ref.
		n (number), PFS and OS (HR [95% CI])					
RCT							
PALOMA-2 PAL+LET vs. LET, 1 L	**n**	444/222	178/93	167/81	99/48	Stratification factor: DFI after completion of (neo-)adjuvant therapy; ET-sensitive: DFI > 12 mos.; ET-resistant: DFI ≤ 12 mos.	[12, 19]
	PFS	0.58 (0.46–0.72)	0.52 (0.36–0.73)	0.67 (0.46–0.99)	0.50 (0.33–0.76)		
	OS	0.96 (0.78–1.18)	0.73 (0.53–1.01)	1.19 (0.84–1.70)	1.02 (0.66–1.58)		
PALOMA-3 PAL+FUL vs. FUL, ≥ 1 L	**n**	347/174	274/136	excluded	73/38	Stratification factor: previous endocrine sensitivity; ET-sensitive: documented clinical benefit ≥ 1 ET for mBC or adjuvant ET ≥ 24 mos. prior to recurrence	[10, 20]
	PFS	0.46 (0.36–0.59)	0.42 (0.32–0.56)	–	0.64 (0.39–1.07)		
	OS	0.81 (0.64–1.03)	0.72 (0.55–0.94)	–	1.14 (0.71–1.84)		
PALOMA-4 PAL+LET vs. LET, 1 L	**n**	169/171	80/85	34/32	55/54	Stratification factor: disease-free interval after completion of (neo-)adjuvant therapy (DFI); ET-sensitive: DFI > 12 mos.; endocrine resistance: DFI ≤ 12 mos.	[23]
	PFS	0.68 (0.53–0.87)	0.61 (0.42–0.88)	0.54 (0.30–0.96)	0.84 (0.56–1.28)		
	OS	immature	immature	immature	immature		
PARSIFAL PAL+FUL vs. PAL +LET, 1 L	**n**	243/243	141/147	102/96	excluded	ET-sensitive: DFI > 12 mos.; 3-year OS (ITT): 79.4% vs. 77.1%	[24, 25]
	PFS	1.13 (0.89–1.45)	1.14 (0.82–1.56)	1.13 (0.77–1.75)	–		
	OS	1.0 (0.68–1.48)	n. r.	n. r.	–		
Young-PEARL PAL+EXE+GnRH vs. Cape, 1–3 L premenop. women	**n**	92/86	16/9	excluded	76/77	Included: progression under TAM; excluded: previous AI therapy (eBC/aBC); relatively low *ESR1mut* at baseline of 3.4%; ET-sensitive: TAM sensitive (DFI > 12 mos.); ET-resistant: TAM resistant (DFI ≤ 12 mos.)	[26]
	PFS	0.66 (0.44–0.99)	n. r.	–	n. r.		
	OS	n. r.	n. r.	–	n. r.		
PEARL PAL+EXE/FUL vs. Cape, 1–4 L	**n**	302/299	226/226	excluded	76/73	Previous disease progression under AI at any time; stratification factor: sensitivity to previous ET; *ESR1mut* at baseline 27.7% vs. 30.1%. Shown here: cohort 1 and 2 pooled	[28, 29]
	PFS	1.09 (0.90–1.31)	1.04 (0.83–1.29)	–	1.30 (0.90–1.88)		
	OS	0.97 (0.79–1.19)	0.89 (0.70–1.13)	–	1.29 (0.88–1.90)		
RWE							
PALOMAGE PAL+AI/FUL, 1 L/≥ 1 L ≥ 70 years	**n**	n. r.	362		378	ET-sensitive: 1 L, *de novo* mBC (63%) without DFI > 12 mos. (cohort A); ET-resistant: DFI ≤ 12 mos. and/or ≥ 2 L (cohort B)	[47, 49]
	rwPFS	n. r.	*mPFS:* 28.1 mos. (25.6–n. ach.)		*mTTF:* 11.6 mos. (10.0–13.0)		
	OS	n. r.	n. r.		n. r.		

▶**Table 2** continued

Study/clinical question		ITT	ET-sensitive	*de novo* mBC	ET-resistant	Comments	Ref.
		n (number), PFS and OS (HR [95 % CI])					
P-REALITY X PAL+AI vs. AI, 1 L	**n**	1324/1564	551/601	541/464	191/429	Shown here after adjustment (sIPTW); DFI defined as time from initial diagnosis until diagnosis of mBC; ET-sensitive: DFI > 5 Y; ET-resistant: DFI > 1–5 Y (subgroup DFI < 1 Y [n = 44/66] not shown)	[36]
	rwPFS	0.70 (0.62–0.78)	0.75 (0.63–0.90)	0.61 (0.51–0.72)	0.88 (0.66–1.19)		
	OS	0.76 (0.65–0.87)	0.74 (0.59–0.93)	0.68 (0.55–0.84)	1.18 (0.86–1.61)		
P-REALITY PAL+LET vs. LET, 1 L	**n**	772/658	308/269	321/254	123/111	Shown here after adjustment (sIPTW); DFI defined as time from initial diagnosis until diagnosis of mBC; ET-sensitive: DFI > 5 Y; ET-resistant: DFI > 1–5 Y (subgroup DFI < 1 Y [n = 19/42] not shown)	[35]
	rwPFS	0.58 (0.49–0.69)	0.58 (0.47–0.72)	0.57 (0.46–0.72)	0.61 (0.44–0.83)		
	OS	0.66 (0.53–0.82)	0.78 (0.58–1.06)	0.56 (0.40–0.78)	0.69 (0.49–0.97)		
SEER analysis CDK4/6i+ET vs. ET, 1 L ≥ 65 years, *de novo* mBC	**n**	169/461	excluded	169/461	excluded	CDK4/6i+ET: ca. 90 % PAL+ET; shown here after multivariable Cox regression analysis; data on 2 L, s. ▶ **Table 4**	[37, 38]
	rwPFS	n. r.	–	n. r.	–		
	OS	0.59 (0.42–0.82)	–	0.59 (0.42–0.82)	–		

1 L = first-line therapy; ≥ 1 L = first-line therapy or higher; aBC = advanced breast cancer; AI = aromatase inhibitor; Cape = capecitabine; CDK4/6i = CDK4/6 inhibitor; CI = confidence interval; DFI = disease-free interval; eBC = early breast cancer; *ESR1mut* = estrogen receptor-1 gene mutation; ET = endocrine therapy; EXE = exemestane; FUL = fulvestrant; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; ITT = intention-to-treat population; LET = letrozole; mBC = metastatic breast cancer; mos. = month(s); mPFS = median progression-free survival; mTTF = median time to treatment failure; n = number of patients reported in the study; n. ach. = not achieved; n. r. = not reported; OS = overall survival; PAL = palbociclib; PFS = progression-free survival; premenop. = premenopausal; RCT = randomized controlled study; RWE = real-world evidence; rwPFS = real-world progression-free survival; sIPTW = stabilized inverse probability of treatment weighting; TAM = tamoxifen; Y = years

are for selected study populations which exclude certain patient cohorts and are obtained under highly controlled study conditions, their transferability to some patient groups in clinical routine may be limited [67]. These limitations also include the fact that endpoints such as efficacy, safety and patients reported health status, functional status and quality of life (patient reported outcome = PRO) are usually only observed until disease progression in RCTs [68, 69].

Real-world data (RWD) are health data which are or were collected in routine clinical practice and outside interventional clinical trials [67]. They include specific patient groups such as older patients, patients with comorbidities or men with breast cancer, which are usually underrepresented or excluded in pivotal clinical trials [64, 70, 71, 72]. The advantage of these data is that they have a high external validity [73]. A therapeutic effect in terms of effectiveness, safety and tolerability can therefore be demonstrated in a broader patient population compared to those of RCTs, which better reflects the situation in clinical routine [64]. An important limitation when collecting RWD is that the selective choice of treatment and the lack of statistical control in clinical practice can result in bias [64, 74]. An uncontrolled study design, gaps or errors in documentation, and other unknown confounding factors can theoretically lead to less robust results. It can be difficult to differentiate whether the observed effect of a treatment is causality (cause–effect relation) or correlation [64, 75, 76]. However, statistical methods are often used as an attempt to make therapy groups more comparable and to thereby minimize bias [36, 76, 77].

Real-world evidence (RWE) can be obtained by evaluating accumulated RWD. It can reflect the reality of clinical care and address questions of clinical relevance related to safety signals, therapy adherence, and therapy sequences. RWE can be a useful addition and expansion to data obtained from RCTs important for registrational approval [64, 65, 67, 77].

This review has therefore also included findings from different real-world studies focussing on endocrine-based therapies with palbociclib for the treatment of HR+/HER2− mBC. High-quality analyses were preferred, which used robust, established statistical methods and addressed clinically relevant, previously unanswered questions. These included single-arm studies such as the ongoing prospective non-interventional study (NIS) PERFORM currently being carried out in Germany and Austria as well as comparative approaches which investigated the effectiveness of palbociclib plus ET versus ET alone [35, 45, 46]. Large retrospective compara-

▶**Table 3** Overview of quality of life, safety, and tolerability.

Dose adjustment		Therapy discontinuation rate (AEs)	Quality of life – under therapy with PAL and/or vs. comparative therapy	Side effects grade ≥ 3, ≥ 5% in the PAL+ET arm, unless otherwise reported	Comments	Ref.
RCT						
PALOMA-1 PAL+LET vs. LET, 1 L						
Reduction	40% vs. n.a.	13% vs. 2%	n. r.	Neutropenia (54%, febrile 0%), leukopenia (19%), anemia (6%)	mFU 29.6 mos.	[11]
Interruption	33% vs. 4%					
Cycle delay	45% vs. n.a.					
mDI	94% vs. n.r					
PALOMA-2 PAL+LET vs. LET, 1 L						
Reduction	36% vs. 1%	9.7% vs. 5.9%	FACT-B maintained QoL; progression (no vs. yes): sig. delayed TTD of QoL vs. LET: sig. improvement of pain	Neutropenia (66.5%, febrile 1.8%), leukopenia (24.8%), anemia (5.4%)	mFU (safety): 23 mos.; neutropenia most important reason for dose reduction	[12, 22, 57]
Interruption	67% vs. 41%					
mDI	93% vs. 100%					
PALOMA-3 PAL+FUL vs. FUL, ≥ 1 L						
Reduction	34% vs. 2%	4% vs. 2%	EORTC QLQ-C30 and QLQ-BR23 maintained gQoL vs. FUL: sig. delayed TTD of gQoL and pain symptom scale; sig. improvement of emotional functionality, pain, nausea/vomiting	Neutropenia (65%, febrile 1%), leukopenia (28%)	mFU (safety): 8.9 mos.; TTD: ad hoc analysis for gQoL and for prespecified pain scale	[10, 58]
Interruption	54% vs. 6%					
Cycle delay	36% vs. 2%					
PALOMA-1, 2, 3 pooled long-term analysis of PAL+ET vs. ET, 1 L, ≥ 1 L						
Dose reduction		11.1% vs. 5.3%	n. r.	PAL+ET (all grades): stable and consistent safety profile; cumulative incidence of hematolog. AEs: peak in 1st Y; ILD/pneumonitis: 0.23%/0.46%; febrile neutropenia: 1.4%; overlapping Gr. 3/4 viral infection with Gr. 3/4 neutropenia 0.2%	Long-term analysis with up to 5 Y FU	[59]
PAL+ET	42.2%/39.4%/41.7%					
ET	n. a./1.8%/1.7%					
PARSIFAL PAL+FUL vs. PAL+LET, 1 L						
Reduction	35.3% vs. 44.6%	5.4% vs. 2.1%	n. r.	PAL+FUL/PAL+LET: neutropenia (66%/68.2%, febrile 1.2%/0.4%), leukopenia (7%/5.8%), pulmonary embolism (5.0%/2.5%)	mFU 32 mos.; management of pulmonary embolism: primarily with low molecular weight heparin, 16.7% dose reduction, 16.7% therapy discontinuation	[24, 25]
Cycle delay	49.0% vs. 50.8%					
mDI (PAL)	91.7% vs. 90.0%					
PATHWAY PAL+TAM vs. TAM, 1 L						
n. r.		3.3% vs. 2.2%	n. r.	Neutropenia (89.0%, febrile n. r.), infections (6.6%), anemia (6.6%), thrombocytopenia (5.5%), elevated ALT (5.5%)	Overall safety profile consistent with known profile of PAL+ET	[30]

▶**Table 3** continued

Dose adjustment		Therapy discontinuation rate (AEs)	Quality of life – under therapy with PAL and/or vs. comparative therapy	Side effects grade ≥ 3, ≥ 5% in the PAL+ET arm, unless otherwise reported	Comments	Ref.
PEARL PAL+EXE/FUL vs. Cape, 1–4 L						
mDI		*Cohort 1:* 5.3% vs. 18.2% *Cohort 2:* 2.0% vs. 10.5%	EORTC QLQ-30, QLQ-BR23, EQ-5DSL maintained QoL vs. Cape: sig. delayed TTD of gQoL; sig. improvement of physical, cognitive and social functionality, fatigue, nausea/vomiting, loss of appetite	PAL+EXE vs. PAL+FUL vs. Cape: neutropenia (61.3%/58.4%/6.2%, febrile 1.3%/0.7%/1.4%), leukopenia (32.0%/34.2%/ 2.8%), thrombocytopenia (6.0%/1.3%/1.3%), hypoalbuminemia (0.0%/6.0%/1.7%), diarrhea (2.0%/1.3%/ 7.6%), hand-foot syndrome (0.0%/0.0%/23.9%) and fatigue (2.7%/1.3%/6.2%)	Cohort 1: PAL+EXE vs. Cape Cohort 2: PAL+FUL vs. Cape	[28, 29, 56]
Cohort 1	95.2% vs. 82.6%					
Cohort 2	92.9% vs. 79.5%					
Young-PEARL PAL+EXE+GnRH vs. Cape, 1–3 L premenop.						
Reduction	48% vs. 48%	1.1% vs. 2.3%	EORTC QLQ-C30; maintained QoL vs. Cape: sig. improved TTD for physical functionality, nausea/vomiting, diarrhea	Neutropenia (64%/16%, febrile 3%/1%), leukopenia (11%/0%), hand-foot syndrome (0%/14%)	mFU (safety): 17 mos.	[26, 55]
Interruption (AEs)	96% vs. 76%					
mDI	78% vs. 88%					
PreCycle PAL+ET: CANKADO-active vs. CANKADO-inform, 1 L, 2 L+						
Reduction	41.2% vs. 47.8%	n. r.	FACT-B CANKADO-active vs. CANKADO-inform: sig. delayed TTD QoL (HR 0.70 [0.51–0.96], p = 0.03)	CANKADO-active vs. CANKADO-inform: lower risk of SAEs (HR 0.67 [0.48–0.94] p = 0.04)	Patient-focused study; prim. EP: TTD QoL; (FACT-G response rate of ≥ 80% up until visit 30)	[33, 34]
Delay	60.1% vs. 57.1%					
Interruption	37.1% vs. 42.2%					
mDI (PAL)	96.7% vs. 93.9%					
RWE						
PalomAGE PAL+AI/FUL, 1 L/≥ 1 L; ≥ 70 years						
ITT		*ITT:* 5.8% *Cohort A:* 6.5% *Cohort B:* 5.3%	EORTC QLQ-C30 and -QLQ-ELD 14 maintained QoL; cohort B: lower symptoms on pain scale	*ITT:* neutropenia (32.3%, febrile 1.1%); no new safety signals; *all AEs grade ≥ 3, 1 L vs. 2 L vs. 2 L+:* 33.7%, 37.3%, 52.9%; no impact of frailty factors	Cohort A: ET-sensitive and 1 L; Cohort B: ET-resistant and/or ≥ 2 L; mFU (safety) 6.7 mos.; QoL survey: at baseline and 18 mos. (cohort A), 3 mos., 6 mos. (cohort B)	[47, 48, 49]
≥ 1 reduction	23.4%					
Red. initial dose	24%					
(more likely if ≥ 80 Y, ECOG PS ≥ 2, G8 ≤ 14 or CCI ≥ 4)						
POLARIS PAL+ET, 1 L, 2 L+						
n. r.		n. r.	EORTC QLQ-C30 maintained QoL	Neutropenia (48.6%, febrile 0.8%), median time from 1 st dose to neutropenia: 27–29 days	Safety: mDOT 19.3 mos. Other AEs in overall population n. r.	[60, 61, 62]
UK study PAL+AI, 1 L; 70 years						
Reduction	50.7%	13%	n. r.	Neutropenia (46.4%, febrile 2.2%); no new safety signals	Hospitalization due to AEs (9.6%); no loss of effectiveness when dose was reduced or delayed	[40]
Red. initial dose	11.6%					
Dose delay	59.3%					

▶Table 3 continued

Dose adjustment		Therapy discontinuation rate (AEs)	Quality of life – under therapy with PAL and/or vs. comparative therapy	Side effects grade ≥ 3, ≥ 5 % in the PAL+ET arm, unless otherwise reported	Comments	Ref.
IRIS (Europe) PAL+AI/PAL+FUL, ≥ 1 L						
Reduction:	15.6 %	3.3 %	n. r.	n. r.	mFU 10.5 mos. (PAL+AI, n = 982) and 8.0 mos. (PAL+FUL, n = 741); shown here: pooled population	[43]
Red. Initial dose	7.8 %					
Most common reasons: prevention of AEs, age						
MADELINE PAL+ET; 1–3 L						
PAL+AI/PAL+FUL		n. r.	General state of health: (SF-12) stable; incidence of depression (CES-D-10), pain and fatigue scores: stable (low); PRO QoL, physical and mental health: maintained (mainly good-excellent); results irrespective of neutropenia. Additional info: s. Comments	SAEs: 9 % Neutropenia: Gr. 3/4 (26 %), all grades (45 %, febrile 2 %); events/pts.: 1 (20 %), 2 (11 %), 3 (14 %)	Patient-focused study; eCRF combined with PRO collection using mobile app; no negative impact on social and family life, physical activity, energy, productivity under therapy	[44]
Adjusted because of neutropenia	7 %/17 %					
Interrupted because of neutropenia	15 %/17 %					
PERFORM PAL+ET, 1 L						
Reduction	35.6 %	3.3 %	n. r.	n. r.	Data from IA2	[46]
Interruption	26.9 %					
Cycle delay	42.9 %					
Skipped cycle	9.3 %					

1 L = first-line therapy; ≥ 1 L = first-line therapy or higher; 2 L+ = second-line therapy or more; AE = adverse events; AI = aromatase inhibitor; ALT = alanine aminotransferase; Cape = capecitabine; CCI = Charlson Comorbidity Index; eCRF = electronic case report form; ET = endocrine therapy; EXE = exemestane; FACT-B = Functional Assessment of Cancer Therapy – Breast; FACT-G = Functional Assessment of Cancer Therapy – General; FU = follow-up; FUL = fulvestrant; GnRH = gonadotropin-releasing hormone; Gr. = grade; gQoL = global quality of life; hematolog. = hematological; HR = hazard ratio; IA = interim analysis; ILD = interstitial lung disease; ITT = intention-to-treat population; LET = letrozole; mDI = median dose intensity; mDOT = median duration of treatment; mFU = median follow-up; mos. = months; n = patients and/or number of patients according to study description; n. a. = not applicable; n. ach. = not achieved; n. r. = not reported; PAL = palbociclib; premenop. = premenopausal; pts. = patients; PRO = patient-reported outcome; RCT = randomized controlled study; RWE = real-world evidence; SAE = serious adverse event; sig = significant(ly); TAM = tamoxifen; TTD = time to deterioration; QoL = quality of life; Y = years(s)

tive analyses were included which used data from the Flatiron database (P-REALITY and P-REALITY X), the SEER Medicare database or the registry of the MD Anderson Cancer Center (▶ **Table 1**) [36, 37, 39]. These retrospective studies use established statistical methods to adjust the two treatment groups with regards to important patient characteristics and to thereby achieve better comparibility. While the SEER analysis focused on older patients and used multivariable Cox regression to control for imbalances in baseline characteristics, the other studies evaluated broad, heterogeneous patient populations. Adjustment was performed using stabilized Inverse Probability of Treatment Weighting (sIPTW) and Propensity Score Matching (PSM) [35, 36, 37, 39]. The multicenter studies P-REALITY and P-REALITY X analyzed the data of 1430 pre- and postmenopausal women who received letrozole alone or in combination with palbociclib and of 2888 postmenopausal women and men who were treated with AI alone compared to combination therapy with palbociclib, respectively [35, 36]. The two studies show a significant PFS and OS benefit for palbociclib plus ET both before and after adjustment (primary analysis with sIPTW; sensitivity analysis with PSM). The single-center study from the MD Anderson Cancer Center in Houston reported a heterogeneous picture for first-line therapy, with a significant PFS benefit for palbociclib plus AI versus AI alone, irrespective of adjustment (primary analysis: PSM; sensitivity analysis: IPTW) and a significant OS benefit after sIPTW but not after PSM. With regards to second-line treatment, palbociclib plus fulvestrant versus fulvestrant alone resulted in a significantly higher OS and PFS (▶ **Table 1**) [39].

This review aims to combine the extensive evidence on palbociclib from randomized clinical trials and real-world data, focusing on defined cohorts and clinical aspects such as safety, tolerability,

quality of life, and efficacy, and to discuss the overall picture with regard to specific questions.

Endocrine Pretreatment

The ABC5 Consensus recommendations differentiate between primary and secondary endocrine resistance [78]. At present, this has only limited impact on therapeutic treatment pathways. As endocrine resistance is associated with a shorter PFS and a poorer prognosis compared to endocrine sensitivity, the therapeutic need is still high [79, 80]. This is why the data on endocrine-sensitive and endocrine-resistant disease are discussed separately below (▶ **Table 2**).

Endocrine sensitivity and *de novo* metastasis

The ABC5 Consensus defines endocrine sensitivity as follows: recurrence > 12 months after completion of adjuvant endocrine therapy or > 6 months after the start of endocrine first-line mBC therapy [78]. A good response to endocrine-based therapy is expected for endocrine-sensitive tumors or *de novo* metastasis. Therefore, even though about 10 % of all newly diagnosed HR+/HER2− metastatic breast cancers show intrinsic (*de novo*) resistance, the two groups will be discussed together here [81].

RCTs

In the first-line therapy of postmenopausal patients with HR+/HER2− mBC, the combination of palbociclib and letrozole showed a statistically significant benefit for PFS (PALOMA-2, $p < 0.001$) compared to letrozole [12]. This benefit was observed in all of the investigated subgroups, including *de novo* metastasis and endocrine sensitivity. For *de novo* mBC, no difference was found with regards to OS. In contrast, a numerical improvement of median OS from 47.4 months in the placebo/letrozole arm to 66.3 months in the palbociclib/letrozole arm was observed for endocrine sensitivity (HR 0.73; 95 % CI: 0.53–1.01) [12, 19, 82]. This observation was confirmed by the prespecified pooled OS analysis of patients with endocrine-sensitive tumors from the PALOMA-1 and 2 trials (HR 0.74; 95 % CI: 0.55–0.98) [82]. Moreover, the phase-III PALOMA-4 trial confirmed the results for PFS in an Asian postmenopausal cohort [23].

In the PALOMA-3 trial, pre- and postmenopausal patients were treated after failure of prior ET. For advanced stage disease, one prior chemotherapy and any number of endocrine therapies were permitted. This means that out of all the CDK4/6 inhibitor approval studies, PALOMA-3 included the most heavily pre-treated study cohort. Endocrine sensitivity or resistance were stratification factors. The combination of palbociclib and fulvestrant resulted in a statistically significant PFS benefit for patients with endocrine-sensitive tumors compared to fulvestrant alone [10]. The median OS in the palbociclib/fulvestrant arm was 39.7 months compared to the placebo/fulvestrant arm with 29.7 months (HR 0.72; 95 % CI: 0.55–0.94) [20].

In the phase-II trial PARSIFAL, 486 patients with endocrine-sensitive or endocrine-naive mBC received palbociclib plus fulvestrant or palbociclib plus letrozole as first-line therapy. The primary endpoint PFS was 32.8 months in median under palbociclib/letrozole compared to 27.9 months under palbciclib/fulvestrant (HR 1.13; 95 % CI: 0.89–1.45; $p = 0.321$). With hazard ratios of 1.14 and 1.13 respectively, the PFS results for endocrine-sensitive and *de novo* metastatic tumors did not differ from that of the overall group. The 3-year OS rates were 77.1 % versus 79.4 % [24]. The follow-up study PARSIFAL-Long with 389 patients from PARSIFAL provided results with a longer median follow-up of about 5 years [25]. The median OS of 61.9 months for the palbociclib/letrozole arm and 68.5 months for the palbociclib/fulvestrant arm (HR 0.94; 95 % CI: 0.72–1.23; $p = 0.635$) was comparable to that reported for other CDK4/6 inhibitor trials [25, 50, 51].

Endocrine sensitivity and resistance was also a stratification factor in the phase-III PEARL study. In patients with endocrine sensitivity who had previously experienced disease progression under AI, combination therapy with palbociclib had a similar PFS to that reported for oral chemotherapy. A trend in favor of the endocrine combination therapy was observed for OS (HR 0.89; 95 % CI: 0.70–1.13) [28].

RWD

In addition to data from RCTs, there is also extensive evidence from real-world setting (▶ **Table 2**).

In a retrospective evaluation of the SEER Medicare database, patients aged ≥ 65 years with HR+/HER2− *de novo* mBC were analyzed [37]. The addition of a CDK4/6 inhibitor (palbociclib in about 90 % of cases [38]) to ET during first-line therapy resulted in a statistically significant OS benefit ($p < 0.0001$). This benefit was still apparent after adjustment of important characteristics using Cox regression analysis (HR 0.59; 95 % CI: 0.42–0.82) [37].

P-REALITY X retrospectively evaluated a large first-line cohort consisting of 2888 postmenopausal women and men. Both before and after adjustment with sIPTW and PSM, a statistically significant OS benefit (primary endpoint) was found for palbociclib plus AI compared to AI alone with regards to *de novo* metastasis and also endocrine-sensitive tumors (defined here as time from initial diagnosis to diagnosis of metastasis of more than 5 years) [36]. These subgroups also benefited from endocrine combination therapy with regards to the secondary endpoint rwPFS [36]. The retrospective first-line study P-REALITY with pre- und postmenopausal patients showed comparable results: for endocrine-sensitive or *de novo* mBC, the addition of palbociclib to letrozole was associated with a prolongation of rwPFS (primary endpoint) and OS (secondary endpoint) (unadjusted and after sIPTW and PSM) [35]. A retrospective evaluation of data from Danish patients with endocrine sensitive tumors showed a mOS of 56.9 months (95 % CI: 52.5–NA) for first-line treatment with palbociclib plus AI [83].

Patients aged ≥ 70 years with endocrine-sensitive tumors or *de novo* metastasis were analyzed in cohort A of the French real-world study PalomAGE. A median PFS of 28.1 months confirmed the results of RCTs and RWE also for older patients [49].

CONCLUSION

Real-world evidence has confirmed and expanded the consistent results of RCTs on the efficacy of a endocrine-based combination therapy with palbociclib for *de novo* metastasis or endocrine sensitivity. Patients with endocrine sensitive tumors benefit from prolongation of PFS and OS.

Endocrine resistance

Up to 50 % of patients with HR+/HER2− mBC do not respond initially to ET or develop an endocrine resistance over the course of treatment [84, 85, 86, 87, 88, 89, 90]. However, the data on the use of CDK4/6 inhibitors in cases with endocrine resistance (recurrence ≤ 12 months after the completion of adjuvant endocrine therapy or ≤ 6 months after the start of endocrine first-line mBC therapy) is still comparatively limited. These patients are often excluded from RCTs or underrepresented. Moreover, clinical trials do not always follow the statements and definitions of the Consensus guideline.

RCTs

Endocrine resistance or sensitivity was a stratification factor in the phase-III trials PALOMA-2, 3, and 4 and the inclusion of patients with endocrine-resistant tumors was therefore accepted [10, 12, 23]. The PALOMA-3 study investigated a heavily endocrine pretreated cohort; 54 % of patients who were treated with palbociclib had received at least two prior endocrine therapies. A non-significant PFS benefit was shown for the addition of palbociclib to fulvestrant for the 111 patients with endocrine-resistant tumors (HR 0.64; 95 % CI: 0.39–1.07) [10]. However, this did not translate to a prolongation of OS (HR 1.14; 95 % CI: 0.71–1.84) [20].

In the first-line study PALOMA-2 about 22 % of patients had endocrine-resistant tumors. For this subgroup, endocrine combination therapy resulted in a statistically significant PFS benefit when compared to ET alone (HR 0.50; 95 % CI: 0.33–0.76) [12] but not in an OS benefit (HR 1.02; 95 % CI: 0.66–1.58) [19]. In contrast, patients with endocrine-resistant tumors experienced no significant PFS benefit from the addition of palbociclib to letrozole in PALOMA-4 (HR 0.84; 95 % CI: 0.56–1.28) [23].

Sensitivity to a previous ET was also a stratification factor in the PEARL study. Similar to the total cohort, patients with endocrine resistant tumors experienced no difference in PFS or OS favoring a specific therapeutic modality [28, 29]. These observations were confirmed by the Young-PEARL trial with a largely tamoxifen-resistant cohort (palbociclib plus ET: 83 %; capecitabine: 90 %) [26].

RWD

The two retrospective studies P-REALITY and P-REALITY X evaluated 234 and 620 patients, respectively, in whom advanced disease was diagnosed 1 to 5 years after the initial diagnosis [35, 36]. The results for the subgroup diagnosed with metastasis within one year are not presented here because of the small sample size. The P-REALITY study found a statistically significant benefit for rwPFS and OS for the subpopulation treated with palbociclib and letrozole (after sIPTW and PSM) [35]. These findings could not be confirmed by the P-REALITY X study. There was a numerical trend in favor of the combination therapy with palbociclib and AI for rwPFS, but not for OS [36].

The cohort B of the PalomAGE study was comprised of patients aged ≥ 70 years with endocrine resistance and/or previous therapy for advanced stage disease who received palbociclib plus ET. The median time to treatment failure was 11.6 months [47].

CONCLUSION

Although patients with endocrine-resistant tumors were included in the PALOMA study program, the overall evidence from RCTs and the real-world regarding efficacy/effectiveness of palbociclib-based therapy is limited. The therapeutic need remains high.

Safety, Tolerability and Quality of Life

An evaluation of the PRAEGNANT registry has shown that in the years 2018 to 2022, about 75 % of patients with HR+/HER2− mBC received endocrine-based combination therapy with a CDK4/6 inhibitor. Endocrine monotherapy (10 %) or chemotherapy (15 %) was administered significantly less often [8]. These data reflect that in this treatment context, maintaining quality of life during treatment is also of central importance nowadays, alongside efficacy and safety (▶ **Table 3**).

Safety profile and tolerability

RCTs

For palbociclib, the pivotal RCTs PALOMA-1, 2, and 3 showed a consistent and well-manageable safety profile (▶ **Table 3**) [10, 11, 12]. This was confirmed in a pooled analysis of the three studies with 872 patients and a five year follow-up [5, 59].

Irrespective of the severity grade, the most common adverse events (≥ 20 %) were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, diarrhea, alopecia and thrombocytopenia. The most common (≥ 2 %) adverse events with a severity grade ≥ 3 were neutropenia, leukopenia, infections, anemia, elevated aspartate aminotransferase (AST) levels, fatigue, and elevated alanine aminotransferase (ALT) levels [5]. Although grade 3/4 neutropenia was more common in the palbociclib arm than in the control arm (approx. 65 % vs. approx. 1 %, respectively), the rate of febrile neutropenia (< 2 %) and the rate of concurrent occurence of viral infections (0.2 %) was generally low in PALOMA-2 and 3 [59]. Treatment discontinuations due to adverse events were required in 4–13 % of patients receiving palbociclib plus ET (PALOMA-1, 2, and 3) [10, 11, 12].

Two clinical trials provided information about the safety and tolerability of palbociclib compared to oral chemotherapy. In the PEARL trial, palbociclib plus ET was better tolerated than capecitabine with comparable efficacy and a lower rate of therapy discontinuations. Under palbociclib plus ET, the most serious grade ≥ 3 adverse events were primarily hematological (neutropenia, leukopenia, thrombocytopenia), whereas under therapy with capecitabine, symptomatic adverse events such as hand-foot symdrome, diarrhea or fatigue occured more frequently and directly affected

quality of life [28]. The findings on side effects of all degrees of severity in the Young-PEARL trial point consistenly in the same direction [55].

In the PALOMA-2 trial, the effect of palbociclib on the frequency-corrected QT-interval (QTc) was evaluated in 77 patients. At the recommended dose of 125 mg per day (3/1 schedule), palbociclib did not result in a clinically relevant prolongation of the QTc interval [5, 91]. According to the prescribing information, there are no warnings for combining palbociclib with ET when administered concurrently with QTc interval-prolonging medications. In line with this, the asian phase-II study PATHWAY confirmed the efficacy and safety of palbociclib when combined with tamoxifen compared to tamoxifen alone [30].

RWD

The prospective Italian-German non-interventional study MARIA emphasizes the clinical relevance of these data. At the time of study enrollment more than half of the women with HR+/HER2− mBC had ≥ 1 concomitant medication or comorbidity that could increase the risk of QTc interval prolongation or of torsade-de-pointes tachycardia [92].

Further RWD have confirmed the safety and tolerability of palbociclib in real-world settings (▶ **Table 3**). Different studies showed that therapy is predominantly managed through dose modifications, which is consistent with data from RCTs. The treatment discontinuation rate was also low in clinical routine (3.3 %–13 %) [40, 43, 44, 46, 48]. The prospective NIS PalomAGE, which evaluated women ≥ 70 years with HR+/HER2− mBC, provided an important contribution [48]. Despite a median age of 78 years, no new safety signals were found and the therapy discontinuation rate after six months was comparable to that reported for RCTs [47].

The consistent safety profile observed in both, RCTs and RWD, is also reflected by the fact that only few new adverse events were added to the prescribing information after approval of palbociclib, including interstitial lung disease (ILD)/pneumonitis) (grade 3/4: 0.1 % = rare), cutaneous lupus erythematosus (grade 3/4: 0.0 % = very rare), and venous thromboembolism (grade 3: 1.3 % = common; grade 4: 0.8 % = occasionally) [5]. The only routinely required form of monitoring is a monthly complete blood count. Additional precautions propose for example that patients should be monitored for signs and symptoms of infection, ILD/pneumonitis and venous thromboembolism [5].

Quality of life

RCTs

Quality-of-life data from RCTs are available for PALOMA-2 and 3 (▶ **Table 3**). In PALOMA-2, the quality of life was maintained under therapy with palbociclib plus letrozole, and there were no differences compared to letrozole alone [22, 57]. Additionally, a significant improvement in physical pain was registered over the course of treatment with endocrine combination therapy ($p = 0.018$) [57]. Patients without disease progression showed significantly delayed deterioration of quality of life compared to patients with disease progression (HR 0.53; $p < 0.001$) [57].

PALOMA-3 demonstrated a significantly longer time to deterioration of global quality of life with palbociclib plus fulvestrant compared to fulvestrant alone ($p = 0.031$) as well as a significant improvement in pain scores compared to baseline ($p = 0.001$) [58]. There were no significant differences between treatment arms in other functional domains or in breast or arm symptoms [58].

Additionally, the studies Young-PEARL and PEARL have shown clear benefits in quality of life for the combination therapy with palbociclib when compared to a chemotherapy with capecitabine [26, 55].

RWD

Several prospective real-world studies have provided evidence on quality of life under palbociclib combination therapy [44, 47, 49, 60]. The POLARIS study confirmed that quality of life under palbociclib is maintained across all assessed symptom and functional scales, including cognitive, emotional, physical and social parameters, even during routine treatment [60].

The MADELINE study has shown that physical and mental health and the self-reported quality of life of the female patients remained constant over the course of 6 months of endocrine-based therapy with palbociclib. Moreover, therapy did not appear to have a negative effect on social and family life or on the physical activity, energy, stamina, or productivity of patients. 75–90 % of patients reported no or moderate interference. These results were reported, irrespective of whether patients experienced neutropenia or not [44]. The PalomAGE study confirmed and expanded findings from the PALOMA-2 and 3 trials for older female patients (≥ 70 years) (s. also the chapter on older patients below) [47, 49].

Outlook: innovative health applications as treatment support

There are increasing numbers of eHealth smartphone applications (apps) available for oncological patients. These apps may ask questions about the patient's current health status and symptoms, with the aim of improving the patient's quality of life.

The randomized phase-IV trial PreCycle investigated the effects of the interactive autonomous eHealth app CANKADO PRO-React on the quality of life of patients with HR+/HER2− mBC during endocrine-based therapy with palbociclib [33]. Compared to patients who were only able to access the basic functions of the app (CANKADO-inform), the time to deterioration of quality of life (TTD QoL, primary endpoint) was significantly longer for patients in the CANKADO-active arm (HR 0.70; 95 % CI: 0.51–0.96; $p = 0.03$) [34]. Patients in the CANKADO-active arm had a more favorable HR of 0.67 (95 % CI: 0.46–0.97; $p = 0.04$) for the time until the first serious adverse event (SAE) occurred and a significantly lower probability of suffering an SAE overall than patients in the CANKADO-inform arm [93]. PFS and OS did not differ significantly between the two treatment arms [33]. PreCycle is therefore the first randomized multicenter study in breast cancer to demonstrate a significant clinical benefit of an interactive autonomous eHealth app for mBC patients receiving an oral tumor therapy.

CONCLUSION

The safety profile and the associated therapy management are essential to prevent patients from discontinuing therapy. In RCTs and RWE, palbociclib demonstrated a consistent safety profile with few side effects. With 2–13 %, the number of discontinuations due to adverse events is low. Patients need to be informed about the most common side effects (usually asymptomatic hematological toxicities), particularly the infection risk associated with neutropenia as well as rare adverse events such as ILD. The requirements for routine monitoring under palbociclib treatment are low. The stable, and in some cases improved, quality of life during treatment can be interpreted as a manifestation of a manageable toxicity profile and, in many cases, better symptom control. There are clear advantages in terms of quality of life for palbociclib plus ET compared to chemotherapy.

Digital healthcare apps can offer patients additional support to manage their therapy. They can contribute to maintain patients' quality of life and reduce therapeutic toxicity.

To sum up the existing extensive data from RCTs and the real-world setting, palbociclib is a generally well tolerated therapeutic option with low therapy discontinuation rates and maintainance of patients' quality of life.

Special Patient Populations

RCTs are indispensible when drawing causal conclusions about therapeutic interventions. In clinical practice, many patients are treated, who are not eligible for RCTs or who are underrepresented, resulting in a lack of evidence-based guideline recommendations for them [94]. This group includes patients with comorbidities and/or patients of advanced age. For breast cancer, this group also includes rarely affected male patients [95]. For palbociclib treatment, there is extensive information available from clinical routine for these special patients populations, which complements and confirms findings from RCTs (▶ **Table 4**).

Older patients

Higher age is the most important risk factor for the increasing incidence of breast cancer. At least half of all cases occur in patients aged 65 years and above and more than 25 % of patients are aged 75 or older [95, 106, 107]. Age-specific characteristics such as comorbidities, immune deficiencies, polypharmacy, reduced organ functions, differences in metabolization or frailty may significantly affect the outcomes of cancer therapies. To prevent over- and undertreatment, it is therefore essential to be familiar with the data on this special population [108].

RCTs

Despite the high incidence of breast cancer in older patients, there are only limited data available from RCTs for this patient population. In PALOMA-1, 2, and 3, the median age was 57–62 years and only 9.5 % of patients were aged 75 or older [8, 10, 12, 109]. The percentage of female patients with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of ≥ 2 was very low, at 0 % to 2 % [10, 11, 12].

In a pooled analysis of PALOMA-1, 2, and 3, a prolonged median PFS was observed for female patients aged 65-74 years receiving palbociclib plus letrozole or plus fulvestrant compared to ET alone ($p < 0.016$ and $p < 0.001$, resp.). The same applied to female patients aged ≥ 75 years under palbociclib plus letrozole therapy ($p < 0.001$) [96]. In the pooled analysis, the palbociclib exposure was comparable between age groups. Although myelosuppression occurred more frequently in patients aged over 75 years, the grade ≥ 3 rates were comparable across all age groups. The febrile neutropenia rate was low (0.9–2.4 %), and no new safety signals were observed. The overall safety profile was consistent with that of younger patients. The functional status and quality of life reported by patients aged 65–74 years and ≥ 75 years was maintained, and certain aspects were improved (▶ **Table 3**) [96].

RWD

Several real-world studies have focused on the use of palbociclib in older patients (▶ **Table 4**).

Effectiveness: The one-arm prospective study PalomAGE observed exclusively female patients aged ≥ 70 years (median age: 78 Y). About 68 % were characterized as potentially frail and 18 % had an ECOG-PS ≥ 2. The results confirmed that palbociclib plus ET is an effective therapeutic option for older patients with mBC: patients with endocrine sensitivity during first-line therapy had a median PFS of 28.1 months [47, 48, 49]. These observations were supported by the findings of the prospective NIS PERFORM: female and male patients from Germany and Austria aged ≥ 75 years presented more frequently with *de novo* metastasis (44.3 %) and an ECOG-PS ≥ 2 (21.6 %) compared to the younger control group. No differences could be observed in terms of tumor response or 6- and 12-months PFS rates compared to the overall population [46]. A British retrospective study with female patients aged ≥ 75 years (median age: 78 years, 19.6 % with ECOG-PS ≥ 2) who received palbociclib plus AI as first-line therapy confirmed these results. The 12- and 24-month PFS rates were 75.9 % and 64.9 %, respectively, and the OS rates were 85.1 % and 74.0 % [40].

Three large retrospective analyses compared the effectiveness of palbociclib or a CDK4/6 inhibitor plus ET vs. ET alone. In P-REALITY, a specific analysis was carried out for female patients aged ≥ 65 years (median age: 74.0 years). After statistical adjustment using sIPTW, the median PFS was 22.2 versus 15.8 months ($p < 0.0001$), and a significant OS benefit from the addition of palbociclib to letrozole was demonstrated ($p < 0.0001$) [97]. The superiority of the combination of palbociclib plus ET compared to ET alone with regards to PFS and OS was confirmed in an analysis of the P-REALITY X study observing a large cohort aged ≥ 75 years: median OS, median PFS, and time to first subsequent chemotherapy were significantly prolonged by the addition of palbociclib to an AI ($p = 0.0007$; $p = 0.0021$; $p = 0.0014$ after sIPTW) [98]. A specific analysis of the SEER Medicare database compared the data of women aged ≥ 65 years with *de novo* HR+/HER2− mBC who were treated with a CDK4/6 inhibitor plus AI (ca. 90 % palbociclib) or with AI monotherapy [37, 38]. The analysis demonstrated a significant advantage for the endocrine based combination therapy: the

▶**Table 4** Review of study results for selected patient groups: older patients, comorbid patients, men.

Patient group information	PFS, HR (95% CI)	OS, HR (95% CI)	Quality of life (QoL)	Comments	Ref.
Older female patients: RCT					
Analysis PALOMA-1, 2, 3 (PAL+LET vs. LET,1 L; PAL+FUL vs. FUL, ≥ 1 L; age-specific analysis ≥ 75 Y vs. 65–74 Y vs. < 65 Y)					
PAL+ET vs. ET, ≥ 75 Y: n = 83/32; *PAL+ET vs. ET, 65–74 Y:* n = 221/129; *PAL+ET vs. ET, < 65 Y:* n = 310/183	*≥ 75 Y vs. 65–74 Y vs.< 65 Y PAL+LET vs. LET:* HR 0.31 (0.16–0.61)/0.66 (0.45–0.97)/0.50 (0.40–0.64) *PAL+FUL vs. FUL:* HR 0.59 (0.19–1.8)/0.27 (0.16–0.48)/0.59 (0.46–0.75)	n. r.	FACT-B (PALOMA-2), EORTC-QLQ-30,-QLQ-BR23 (PALOMA-3); 65–74 Y and ≥ 75 Y: maintenance of QoL; PALOMA-3, vs. FUL: sig. improvement of loss of appetite (> 75 Y); sig. delayed TTD for pain (65–74 Y)	Efficacy analysis: PALOMA-1, 2 pooled, PALOMA-3; safety analysis: all 3 studies pooled; safety profile: consistent (anemia ≥ grade 3: 8.4%/4.5%/4.2%; myelosuppression ≥ 3 comparable; febrile neutropenia 2.4%/0.9%/1.2%; discontinuation rate: 6.0%/ 5.4%/1.6%; other data: PK, AEs; dose intensity	[96]
Older male and female patients: RWE					
PalomAGE (PAL+AI/FUL, 1 L/≥ 1 L, women ≥ 70 Y, n = 767)					
Cohort A: PAL + AI (ET-sensitive and 1 L); cohort B: PAL + FUL (ET-resistant and/or ≥ 2 L); median age 78 Y, ca. 45% ≥ 80 Y; ECOG-PS ≥ 2: 15–20%, potentially frail (G8): 68%	*Cohort A:* 28.1 mos. *Cohort B:* 11.6 mos. (mTTF)	n. r.	EORTC QLQC30 & ELD14 (special survey of older pts. with cancer); QoL maintained; cohort B: reduction of symptoms on pain scale	Prospective; QoL survey: baseline and after 18 mos. (cohort A) or after 3 and 6 mos. (cohort B); no new safety signals; discontinuation rate (at patient's request) 6.7% (cohort A) and 2.9% (cohort B)	[47, 48, 49]
P-REALITY (PAL+LET vs. LET, 1 L; specific evaluation of patients ≥ 65 Y; n = 406/390)					
Median age: 72/77 Y, after sIPTW: 74 Y	*ITT:* 22.2 vs. 15.8 mos. aHR 0.59 (0.47–0.74) p < 0.0001 *65–74 Y:* HR 0.71 (0.52–0.97) *≥ 75 Y:* HR 0.51 (0.36–0.71)	*ITT:* n. ach. vs. 43.4 mos.; aHR 0.55 (0.42–0.72) p < 0.0001 *65–74 Y:* HR 0.76 (0.52–1.11) *≥ 75 Y:* HR 0.47 (0.32–0.70)	n. r.	Adjustment: none and after sIPTW; mFU: 20.2 vs. 18.6 mos.; other data: rwBTR	[97]
P-REALITY X (PAL+AI vs. AI, 1 L; specific evaluation of female and male pts. ≥ 75 Y; n = 313/648)					
Median age: 80 Y, after sIPTW: 80 Y	*ITT:* 20.0 vs. 15.0 mos. aHR 0.72 (0.59–0.89) p = 0.0021 Shown here: adjusted (sIPTW)	*ITT:* 43.0 vs. 32.4 mos. aHR 0.66 (0.51–0.84) p = 0.0007 Shown here: adjusted (sIPTW)	n. r.	Adjustment: none, PSM, sIPTW; mFU: 23.7 vs. 21.4 mos.; other data: TTC, initial dose (red. in 24.8%), dose adjustments, subsequent therapies	[98]
SEER analysis (CDK4/6i+ET vs. ET, 1 L; postmenop. women ≥ 65 Y, *de novo* mBC)					
1 L: n = 169/461; ≥ 75 Y: 49.12% vs. 59% 2 L: n = 118/86	n. r.	1 L: aHR 0.59, (0.42–0.82) 2 L: aHR: 0.42 (0.24–0.75) Shown here: adjusted (Cox)	n. r.	SEER Medicare database (USA), here after multivariable Cox regression analysis; CDK4/6i +ET: ca. 90% PAL+ET in 1 L [38] (2 L: percentage of PAL n. r.)	[37]

▶Table 4 continued

Patient group information	PFS, HR (95% CI)	OS, HR (95% CI)	Quality of life (QoL)	Comments	Ref.
UK study (PAL+AI, 1 L; female patients ≥ 75 Y; n = 276)					
Median age 78 Y; ECOG PS ≥ 2: 19.6%; ACCI > 10: 31.5%	*12 mos. PFS rate:* 75.9% *24 mos. PFS rate:* 64.9%	*12 mos. OS rate:* 85.1% *24 mos. OS rate:* 74.0%	n. r.	PFS and OS with vs. without dose delay; multivariable Cox regression analysis: PS, ACCI, number of metastasis sites as independent predictors for PFS, baseline ACCI for development and severity of neutropenia	[40]
POLARIS (PAL+ET, 1 L, 2 L+; subgroup analysis of female and male patients ≥ 70 Y; n = 287 [ITT n = 1282])					
1 L n = 219; 2 L+ n = 68 Median age: 75 Y, ca. 5% ≥ 85 Y; ECOG PS ≥ 2: 10.4%, potentially frail (G8): 59%	n. r.	n. r.	n. r.	Geriatric assessments: stable G8 (n = 248) and ADL scores (n = 256) over time (baseline, 6 mos.); 96.5% with comorb.; no new safety signals; ≥ 70 Y vs. < 70 Y: 12.2% vs. 4.7% red. initial dose; 16% vs. 9.7% dose modification; 74.2% vs. 46.2% hypertension	[99]
PERFORM (PAL+ET, 1 L; subgroup analysis ≥ 75 Y; n = 185)					
Median age: 80 Y, ECOG PS ≥ 2: 21.6%	*12 mos. PFS rate* *< 75 Y:* 71.1% (65.5–75.9) *≥ 75 Y:* 73.4% (64.9–80.2)	n. r./immature	n. r./immature	Pts. ≥ 75 Y vs. < 75 Y: ORR, CBR comparable, therapy modifications and discontinuation due to AEs numerically more common if ≥ 75 Y; dose adjustments 45.4% vs. 31.4%; discontinuation rates comparable	[46]
Comorbid female patients: RCT					
PALOMA-2 (PAL+LET vs. LET, 1 L; analysis according to comorbidity)					
Comorbidity (baseline): 58.6% musculoskeletal, 57.4% vasc./cardiac, 41.4% GI, 38.9% metabolic	*GI:* HR 0.57 (0.42–0.78) *musculoskeletal:* HR 0.53 (0.41–0.69) *metabolic:* HR 0.62 (0.44–0.87) vasc./cardiac: HR 0.51 (0.39–0.66)	n. r.	n. r.	Ad hoc analysis; side effects profile and dose modifications consistent for the different comorb. and compared to ITT	[100]
Comorbid female and male patients: RWE					
POLARIS (PAL+ET, 1 L, 2 L+; comorb.-specific analysis; n = 1250)					
Comorb. (baseline): median 2 (0–9); CCI 1–2: 54.6%, CCI ≥ 3: 15.3%; vasc.: 54.3%, psych.: 26.6%, blood/lymphatic vascular system: 18.4%, metabolic/nutritional: 18.2%	*mPFS: CCI 0 vs. 1–2 vs. ≥ 3:* *1 L:* 20.3 vs. 24.2 vs. 16.8 mos. *2 L+:* 13.7 vs. 13.2 vs. 14.9 mos.	*mOS: CCI 0 vs. 1–2 vs. ≥ 3:* *1 L:* 48.8 vs. n. ach. vs. 34.8 mos. *2 L+:* 39.0 vs. 37.9 vs. 31.6 mos.	Global QoL – CCI 0 vs. 1–2 vs. ≥ 3: maintained QoL under PAL + ET in all 3 groups QoL red. in CCI ≥ 3 vs. 0 at baseline	Some subgroups very small (CCI ≥ 3 2 L n = 53); no age adjustment; for information on efficacy with regards to investigated comorb., see [13]	[101, 102]

▶**Table 4** continued

Patient group information	PFS, HR (95% CI)	OS, HR (95% CI)	Quality of life (QoL)	Comments	Ref.
Analysis ADELPHI DSP (1 L HR+ HER2− mBC; focus on comorb.; n = 1.036)					
Median age: 64 Y, 26% ≥ 70 Y; ECOG PS ≥ 2: 17%; 46% ≥ 1 comorbidity; treatment 1 L: 73% CDK4/6i, 12% CTx, 9% ET-mono, 6% other	n. r.	n. r.	n. r.	Retrospective analysis; comorb. with mBC diagnosis (n = 1015): 35% cardiovasc., 11% metabolic, 5% GI, 3% organ, 1% neurological; use of CDK4/6i: 73% ITT vs. 61% CCI ≥ 3; Europe (also in D)	[103]
P-REALITY X (PAL+AI vs. AI, 1 L; specific evaulation of female and male patients with cardiovascular disease; n = 192/144)					
After sIPTW: median age: 73.3 Y/73.6 Y; ECOG PS ≥ 2: 26.6 /25.0%	*mPFS:* 20.0 vs. 12.5 mos. aHR 0.68 (0.51–0.90) p = 0.007 Shown here: adjusted (sIPTW)	*mOS:* 40.7 vs. 26.5 mos. aHR 0.73 (0.554–0.997) p = 0.048; Shown here: adjusted (sIPTW)	n. r.	Adjustment: none and after sIPTW; mFU: 19.7 vs. 18.9 mos.; other data: type of second-line therapy	[104]
Male patients: RWE					
IQVIA, Pfizer safety database & Flatiron analysis (PAL+ET, 1 L, 2 L; men)					
Effectiveness 1 L PAL+LET vs. LET (n = 26/63), 1 L PAL+ET vs. ET (n = 37/214), 2 L PAL+FUL vs. FUL (n = 10/24); safety analysis PAL+ET: n = 362	*mDOT* *1 L PAL+LET vs. LET:* 9.4 vs. 3.0 mos. *1 L PAL+ET vs. ET:* 8.5 vs. 4.3 mos. *2 L PAL+FUL vs. FUL:* 2.7 vs. 1.8 mos.	n. r.	n. r.	Retrospective analysis (3 datasets on efficacy and/or safety); no new safety signals, AEs> 10%: fatigue (28%), neutropenia (17%), lower WBC (15%), nausea (12%), diarrhea (10%); PFS n. r.	[71]
P-REALITY X (PAL+AI vs. AI, 1 L; men [subgroup analysis])					
PAL+AI n = 17/1.572 (1.1%) men vs. AI n = 12/1.137 (1.0%) men	aHR 0.11 (0.03–0.45) Shown here: adjusted (sIPTW)	aHR 0.11 (0.01–0.95) Shown here: adjusted (sIPTW)	n. r.	Flatiron database (USA); adjustment: none, sIPTW and PSM; after PSM: PFS (aHR 0.25 [0.05–1.31]), OS (aHR 0.42 [0.05–3.76])	[36]
POLARIS (PAL+ET, 1 L, 2 L+; men [subgroup analysis]; n = 15)					
Median age: 66 Y; 33% ≥ 70 Y; ECOG PS 2: 13.3%; ≥ 1 comorbidity 93.3%; visceral metastasis: 46.7%; 1 L: 60.0%; ≥ 2 L: 40%	*mPFS* *1 L:* 21.8 mos. (4.8–38.0) *2 L+:* 14.8 (5.7–n. ach.) *all pts.:* 19.8 (7.4–38.0)	n. r.	EORTC QLQ-C30 Maintained QoL under therapy	mFU 24 : 7 mos.; 87% with initial dose of 125 mg; mDOT 20 cycles; Gr. ≥ 3 AE: 73%; consistent safety profile; 2 pts. discontinued therapy due to AEs; mPFS consistent for patient population	[105]

1 L = first-line therapy, 2 L+ = second-line therapy or later; ACCI = age-adjusted Charlson Comorbidity Index; AEs = adverse events; aHR = adjusted HR; AI = aromatase inhibitor; Cape = capecitabine; CBR = clinical benefit rate; CCI = Charlson Comorbidity Index; CI = confidence interval; CDK4/6i = CDK4/6 inhibitor; CTx = chemotherapy; D = Germany; DOT = duration of treatment; ET = endocrine therapy; ET-mono = endocrine monotherapy; FUL = fulvestrant; Gr. = grade; HER2− = Her2-negative; HR+ = hormone receptor-positive; HR = hazard ratio; GI = gastrointestinal; IA = interim analysis; ITT = intention-to-treat population; comorb. = comorbidities; LET = letrozole; mBC = metastatic breast cancer; mFU = median follow-up; mos. = month(s); mOS = median overall survival; mPFS = median progression-free survival; mTTF = median time to treatment failure; n = number of patients according to study description; n. ach. = not achieved; n. r. = not reported; OS = overall survival; ORR = objective response rate; PAL = palbociclib; PFS = progression-free survival; phys. = physical; PK = pharmacokinetic analyses; postmenop. = postmenopausal; PS = performance status; PSM = propensity score matching; psych. = psychological; pts. = patients; red. = reduced; RCT = randomized controlled study; rwBTR = best real-world tumor response; RWE = real-world evidence; sig. = significant(ly); sIPTW = stabilized inverse probability of treatment weighting; TTC = time to first subsequent chemotherapy; TTD = time to deterioration; USA = United States of America; vasc. = vascular; WBC = white blood cells; Y = year(s)

3-year OS rate for first-line treatment with a CDK4/6 inhibitor plus ET was 73.0% compared to 49.1% under ET alone ($p < 0.0001$). In a multivariable Cox regression analysis, the combination therapy was associated with a 41% reduced mortality rate compared to ET alone (adjusted HR 0.59; 95% CI: 0.42–0.82). A benefit for CDK4/6 inhibitor-based therapy was also found for second-line treatment (adjusted HR 0.42; 95% CI: 0.24–0.746) [37].

Safety and tolerability: The PalomAGE trial confirmed the well-known safety and tolerability profile of palbociclib in female patients aged ≥ 70 years. Therapy discontinuation rates due to adverse events were in the single-digit range both for patients with endocrine-sensitive tumors undergoing first-line therapy (cohort A) and for patients with endocrine-resistant tumors and/or prior endocrine treatment for mBC (cohort B) (mFU 6.7 months) [48]. Only a few patients discontinued therapy at their own request (A: 6.7% after 18 months; B: 2.9% after 6 months) [47, 49]. The POLARIS study demonstrated that patients aged ≥ 70 years required dose delays and modifications more often than younger patients [99]. This observation was confirmed in the PERFORM study for subgroups aged ≥ 75 years and < 75 years [46]. In a British study of female patients aged ≥ 75 years, dose reduction or delay was required in 50.7% and 59.3% of cases. One important finding was that dose modifications were not associated with a loss of effectiveness. The low hospitalization rate due to toxicity of 9.6% highlights the good tolerability despite specific patient characteristics, such as older age, higher percentage of patients presenting with comorbidities, ECOG-PS ≥ 2 and frailty [40]. No new safety signals were identified for older patients [40, 48, 99].

Quality of life: PalomAGE provided robust data on the quality of life of female patients aged ≥ 70 years by also including a questionnaire specifically designed for older patients with cancer (EORTC ELD-14) in addition to the standard EORTC QLQ-C30 questionnaire. Maintainance of quality of life in functional and global domains was demonstrated. Notably, a clinically relevant pain reduction was observed for patients with endocrine resistance or pretreatment for mBC (cohort B), which was in accordance to findings reported in the PALOMA-3 trial [47, 48, 49, 92]. In a subgroup analysis of the POLARIS study, it was demonstrated that the ECOG-PS, geriatric assement (G8 screening tool) and activitites of daily living (ADL) score were maintained for 287 patients aged ≥ 70 years during the first 6 months of palbociclib based treatment [99].

CONCLUSION

The extensive evidence confirms the efficacy, safety, and tolerability of a palbociclib treatment for older and often preburdened patients who are usually underrepresented in RCTs. A dose modification in older patients does not appear to be associated with reduced effectiveness. Despite the addition of palbociclib to ET, quality of life is maintained during treatment and is not worsening compared to endocrine monotherapy.

Patients with comorbidities

Taking account of the comorbidities of patients with mBC is an important part of clinical routine. The findings and observations about the combination therapy with palbociclib of comorbid patients are therefore particularly important.

RCTs

According to a post hoc analysis of the PALOMA-2 trial, palbociclib plus letrozole prolonged PFS compared to placebo plus letrozole, irrespective of concomitant vascular/cardiac, musculoskeletal, metabolic, or gastrointestinal disease [100]. Adverse events and dose modifications due to adverse events under palbociclib plus letrozole were comparable for all subgroups with comorbidities and consistent with the overall population. At the start of the study, 41.4% of enrolled patients had pre-existing gastrointestinal disorders, 58.6% presented with musculoskeletal disorders, 38.9% had metabolic disorders and 57.4% had vascular/cardiac disease [100].

RWD

The fact that the risk for comorbidities increases with age was also shown in the real-world study PalomAGE which investigated palbociclib use in older patients: 86.7% of patients had an adjusted Charlson Comorbidity Index (CCI) score ≥ 4 [47]. According to the prospective non-interventional study POLARIS, the CCI score appears to correlate with global quality of life and treatment outcome. A CCI ≥ 3 tends to be associated with a lower rwPFS, OS and a poorer quality of life. At the same time, quality of life was maintained under palbociclib based therapy, irrespective of the CCI score [101, 102].

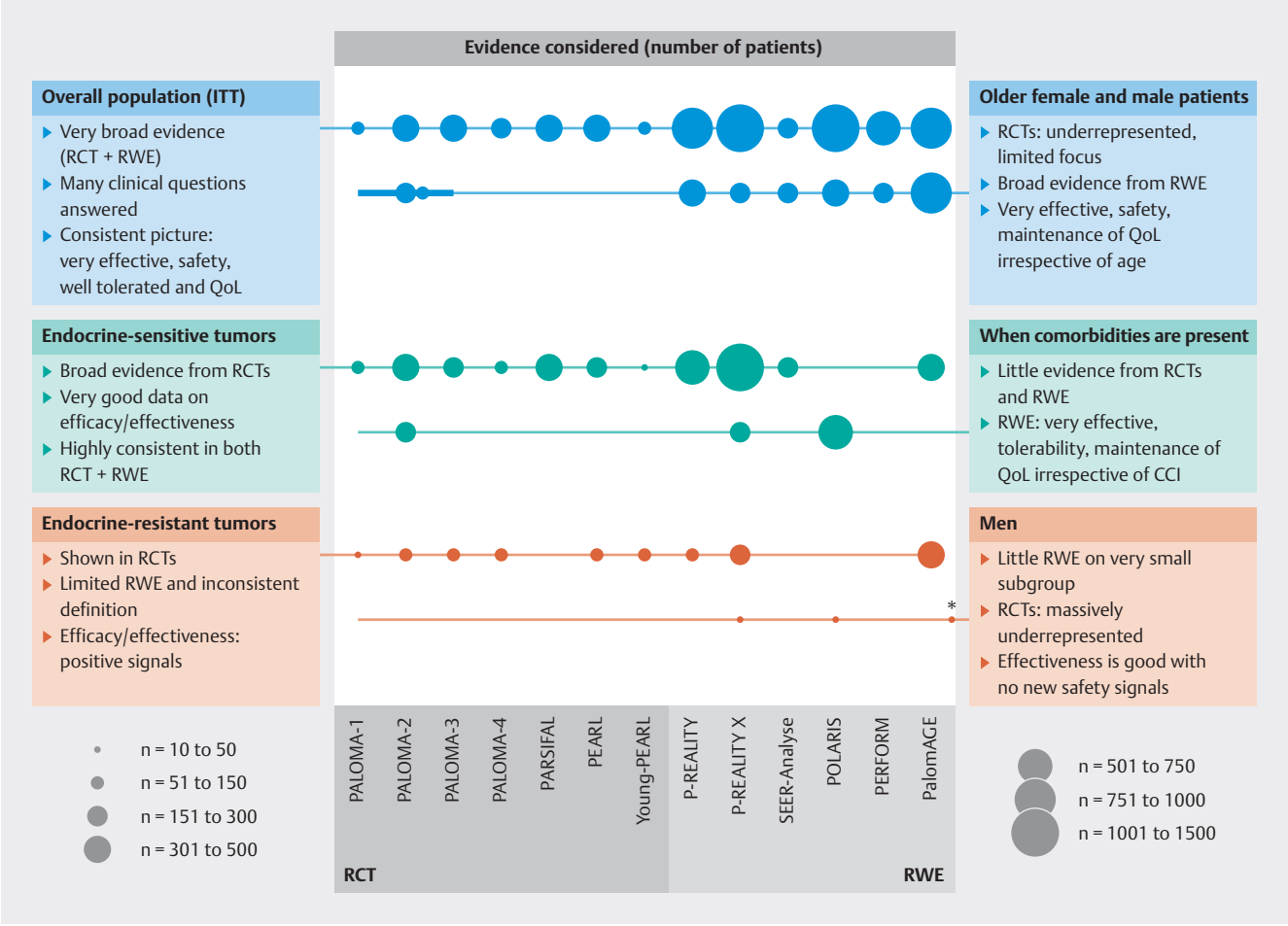
But comorbidities do not occur exclusively in older patients. As confirmed in a European real-world study, patients with mBC may also suffer from cardiovascular (36%), metabolic (11%), and gastrointestinal (5%) comorbidities. 38% of patients had one or two comorbidities, 8% had three or more [103]. Combination therapy consisting of a CDK4/6 inhibitor plus ET – as recommended in the international guidelines – was the most commonly prescribed first-line treatment for these patients [103]. An analysis in the P-REALITY X study of 469 female and male patients with pre-existing cardiovascular disorders showed a significant benefit after sIPTW from the addition of palbociclib to an AI vs. AI alone with regards to PFS ($p = 0.007$) and OS ($p = 0.048$) [104].

CONCLUSION

The combination of palbociclib plus ET is an effective and well-tolerated treatment option for comorbid patients with HR+/HER2− mBC and can maintain patient's quality of life.

Men with breast cancer

Men with HR+/HER2− mBC were not included in the approval-relevant trials and are not represented or are underrepresented in other RCTs investigating CDK4/6 inhibitors. This makes data and findings obtained from real-world studies even more important.



▶ **Fig. 1** Excerpt from relevant palbociclib studies which were consulted for this review. The cohort sizes of the discussed subgroups are shown, with the respective core messages. As the legend in gray states, circle sizes correlate to the number of patients in the palbociclib arm which were assessed in the respective studies (RCT: randomized clinical trials; RWE: real-world evidence). The thick bar for the older patients symbolizes the pooled analysis from PALOMA-1, 2, 3, with the large circle standing for patients aged 65–74 years and the smaller circle standing for patients aged ≥ 75 years. * symbolizes the approval-relevant analysis of palbociclib in men [71]. CCI = Charlson Comorbidity Index; ITT = intention-to-treat; QoL = quality of life

RWD

Real-world data on palbociclib use from three databases indicates that male patients experience clinical benefit from combination therapy. A longer median duration of treatment was possible when patients received combination therapy in the first-line setting compared to endocrine monotherapy (8.5 vs. 4.3 months). A response to treatment was observed in 33.3 % versus 12.5 % of male patients. The safety profile corresponded to that reported for women treated with palbociclib plus ET. A review of a global safety database yielded no new safety signals for men treated with palbociclib plus ET [71].

P-REALITY X demonstrated that palbociclib plus ET appears to be associated with impoved outcomes for male patients in terms of PFS and OS compared to endocrine monotherapy. An OS benefit was found after adjustment using sIPTW (17 vs. 12 patients; HR 0.11; 95 % CI: 0.01–0.95) [36].

Other information from the prospective observational study POLARIS is available, which enrolled 15 male patients with a median age of 66 years. Nine received palbociclib as part of first-line therapy and six received palbociclib in a subsequent therapy line. The median PFS was 19.8 months. Moreover, data on this small cohort indicate that the global quality of life under palbociclib plus ET was maintained in male patients with breast cancer [105]. During the first six treatment cycles, three patients discontinued therapy due to their own decision, toxicity or other reasons [105]. A multicenter real-world study analyzed the data of 25 men with HR+/HER2− mBC, 16 of whom received palbociclib. It was confirmed that CDK4/6 inhibitors are as effective and safe for male patients in this indication as they are for women [110].

In Germany, palbociclib has been approved in combination with an AI to treat men with HR+/HER2− locally advanced or metastatic breast cancer [5]. International guidelines also recommend combination therapy consisting of a CDK4/6 inhibitor such as palbociclib plus ET for men with HR+/HER2− mBC [111].

CONCLUSION

Palbociclib plus ET was found to be more effective in men compared to endocrine monotherapy. The safety profile is comparable to that reported for women, and initial data indicate that the quality of life for men is maintained during treatment.

Summary and Outlook

This review aims to present the evidence of the first-in-class CDK4/6 inhibitor palbociclib in detail, focussing on clinically relevant aspects such as safety, tolerability, quality of life and efficacy.

The addition of palbociclib consistently delayed disease progression and prolonged the time to subsequent systemic toxic chemotherapies. The efficacy, simple therapy management, and good tolerability of palbociclib has led to prolongation of a consistently good quality of life for patients, one of the primary objectives in palliative care. These clinically relevant findings are not only confirmend in RCT cohorts but also in real-world settings. The latter one takes account of factors which are highly relevant in daily clinical care and are often not fully reflected in RCTs. This includes, for example, gender, comorbidities or older age (▶ **Fig. 1**).

The data on overall survival have been less consistent. PALOMA-1, 2, and 3 showed a statistically significant benefit for ET combined with palbociclib compared to ET alone in the overall population with regards to the primary endpoint PFS but not for the secondary endpoint OS. In RCTs, cohorts with endocrine sensitive tumors showed positive signals indicating potentially prolonged overall survival with palbociclib-ET combination therapy. In routine medical care, several high-quality comparative studies of large heterogeneous real-world populations showed that this endocrine combination appears to be associated with an overall survival benefit (▶ **Fig. 1**).

Not least due to the low risk of interaction and generally good tolerability, palbociclib plays an important role in numerous clinical trials investigating innovative therapeutic concepts. Currently ongoing trials include combination strategies with the new oral PROTAC ER degrader vepdegestrant (VERITAC-3; NCT05909397) [112] or the triplet of palbociclib, fulvestrant and the PI3 K inhibitor inavolisib (INAVO120;NCT04191499) [113]. In the INAVO120 trial, patients benefited from the first-line triple combination therapy compared to palbociclib/fulvestrant (PFS: HR 0.43; 95 % CI: 0.32–0.59; p = 0.0001). This serves an identified medical need in patients with HR+/HER2− mBC and endocrine resistance and, in this context, confirmed *PIK3CA* mutation [114]. Whether continuing with CDK4/6 inhibition beyond progression is superior to endocrine monotherapy was addressed in the phase-II studies PACE and PALMIRA. Continuation of palbociclib therapy with a different endocrine partner after clinical progression was not associated with prolonged PFS [115, 116]. These findings were expanded by a retrospective real-world analysis of 839 female patients from the Flatiron database. After receiving a CDK4/6 inhibitor as first-line therapy, 36 % received a CDK4/6 inhibitor as second-line treatment. These patients had a better prognosis (rwPFS: HR 0.48; 95 % CI: 0.43–0.53; p < 0.0001 and OS: HR 0.30; 95 % CI: 0.26–0.35; p < 0.0001) compared to those who received chemotherapy as their second-line treatment [117]. This is supported by the retrospective analysis of the GuardantINFORM database [118]. The future must show how concepts of therapy beyond progression or in combination with other targeted substances can lead to an improvement in prognosis with few side effects.

As shown in the review presented here, there is an abundance of evidence from RCTs and RWE on palbociclib-based combination therapies. Palbociclib continues to be an important agent in the treatment of patients with HR+/HER2− advanced breast cancer.

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Conflict of Interest

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References/Literatur

[1] Mertz S, Benjamin C, Girvalaki C et al. Progression-free survival and quality of life in metastatic breast cancer: The patient perspective. Breast 2022; 65: 84–90. DOI: 10.1016/j.breast.2022.07.006

[2] Harbeck N, Penault-Llorca F, Cortes J et al. Breast cancer. Nat Rev Dis Primers 2019; 5: 66. DOI: 10.1038/s41572-019-0111-2

[3] Leitlinienprogramm Onkologie. Interdisziplinäre S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.4 – Juni 2021. Office des Leitlinienprogrammes Onkologie. 2021. Accessed October 12, 2023 at: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Mammakarzinom_4_0/Version_4.4/LL_Mammakarzinom_Langversion_4.4.pdf

[4] Howlader N, Altekruse SF, Li CI et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014; 106: dju055. DOI: 10.1093/jnci/dju055

[5] Pfizer. Fachinformation. Ibrance®. 2023. Accessed October 12, 2023 at: https://www.fachinfo.de/pdf/022953

[6] Novartis. Fachinformation. Kisqualli®. 2023. Accessed October 12, 2023 at: https://www.fachinfo.de/pdf/021677

[7] Lilly. Fachinformation. Verzenios®. 2023. Accessed October 12, 2023 at: https://www.fachinfo.de/pdf/022221

[8] Engler T, Fasching PA, Luftner D et al. Implementation of CDK4/6 Inhibitors and its Influence on the Treatment Landscape of Advanced Breast Cancer Patients – Data from the Real-World Registry PRAEGNANT. Geburtshilfe Frauenheilkd 2022; 82: 1055–1067. DOI: 10.1055/a-1880-0087

[9] Harbeck N, Bartlett M, Spurden D et al. CDK4/6 inhibitors in HR+/HER2− advanced/metastatic breast cancer: a systematic literature review of real-world evidence studies. Future Oncol 2021; 17: 2107–2122. DOI: 10.2217/fon-2020-1264

[10] Cristofanilli M, Turner NC, Bondarenko I et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016; 17: 425–439. DOI: 10.1016/S1470-2045(15)00613-0

[11] Finn RS, Crown JP, Lang I et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015; 16: 25–35. DOI: 10.1016/S1470-2045(14)71159-3

[12] Finn RS, Martin M, Rugo HS et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016; 375: 1925–1936. DOI: 10.1056/NEJMoa1607303

[13] Hortobagyi GN, Stemmer SM, Burris HA et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med 2016; 375: 1738–1748. DOI: 10.1056/NEJMoa1609709

[14] Slamon DJ, Neven P, Chia S et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol 2018; 36: 2465–2472. DOI: 10.1200/JCO.2018.78.9909

[15] Tripathy D, Im SA, Colleoni M et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol 2018; 19: 904–915. DOI: 10.1016/S1470-2045(18)30292-4

[16] Goetz MP, Toi M, Campone M et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol 2017; 35: 3638–3646. DOI: 10.1200/JCO.2017.75.6155

[17] Sledge GW jr., Toi M, Neven P et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2− Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol 2017; 35: 2875–2884. DOI: 10.1200/JCO.2017.73.7585

[18] Finn RS, Boer K, Bondarenko I et al. Overall survival results from the randomized phase 2 study of palbociclib in combination with letrozole versus letrozole alone for first-line treatment of ER+/HER2− advanced breast cancer (PALOMA-1, TRIO-18). Breast Cancer Res Treat 2020; 183: 419–428. DOI: 10.1007/s10549-020-05755-7

[19] Slamon DJ, Dieras V, Rugo HS et al. Overall Survival With Palbociclib Plus Letrozole in Advanced Breast Cancer. J Clin Oncol 2024; 42: 994–1000. DOI: 10.1200/JCO.23.00137

[20] Turner NC, Slamon DJ, Ro J et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. N Engl J Med 2018; 379: 1926–1936. DOI: 10.1056/NEJMoa1810527

[21] Cristofanilli M, Rugo HS, Im SA et al. Overall Survival with Palbociclib and Fulvestrant in Women with HR+/HER2− ABC: Updated Exploratory Analyses of PALOMA-3, a Double-blind, Phase III Randomized Study. Clin Cancer Res 2022; 28: 3433–3442. DOI: 10.1158/1078-0432.CCR-22-0305

[22] Rugo HS, Finn RS, Diéras V et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. Breast Cancer Res Treat 2019; 174: 719–729. DOI: 10.1007/s10549-018-05125-4

[23] Xu BH, Hu XC, Li W et al. Palbociclib plus letrozole versus placebo plus letrozole in Asian postmenopausal women with oestrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: Primary results from PALOMA-4. Eur J Cancer 2022; 175: 236–245. DOI: 10.1016/j.ejca.2022.08.012

[24] Llombart-Cussac A, Perez-Garcia JM, Bellet M et al. Fulvestrant-Palbociclib vs Letrozole-Palbociclib as Initial Therapy for Endocrine-Sensitive, Hormone Receptor-Positive, ERBB2-Negative Advanced Breast Cancer: A Randomized Clinical Trial. JAMA Oncol 2021; 7: 1791–1799. DOI: 10.1001/jamaoncol.2021.4301

[25] Llombart-Cussac A, Perez-Garcia JM, Bellet M et al. PARSIFAL-LONG: Extended follow-up of hormone receptor-positive/HER2-negative advanced breast cancer patients treated with fulvestrant and palbociclib vs letrozole and palbociclib in the PARSIFAL study. Cancer Res 2024. DOI: 10.1158/1538-7445.SABCS23-RF01-03

[26] Park YH, Kim TY, Kim GM et al. Palbociclib plus exemestane with gonadotropin-releasing hormone agonist versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (KCSG-BR15–10): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2019; 20: 1750–1759. DOI: 10.1016/S1470-2045(19)30565-0

[27] Sonke GS, Van Ommen-Nijhof A, Wortelboer N et al. Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017–03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2 − advanced breast cancer (ABC). J Clin Oncol 2023. DOI: 10.1200/JCO.2023.41.17_suppl.LBA1000

[28] Martin M, Zielinski C, Ruiz-Borrego M et al. 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. Eur J Cancer 2022; 168: 12–24. DOI: 10.1016/j.ejca.2022.03.006

[29] Martin M, Zielinski C, Ruiz-Borrego M et al. Palbociclib in combination with endocrine therapy versus capecitabine in hormonal receptor-positive, human epidermal growth factor 2-negative, aromatase inhibitor-resistant metastatic breast cancer: a phase III randomised controlled trial-PEARL. Ann Oncol 2021; 32: 488–499. DOI: 10.1016/j.annonc.2020.12.013

[30] Kogawa T, Noguchi E, Yamanaka T et al. Palbociclib (P) plus tamoxifen (TAM) ± goserelin in women with hormone receptorpositive (HR+)/HER2-negative (HER2−) advanced breast cancer (ABC): Primary results of NCCH1607/PATHWAY, an Asian international double-blind randomized phase 3 trial. J Clin Oncol 2023. DOI: 10.1200/JCO.2023.41.17_suppl.LBA106

[31] Bidard FC, Hardy-Bessard AC, Dalenc F et al. Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2022; 23: 1367–1377. DOI: 10.1016/S1470-2045(22)00555-1

[32] Cabel L, Delaloge S, Hardy-Bessard A-C et al. Dynamics and type of ESR1 mutations under aromatase inhibitor or fulvestrant combined with palbociclib after randomization in the PADA-1 trial. J Clin Oncol 2023. DOI: 10.1200/JCO.2023.41.16_suppl.1002

[33] Harbeck N, Fasching PA, Wuerstlein R et al. Significantly longer time to deterioration of quality of life due to CANKADO PRO-React eHealth support in HRD HER2L metastatic breast cancer patients receiving palbociclib and endocrine therapy: primary outcome analysis of the multicenter randomized AGO-B WSG PreCycle trial. Ann Oncol 2023; 34: 660–669. DOI: 10.1016/j.annonc.2023.05.003

[34] Harbeck N, Fasching PA, Wuerstlein R et al. CANKADO PRO-React eHealth support in patients with HR+HER2− metastatic breast cancer receiving palbociclib and endocrine therapy and the affect on time to deterioration of quality of life: Primary outcome analysis of the multicenter randomized PreCycle trial. J Clin Oncol 2023. DOI: 10.1200/JCO.2023.41.16_suppl.1008

[35] DeMichele A, Cristofanilli M, Brufsky A et al. Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2− metastatic breast cancer in US real-world clinical practice. Breast Cancer Res 2021; 23: 37. DOI: 10.1186/s13058-021-01409-8

[36] Rugo HS, Brufsky A, Liu X et al. Real-world study of overall survival with palbociclib plus aromatase inhibitor in HR+/HER2− metastatic breast cancer. NPJ Breast Cancer 2022; 8: 114. DOI: 10.1038/s41523-022-00479-x

[37] Goyal RK, Chen H, Abughosh SM et al. Overall survival associated with CDK4/6 inhibitors in patients with HR+/HER2− metastatic breast cancer in the United States: A SEER-Medicare population-based study. Cancer 2023; 129: 1051–1063. DOI: 10.1002/cncr.34675

[38] Trapani D, Mayer EL. What's the reality for CDK4/6 inhibitors: Clinical trials or real-world evidence? Cancer 2023; 129: 986–988. DOI: 10.1002/cncr.34672

[39] Ha MJ, Singareeka Raghavendra A, Kettner NM et al. 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. Int J Cancer 2022; 150: 2025–2037. DOI: 10.1002/ijc.33959

[40] El Badri S, Tahir B, Balachandran K et al. Palbociclib in combination with aromatase inhibitors in patients ≥ 75 years with oestrogen receptor-positive, human epidermal growth factor receptor 2 negative advanced breast cancer: A real-world multicentre UK study. Breast 2021; 60: 199–205. DOI: 10.1016/j.breast.2021.10.010

[41] Taylor-Stokes G, Mitra D, Waller J et al. 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. Breast 2019; 43: 22–27. DOI: 10.1016/j.breast.2018.10.009

[42] Mycock K, Zhan L, Taylor-Stokes G et al. Real-World Palbociclib Use in HR+/HER2− Advanced Breast Cancer in Canada: The IRIS Study. Curr Oncol 2021; 28: 678–688. DOI: 10.3390/curroncol28010066

[43] Mycock K, Zhan L, Hart K et al. Real-world treatment of patients with palbociclib for HR+/HER2− advanced/metastatic breast cancer: the Europe IRIS study. Future Oncol 2022; 18: 349–362. DOI: 10.2217/fon-2021-0716

[44] Richardson D, Zhan L, Mahtani R et al. A prospective observational study of patient-reported functioning and quality of life in advanced and metastatic breast cancer utilizing a novel mobile application. Breast Cancer Res Treat 2021; 187: 113–124. DOI: 10.1007/s10549-020-06082-7

[45] Lux MP, Runkel ED, Glastetter E et al. PERFORM: a non-interventional study assessing the patients' treatment starting with 1 L palbociclib in HR+/HER2− ABC. Future Oncol 2022; 18: 3971–3982. DOI: 10.2217/fon-2022-0552

[46] Radosa JC, Fietz T, Wilke J et al. Palbociclib plus endocrine therapy in HR+/HER2− advanced breast cancer patients: Interim results of the PERFORM study. Ann Oncol 2023; 34: S353–S354. DOI: 10.1016/j.annonc.2023.09.584

[47] Brain E, Pulido M, Paillaud E et al. Feasibility of palbociclib in women aged 70 and older with resistant and/or pretreated advanced breast cancer in the PALOMAGE study. Cancer Res 2022; 82. DOI: 10.1158/1538-7445.Sabcs21-P1-18-04

[48] Caillet P, Pulido M, Brain E et al. PALOMAGE, a French real-world cohort of elderly women beyond age 70 with advanced breast cancer receiving palbociclib: Baseline characteristics and safety evaluation. J Clin Oncol 2021; 39. DOI: 10.1200/JCO.2021.39.15_suppl.1012

[49] Carola E, Pulido M, Falandry C et al. First-line systemic treatment with palbociclib in women aged ≥ 70 years presenting with hormone receptor-positive advanced breast cancer: Results from the PALOMAGE program. J Clin Oncol 2023. DOI: 10.1200/JCO.2023.41.16_suppl.1018

[50] Goetz MT, Toi M, Huober J et al. MONARCH 3: Final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first-line therapy for HR+, HER2− advanced breast cancer. Cancer Res 2024. DOI: 10.1158/1538-7445.SABCS23-GS01-12

[51] Hortobagyi GN, Stemmer SM, Burris HA et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. N Engl J Med 2022; 386: 942–950. DOI: 10.1056/NEJMoa2114663

[52] Berger F, Marce M, Delaloge S et al. Randomised, open-label, multicentric phase III trial to evaluate the safety and efficacy of palbociclib in combination with endocrine therapy, guided by ESR1 mutation monitoring in oestrogen receptor-positive, HER2-negative metastatic breast cancer patients: study design of PADA-1. BMJ Open 2022; 12: e055821. DOI: 10.1136/bmjopen-2021-055821

[53] Carausu M, Bidard FC, Callens C et al. ESR1 mutations: a new biomarker in breast cancer. Expert Rev Mol Diagn 2019; 19: 599–611. DOI: 10.1080/14737159.2019.1631799

[54] Brett JO, Spring LM, Bardia A et al. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res 2021; 23: 85. DOI: 10.1186/s13058-021-01462-3

[55] Lee S, Im SA, Kim GM et al. Patient-Reported Outcomes of Palbociclib Plus Exemestane with GnRH Agonist versus Capecitabine in Premenopausal Women with Hormone Receptor-Positive Metastatic Breast Cancer: A Prospective, Open-Label, Randomized Phase II Trial (KCSG-BR 15–10). Cancers (Basel) 2020; 12: 3265. DOI: 10.3390/cancers12113265

[56] Kahan Z, Gil-Gil M, Ruiz-Borrego M et al. Health-related quality of life with palbociclib plus endocrine therapy versus capecitabine in postmenopausal patients with hormone receptor-positive metastatic breast cancer: Patient-reported outcomes in the PEARL study. Eur J Cancer 2021; 156: 70–82. DOI: 10.1016/j.ejca.2021.07.004

[57] Rugo HS, Diéras V, Gelmon KA et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. Ann Oncol 2018; 29: 888–894. DOI: 10.1093/annonc/mdy012

[58] Harbeck N, Iyer S, Turner N et al. Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial. Ann Oncol 2016; 27: 1047–1054. DOI: 10.1093/annonc/mdw139

[59] Finn RS, Rugo HS, Gelmon KA et al. Long-Term Pooled Safety Analysis of Palbociclib in Combination with Endocrine Therapy for Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Updated Analysis with up to 5 Years of Follow-Up. Oncologist 2021; 26: E749–E755. DOI: 10.1002/onco.13684

[60] Karuturi MS, Rocque GB, Cappelleri JC et al. Real-world quality of life (QoL) in patients with hormone receptor-positive (HR plus), human epidermal growth factor receptor 2-negative (HER2−), advanced breast cancer (ABC) treated with palbociclib: A patient-reported outcome (PRO) analysis from POLARIS. Cancer Res 2022. DOI: 10.1158/1538-7445.Sabcs21-P1-18-25

[61] Rocque G, Blum JL, Ji Y et al. Real-world quality of life (QoL) in patients with HR+/HER2− advanced breast cancer (ABC) treated with palbociclib: Final clinical outcome assessment (COA) analysis from POLARIS. Ann Oncol 2022; 33: S88–S121

[62] Tripathy D, Blum JL, Sleckman B et al. Characterization of neutropenia in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer on palbociclib in a real-world setting: Results from POLARIS. Cancer Res 2023. DOI: 10.1158/1538-7445.Sabcs22-P3-01-03

[63] ClinicalTrails.gov. Endocrine Therapy Plus CDK4/6 in First or Second Line for Hormone (SONIA) Receptor Positive Advanced Breast Cancer. 2023. Accessed November 24, 2023 at: https://classic.clinicaltrials.gov/show/NCT03425838

[64] Azoulay L. Rationale, Strengths, and Limitations of Real-World Evidence in Oncology: A Canadian Review and Perspective. Oncologist 2022; 27: E731–E738. DOI: 10.1093/oncolo/oyac114

[65] Monti S, Grosso V, Todoerti M et al. Randomized controlled trials and real-world data: differences and similarities to untangle literature data. Rheumatology (Oxford) 2018; 57: vii54–vii58. DOI: 10.1093/rheumatology/key109

[66] Revicki DA, Frank L. Pharmacoeconomic evaluation in the real world. Effectiveness versus efficacy studies. Pharmacoeconomics 1999; 15: 423–434. DOI: 10.2165/00019053-199915050-00001

[67] Khozin S, Blumenthal GM, Pazdur R. Real-world Data for Clinical Evidence Generation in Oncology. J Natl Cancer Inst 2017; 109. DOI: 10.1093/jnci/djx187

[68] Di Maio M, Perrone F, Conte P. Real-World Evidence in Oncology: Opportunities and Limitations. Oncologist 2020; 25: e746–e752. DOI: 10.1634/theoncologist.2019-0647

[69] Caffo O. Treatment sequencing in oncology: balancing clinical trial and real-world evidence Foreword. Future Oncology 2019; 15: 2887–2889. DOI: 10.2217/fon-2019-0415

[70] Batra A, Kong SY, Cheung WY. Eligibility of real-world patients with metastatic breast cancer for clinical trials. Breast 2020; 54: 171–178. DOI: 10.1016/j.breast.2020.10.005

[71] Kraus AL, Yu-Kite M, Mardekian J et al. Real-World Data of Palbociclib in Combination With Endocrine Therapy for the Treatment of Metastatic Breast Cancer in Men. Clin Pharmacol Ther 2022; 111: 302–309. DOI: 10.1002/cpt.2454

[72] Mues KE, Liede A, Liu J et al. Use of the Medicare database in epidemiologic and health services research: a valuable source of real-world evidence on the older and disabled populations in the US. Clin Epidemiol 2017; 9: 267–277. DOI: 10.2147/Clep.S105613

[73] Blonde L, Khunti K, Harris SB et al. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. Adv Ther 2018; 35: 1763–1774. DOI: 10.1007/s12325-018-0805-y

[74] Sherman RE, Anderson SA, Dal Pan GJ et al. Real-World Evidence – What Is It and What Can It Tell Us? N Engl J Med 2016; 375: 2293–2297. DOI: 10.1056/NEJMsb1609216

[75] Schneeweiss S. Learning from Big Health Care Data. N Engl J Med 2014; 370: 2161–2163. DOI: 10.1056/NEJMp1401111

[76] Yuan HB, Ali MS, Brouwer ES et al. Real-World Evidence: What It Is and What It Can Tell Us According to the International Society for Pharmacoepidemiology (ISPE) Comparative Effectiveness Research (CER) Special Interest Group (SIG). Clin Pharmacol Ther 2018; 104: 239–241. DOI: 10.1002/cpt.1086

[77] Castelo-Branco L, Pellat A, Martins-Branco D et al. ESMO Guidance for Reporting Oncology real-World evidence (GROW). Ann Oncol 2023; 34: 1097–1112. DOI: 10.1016/j.annonc.2023.10.001

[78] Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31: 1623–1649. DOI: 10.1016/j.annonc.2020.09.010

[79] Burstein HJ. Systemic Therapy for Estrogen Receptor-Positive, HER2-Negative Breast Cancer. N Engl J Med 2020; 383: 2557–2570. DOI: 10.1056/NEJMra1307118

[80] Harbeck N, Gnant M. Breast cancer. Lancet 2017; 389: 1134–1150. DOI: 10.1016/s0140-6736(16)31891-8

[81] Papadimitriou MC, Pazaiti A, Iliakopoulos K et al. Resistance to CDK4/6 inhibition: Mechanisms and strategies to overcome a therapeutic problem in the treatment of hormone receptor-positive metastatic breast cancer. Biochim Biophys Acta Mol Cell Res 2022; 1869: 119346. DOI: 10.1016/j.bbamcr.2022.119346

[82] Finn RS, Rugo HS, Dieras VC et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL plus LET) versus placebo plus letrozole (PBO plus LET) in women with estrogen receptor positive/human epidermal growth factor receptor 2-negative advanced breast cancer (ER+/HER2− ABC): Analyses from PALOMA-2. J Clin Oncol 2022. DOI: 10.1200/JCO.2022.40.17_suppl.LBA1003

[83] Garly R, Berg T, Jensen MB et al. A retrospective, non-interventional study of breast cancer patients diagnosed with ER+/HER2 negative, locally advanced or metastatic breast cancer treated with palbociclib in Denmark. Acta Oncol 2023; 62: 290–297. DOI: 10.1080/0284186X.2023.2194030

[84] Bedard PL, Freedman OC, Howell A et al. Overcoming endocrine resistance in breast cancer-are signal transduction inhibitors the answer? Breast Cancer Res Treat 2008; 108: 307–317. DOI: 10.1007/s10549-007-9606-8

[85] Dean JL, Thangavel C, McClendon AK et al. Therapeutic CDK4/6 inhibition in breast cancer: key mechanisms of response and failure. Oncogene 2010; 29: 4018–4032. DOI: 10.1038/onc.2010.154

[86] Hamilton E, Infante JR. Targeting CDK4/6 in patients with cancer. Cancer Treat Rev 2016; 45: 129–138. DOI: 10.1016/j.ctrv.2016.03.002

[87] Lange CA, Yee D. Killing the second messenger: targeting loss of cell cycle control in endocrine-resistant breast cancer. Endocr Relat Cancer 2011; 18: C19–C24. DOI: 10.1530/Erc-11-0112

[88] Normanno N, Di Maio M, De Maio E et al. Mechanisms of endocrine resistance and novel therapeutic strategies in breast cancer. Endocr Relat Cancer 2005; 12: 721–747. DOI: 10.1677/erc.1.00857

[89] Pink JJ, Bilimoria MM, Assikis J et al. Irreversible loss of the oestrogen receptor in T47D breast cancer cells following prolonged oestrogen deprivation. Brit J Cancer 1996; 74: 1227–1236. DOI: 10.1038/bjc.1996.521

[90] Thangavel C, Dean JL, Ertel A et al. Therapeutically activating RB: reestablishing cell cycle control in endocrine therapy-resistant breast cancer. Endocr Relat Cancer 2011; 18: 333–345. DOI: 10.1530/Erc-10-0262

[91] Durairaj C, Ruiz-Garcia A, Gauthier ER et al. Palbociclib has no clinically relevant effect on the QTc interval in patients with advanced breast cancer. Anticancer Drugs 2018; 29: 271–280. DOI: 10.1097/Cad.0000000000000589

[92] Harbeck N, Law EH, Ajmera M et al. Prevalence of risk factors for QT prolongation and torsades de pointes among women with HR+/HER2– advanced or metastatic breast cancer treated in real-world settings in Italy and Germany. Ann Oncol 2019. DOI: 10.1093/annonc/mdz100.016

[93] Harbeck N, Kates R, Schinköthe T et al. Favorable impact of therapy management by an interactive eHealth system on severe adverse events in patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer treated by palbociclib and endocrine therapy. Cancer Treat Rev 2023. DOI: 10.1016/j.ctrv.2023.102631

[94] Rached L, Frelaut M, Baldini C. Bridging the gap: addressing disparities of access to oncology clinical trials in the geriatric population. ESMO Open 2023; 8: 102029. DOI: 10.1016/j.esmoop.2023.102029

[95] RKI. Krebs in Deutschland. 2023. Accessed November 09, 2023 at: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2021/kid_2021_c50_brust.pdf?__blob=publicationFile

[96] Rugo HS, Turner NC, Finn RS et al. Palbociclib plus endocrine therapy in older women with HR+/HER2− advanced breast cancer: a pooled analysis of randomised PALOMA clinical studies. Eur J Cancer 2018; 101: 123–133. DOI: 10.1016/j.ejca.2018.05.017

[97] Rugo HS, Liu XC, Li B et al. Real-world comparative effectiveness of palbociclib plus letrozole versus letrozole in older patients with metastatic breast cancer. Breast 2023; 69: 375–381. DOI: 10.1016/j.breast.2023.03.015

[98] Brufsky A, Liu XC, Li B et al. Real-world treatment patterns and effectiveness of palbociclib plus an aromatase inhibitor in patients with metastatic breast cancer aged 75 years or older. Front Oncol 2023; 13. DOI: 10.3389/fonc.2023.1237751

[99] Karuturi MS, Cappelleri JC, Blum JL et al. Measures of functional status in older patients treated with palbociclib for advanced breast cancer. J Geriatr Oncol 2024; 15: 101670. DOI: 10.1016/j.jgo.2023.101670

[100] Gelmon K, Walshe JM, Mahtani R et al. Efficacy and safety of palbociclib in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with preexisting conditions: A post hoc analysis of PALOMA-2. Breast 2021; 59: 321–326. DOI: 10.1016/j.breast.2021.07.017

[101] Tripathy D, Blum JL, Karuturi MS et al. Impact of comorbidities on real-world (rw) clinical outcomes of patients (pts) with hormone receptor-positive/human epidermal growth factor 2-negative (HR+/HER2−) advanced breast cancer (ABC) treated with palbociclib and enrolled in POLARIS. Ann Oncol 2023; 34: S332. DOI: 10.1016/j.annonc.2023.09.551

[102] Blum JL, Rocque G, Ji Y et al. Impact of comorbidities on real-world patient-reported outcomes of patients (pts) with hormone receptor-positive human epidermal growth factor 2-negative (HR+/HER2−) advanced breast cancer (ABC) enrolled in the POLARIS trial. Ann Oncol 2023; 34: S375. DOI: 10.1016/j.annonc.2023.09.637

[103] Mahtani RL, Hanson KA, Lewis K et al. Treatment patterns and comorbidities in patients with HR+/HER2− MBC: A real-world study in five European countries. ESMO Open 2023. DOI: 10.1016/j.esmoop.2023.101415

[104] Brufsky A, Liu X, Li B et al. Real-world effectiveness of palbociclib plus aromatase inhibitors (AI) in metastatic breast cancer patients with cardiovascular diseases. Cancer Res 2024. DOI: 10.1158/1538-7445.SABCS23-PO1-17-05

[105] Blum JL, Dicristo C, Gordon D et al. Outcomes of male patients with HR+/HER2− advanced breast cancer receiving palbociclib in the real-world POLARIS study. Breast Cancer Res Treat 2024; 203: 463–475. DOI: 10.1007/s10549-023-07145-1

[106] onkopedia. Mammakarzinom der Frau. 2018. Accessed November 09, 2023 at: https://www.onkopedia.com/de/onkopedia/guidelines/mammakarzinom-der-frau/@@guideline/html/index.html

[107] Tumorregister. München ICD-10 C50: Mammakarzinom (Frauen) – Inzidenz und Mortalität. 2021. Accessed November 09, 2023 at: https://www.tumorregister-muenchen.de/facts/base/bC50f_G-ICD-10-C50-Mammakarzinom-Frauen-Inzidenz-und-Mortalitaet.pdf

[108] Soto-Perez-de-Celis E, Li DN, Yuan Y et al. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. Lancet Oncol 2018; 19: E305–E316. DOI: 10.1016/S1470-2045(18)30348-6

[109] Fietz T, Tesch H, Rauh J et al. Palliative systemic therapy and overall survival of 1,395 patients with advanced breast cancer – Results from the prospective German TMK cohort study. Breast 2017; 34: 122–130. DOI: 10.1016/j.breast.2017.05.014

[110] Yildirim HC, Mutlu E, Chalabiyev E 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: 85–88. DOI: 10.1016/j.breast.2022.09.009

[111] Burstein HJ, Somerfield MR, Barton DL et al. Endocrine Treatment and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol 2021; 39: 3959. DOI: 10.1200/Jco.21.01392

[112] ClinicalTrails.gov. A Study of ARV-471 (PF-07850327) Plus Palbociclib Versus Letrozole Plus Palbociclib in Participants With Estrogen Receptor Positive, Human Epidermal Growth Factor Negative Advanced Breast Cancer (VERITAC-3). U.S. National Library of Medicine 2024. Accessed February 21, 2024 at: https://classic.clinicaltrials.gov/ct2/show/NCT05909397

[113] ClinicalTrails.gov. A Study Evaluating the Efficacy and Safety of Inavolisib + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer (INAVO120). 2024. Accessed February 21, 2024 at: https://classic.clinicaltrials.gov/ct2/show/NCT04191499

[114] Jhaveri KL, Im SA, Saura C et al. Inavolisib or placebo in combination with palbociclib and fulvestrant in patients with PIK3CA mutated, hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer: Phase III INAVO120 primary analysis. SABCS; 2023; San Antonio, Texas, U.S.A.

[115] Mayer EL, Ren Y, Wagle N et al. PACE: A Randomized Phase II Study of Fulvestrant, Palbociclib, and Avelumab After Progression on Cyclin-Dependent Kinase 4/6 Inhibitor and Aromatase Inhibitor for Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor-Negative Metastatic Breast Cancer. J Clin Oncol 2024; 42: 2050–2060. DOI: 10.1200/JCO.23.01940

[116] Llombart-Cussac A, Harper-Wynne C, Perello A et al. Second-line endocrine therapy (ET) with or without palbociclib (P) maintenance in patients (pts) with hormone receptor-positive (HR [+])/human epidermal growth factor receptor 2-negative (HER2 [-]) advanced breast cancer (ABC): PALMIRA trial. J Clin Oncol 2023; 41: 1001–1001. DOI: 10.1200/JCO.2023.41.16_suppl.1001

[117] Martin JM, Handorf EA, Montero AJ et al. Systemic Therapies Following Progression on First-line CDK4/6-inhibitor Treatment: Analysis of Real-world Data. Oncologist 2022; 27: 441–446. DOI: 10.1093/oncolo/oyac075

[118] Clifton KK, Wander SA, Ma C et al. Abstract P4–01–18: Real-world second-line treatment patterns and associated clinical outcomes for 2795 patients with advanced HR+ HER2− breast cancer treated with first-line CDK4/6 inhibitors. Cancer Res 2023; 83: P4-01-18. DOI: 10.1158/1538-7445.Sabcs22-p4-01-18