REVIEW ARTICLE

Inhibiting CDK4/6 in Breast Cancer with Palbociclib, Ribociclib, and Abemaciclib: Similarities and Differences

C. Louwrens Braal[1] · Elisabeth M. Jongbloed[1] · Saskia M. Wilting[1] · Ron H. J. Mathijssen[1] · Stijn L. W. Koolen[1,2] · Agnes Jager[1]

Abstract

The cyclin-dependent kinase (CDK) 4/6 inhibitors belong to a new class of drugs that interrupt proliferation of malignant cells by inhibiting progression through the cell cycle. Three such inhibitors, palbociclib, ribociclib, and abemaciclib were recently approved for breast cancer treatment in various settings and combination regimens. On the basis of their impressive efficacy, all three CDK4/6 inhibitors now play an important role in the treatment of patients with HR+, HER2− breast cancer; however, their optimal use still needs to be established. The three drugs have many similarities in both pharmacokinetics and pharmacodynamics. However, there are some differences on the basis of which the choice for a particular CDK4/6 inhibitor for an individual patient can be important. In this article, the clinical pharmacokinetic and pharmacodynamic profiles of the three CDK4/6 inhibitors are reviewed and important future directions of the clinical applicability of CDK4/6 inhibitors will be discussed.

Key Points

CDK4/6 inhibitors play an eminent role in the treatment of advanced HR+, HER2− breast cancer and are of potential value in the (neo)adjuvant setting.

Biomarkers need to be identified to optimize the therapy in patients treated with CDK4/6 inhibitors and to select patients with other types of (breast) cancer who could potentially benefit.

Combinations with other drug modalities with a different pharmacodynamic profile need to be defined to further enhance the efficacy, overcome resistance, and widen the applicability of CDK4/6 inhibitors.

✉ C. Louwrens Braal
c.braal@erasmusmc.nl

1 Department of Medical Oncology, Erasmus University MC Cancer Institute, Dr. Molewaterplein 40, PO Box 2040, 3000 CA Rotterdam, The Netherlands

2 Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands

1 Introduction

Of all patients with stage IV breast cancer, approximately 75% are hormone receptor-positive (HR+) and human epidermal growth factor receptor 2 negative (HER2−) [1–3]. As advanced or metastatic breast cancer represents an incurable disease, the main purpose of treatment is to delay disease progression, preferably with anticancer drugs that are patient friendly in their use and toxicity [4]. Patients with HR+, HER2− breast cancer are often treated with single-agent endocrine therapy. However, endocrine resistance always develops, resulting in the need for cytotoxic chemotherapy [5–7].

Recently, a novel drug class, the cyclin dependent kinase (CDK) 4/6 inhibitors, has been introduced as a treatment option for patients with HR+, HER2− advanced breast cancer, either as first-line therapy combined with an aromatase inhibitor or as second-line therapy in combination with fulvestrant [8–13]. The CDK-RB1-E2F pathway targeted by CDK4/6 inhibitors is essential for progression through the cell cycle and is disrupted in the majority of cancers [14–18]. In breast cancer, the activation of estrogen receptors as well as other proliferation-inducing signals stimulate the complexation of CDK4/6 with cyclin D1 [19]. Binding of CDK4/6 to cyclin D1 induces phosphorylation of the retinoblastoma (Rb) tumor suppressor protein, releasing its inhibitory effect

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and thereby providing the starting signal for cell division [16, 18, 20–22]. Normally, CDK4 and CDK6 are inhibited by the protein p16. However, in cancer this mechanism of cell cycle control is often disrupted [19, 23]. Furthermore, cyclin D1, the binding partner of CDK4/6, is often overexpressed in patients with HR+, HER2− breast cancer leading to continuous activation of the cyclin D1–CDK4/6 complex [24–26]. Inhibition of CDK4/6 induces complete dephosphorylation of Rb, resulting in sequestration of the transcription factor E2F and subsequent inhibition of cell cycle progression [27–29].

The effectiveness of CDK4/6 inhibitors can be increased by combining them with drugs that prevent the downstream estrogen-dependent stimulation of the cancer cell. Inhibition of the estrogen pathway—by endocrine therapy—results in downregulation of cyclin D1 and reduced complexation of CDK4 and CDK6 [30]. Therefore, the selective CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib are given in combination with endocrine therapy (aromatase inhibitors or fulvestrant) in the treatment of HR+, HER2− breast cancer [31–33].

So far, no head-to-head comparison has been carried out between the three different CDK4/6 inhibitors in HR+, HER2− advanced breast cancer. At present, CDK4/6 inhibitors are prescribed based on individual physicians' experience with these CDK4/6 inhibitors, differences in toxicity profiles, costs, or the preference policy of the hospital. Insights into pharmacological profiles of these three CDK4/6

inhibitors may help to rationalize the selection of the most optimal inhibitor for the individual patient. In this review, the pharmacokinetics, pharmacodynamics, efficacy, and tolerability of palbociclib, ribociclib, and abemaciclib for the treatment of breast cancer are discussed. Furthermore, future directions of the clinical applicability of the CDK4/6 inhibitors are discussed such as the potential role of biomarkers in determining treatment strategy in specific patient groups, the combination with other drug modalities, and the use of these therapies in other types of (breast) cancer (Fig. 1).

2 Pharmacokinetics

2.1 Pharmacokinetic Profiles

Palbociclib (Ibrance®, Pfizer, New York, USA) received US FDA approval in 2015, with a recommended starting dosage of 125 mg once daily in a '3 weeks on and 1 week off' schedule in combination with a non-steroidal aromatase inhibitor or the selective estrogen receptor degrader (SERD) fulvestrant [32]. After rapid absorption of palbociclib, the maximum concentration (C_{max}) is achieved within 6–12 h and the drug is being eliminated with an elimination half-life of 24–34 h. Steady-state will be achieved after 4–5 elimination half-lives, which is important to predict the onset of action or improvement of toxicity after treatment discontinuation. Ribociclib (Kisqali®, Novartis, Basel, Switzerland)
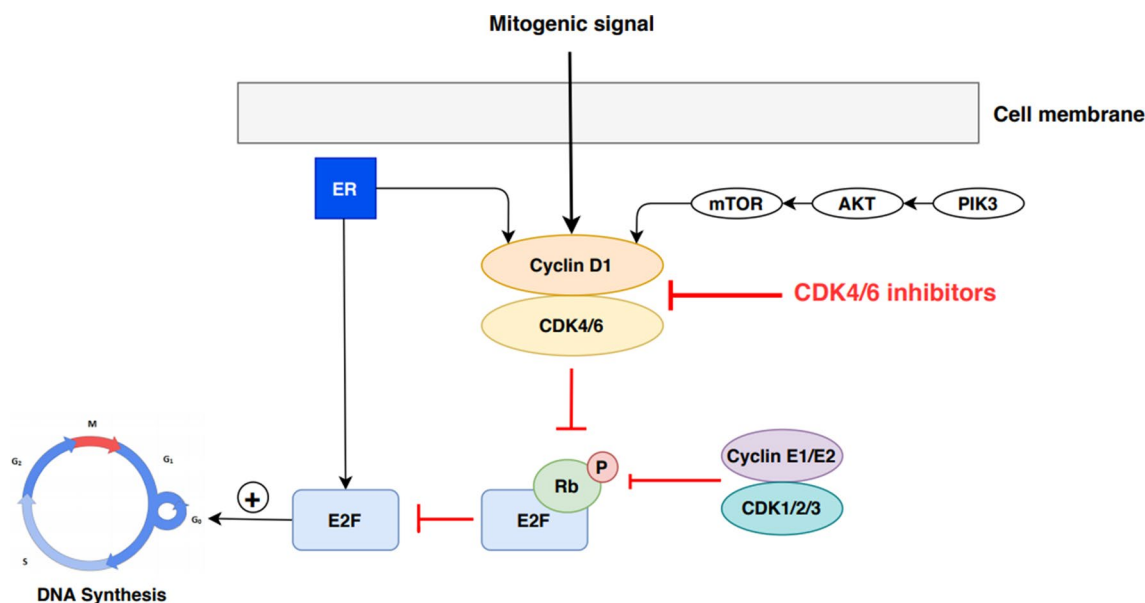

Fig. 1 Mechanism of action of CDK4/6 inhibitors. The CDK4/6-cyclin D1 complex induces phosphorylation of the retinoblastoma (Rb) tumor-suppressor protein. Free transcription factor E2F stimulates cell transition from the G1 to the S phase and cell division. *AKT* protein kinase B, *CDK4/6* cyclin dependent kinase 4 and 6, *ER* estrogen receptor, *E2F* transcription factor family, *HER2* human epidermal growth factor receptor-2, *PIK3* phosphoinositide 3-kinase, *Rb* retinoblastoma tumor suppressor protein, *mTOR* mammalian target of rapamycin

received US FDA approval in 2017, with a recommended starting dosage of 600 mg once daily in a '3 weeks on/1 week off' schedule in combination with an aromatase inhibitor or fulvestrant [33]. Ribociclib has a high absorption rate and reaches C_{max} within 1–4 h upon intake. The elimination half-life of ribociclib is 30–55 h. Finally, abemaciclib (Verzenios®, Eli Lilly, Indianapolis, USA) received US FDA approval in 2017, with a recommended starting dosage of 150 mg twice daily in a continuous dosing schedule combined with an aromatase inhibitor or fulvestrant. In addition, abemaciclib is also approved for administration as monotherapy with a starting dosage of 200 mg twice daily [31]. Abemaciclib achieves its C_{max} within 8 h upon intake and the drug elimination half-life is 17–38 h. Pharmacokinetic parameters of palbociclib, ribociclib, and abemaciclib are depicted in Table 1.

2.2 Similarities and Differences in Pharmacokinetics

2.2.1 Absorption

The pharmacokinetic profiles of the three inhibitors are strikingly similar. After rapid absorption and distribution, all three CDK4/6 inhibitors are metabolized mainly by CYP3A4. Abemaciclib is given in a continuous schedule of two doses per day, whereas palbociclib and ribociclib are given once daily in '3 weeks on/1 week off' schedules. Only for abemaciclib, preclinical studies have displayed saturation of drug absorption, which supported the development and registration of a twice-daily dosing regimen to improve drug absorption [34, 35]. Furthermore, preclinical studies showed that continuous administration of abemaciclib reduced

Table 1 Pharmacokinetics of palbociclib, ribociclib, and abemaciclib

	Palbociclib (Ibrance®) PD-0332991 [10, 32, 42, 50, 105–108]	Ribociclib (Kisqali®) LEE011 [33, 50, 71, 115]	Abemaciclib (Verzenios®) LY2835219 [31, 34, 39, 77, 116–118]
First US FDA approval In combination with an aromatase inhibitor or fulvestrant	2015	2017	2017
Molecular weight (g/mol)	447.54	434.55	506.59
cLog P	2.7	2.3	5.5
Route of administration	Oral	Oral	Oral
Dose	125 mg qd; 3 weeks on/1 week off	600 mg qd; 3 weeks on/ 1 week off	150 mg bid; continuously
Dosage form and strengths	Capsules	Tablets	Tablets
	75, 100, 125 mg	200 mg	50, 100, 150, 200 mg
C_{trough} (ng/mL)	47 (CV; 48%)	457 (CV; 67%)	176 (CV; 89%)
T_{max} (h)	6–12	1–4	8
C_{max} (ng/mL)	97 (CV; 41%)	1680 (CV; 31%)	249 (CV; 64%)
$T_{1/2}$ (h)	24–34	30–55	17–38
Bioavailability (%)	46	NR	45
Accumulation ratio	2.4 (1.5–4.2)	2.51 (0.97–6.40)	3.2 (CV; 59%)
Protein binding (%)	~85	~70	93–98
Absorption Food effect	No	No	No
Distribution (L)	2583	1090	690.3
Metabolism	CYP3A4 + SULT2A1	CYP3A4	CYP3A4
Metabolites	Yes	Yes	Yes
		M13 (*N*-hydroxylation): 22%	M2 (*N*-desethylation): 25%
	Palbociclib-glucuronide: 1.5%	M4 (*N*-demethylation): 20%	M20 (hydroxylation): 26%
		M1 (secondary glucuronide): 18%	M18 (hydroxy-*N*-desethylation): 13%
Excretion (%)	Feces: 74	Feces: 69	Feces: 81
	Urine: 18	Urine: 23	Urine: 3
Age, weight, gender, race, mild hepatic/renal impairment	No effect on exposure	No effect on exposure	No effect on exposure

bid twice daily, *cLog P* calculated Log P (lipophilicity), *C_max* maximum concentration, *C_trough* trough concentration, *CV* coefficient of variation, *M* metabolite, *NR* not reported, *qd* once daily, *T_{1/2}* half-life, *T_max* time to reach maximum observed concentration

tumor growth more efficiently compared with an intermittent schedule [34–36]. The efficacy of palbociclib and ribociclib in continuous dosing schedules compared with the efficacy of the current intermittent schedule is unknown, but hematological toxicities urged the development of an intermittent schedule.

2.2.2 Distribution

From a biopharmaceutical point of view, a distinguishing feature of abemaciclib in comparison with the other CDK4/6 inhibitors is its theoretical ability to penetrate breast tissue and the blood–brain barrier more efficiently due to its higher lipophilicity (cLog P 5.5 versus 2.7 and 2.3, see Table 1). In support of this theoretical advantage, preclinical data from abemaciclib in human xenograft models showed decreased tumor growth in the brain, and when compared with palbociclib and ribociclib, abemaciclib had the highest unbound brain-to-plasma ratio, suggesting effective penetration [38]. In addition, a clinical study indicated that systemic treatment with abemaciclib resulted in similar concentrations of abemaciclib in both plasma and cerebrospinal fluid [39]. In addition, both palbociclib and ribociclib are substrates for breast cancer resistance protein (BCRP; ABCG2) and P-glycoprotein (P-gP; ABCB1), which is an additional explanation for their limited brain penetration capacity observed in preclinical studies [40, 41]. The efficacy of the three different CDK4/6 inhibitors in treating brain metastases is an important unanswered question in daily clinical practice. Prospective trials are ongoing to evaluate brain penetration and efficacy of palbociclib (NCT02774681), ribociclib (NCT02933736), and abemaciclib (NCT02308020) in the treatment of brain metastases.

2.2.3 Metabolism and Excretion

For all three CDK4/6 inhibitors, metabolization occurs hepatically, and was shown by both in vitro and in vivo studies to be primarily mediated by CYP3A4. Concomitant administration of CDK4/6 inhibitors and strong CYP3A4 inhibitors (i.e., itraconazole, ketoconazole, and ritonavir) can lead to an increase in exposure of CDK4/6 inhibitors in the blood and an increased chance of toxicity. The administration of palbociclib in combination with the strong CYP3A4 inhibitor itraconazole resulted in an increase in area under the concentration–time curve from zero to infinity (AUC$_{0–inf}$) and C_{max} of 87% and 34%, respectively; ribociclib in combination with ritonavir increased ribociclib exposure up to 3.2-fold; and based on an animal model, ketoconazole is predicted to increase the exposure of abemaciclib by up to 16-fold. The FDA therefore advises to avoid concomitant use of CDK4/6 inhibitors and strong CYP3A4 inhibitors [31–33].

Yu et al. published a physiologically based pharmacokinetic model—based on silico, in vitro, and in vivo pharmacokinetic data—in which they simulated the effects of the moderate CYP3A4 inhibitors verapamil and diltiazem on palbociclib pharmacokinetics. They estimated an increase in C_{max} and AUC of 22% and 38% for verapamil and 23% and 42% for diltiazem, respectively. The authors concluded that the risk of drug–drug interactions for palbociclib co-administered with moderate CYP3A4 inhibitors is relatively modest and that no upfront dose adjustment is needed [42]. However, a 40% increase in exposure could still be clinically relevant, especially since a higher palbociclib exposure is associated with increased toxicity [42]. A clear relationship between exposure and toxicity is not described in literature for either ribociclib or abemaciclib. More research is needed to elucidate the plausible relationship between exposure and adverse events. Currently, a randomized pharmacokinetic cross-over trial is ongoing to evaluate the effect of the moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib (Netherlands Trial Register NL7549) and results are expected in 2021.

2.2.4 Metabolism and Pharmacogenetics

Besides CYP3A4-mediated metabolism, palbociclib is also hepatically metabolized by the sulfotransferase enzyme SULT2A1 [43]. SULTs, such as SULT2A1, are highly expressed in the small intestine, liver, and adrenal cortex and metabolize orally administered drugs through sulfate conjugation. Pharmacogenetic variation in SULT2A1 activity could affect the drug's biotransformation and thus its pharmacokinetics [44]. Variability in CYP3A4 and SULT2A1 drug metabolization can often be partly explained by genetic polymorphisms. The extent to which this applies for all three CDK4/6 inhibitors is unclear and requires further research. Sequencing of CYP3A4 and SULT2A1 genes in patients treated with CDK4/6 inhibitors may potentially identify subpopulations requiring dose adjustments. The incidence of any neutropenia and grade 3 neutropenia specifically is higher in the Asian population compared with non-Asian patients treated with palbociclib [10, 45], concordant with the observed higher mean steady-state concentration of palbociclib [45]. The reason for differences in pharmacokinetics between Asian and non-Asian populations is unknown, but could be related to genetic predispositions influencing metabolism or higher numbers of CDK receptors and/or sensitivity of the receptors [46].

3 Pharmacodynamics

CDK4 is a prominent oncogenic driver in breast cancer, while CDK6 plays a crucial role in differentiation of hematopoietic stem cells [47, 48]. Palbociclib, ribociclib,

and abemaciclib display subtle differences in kinase selectivity. Abemaciclib is the most potent CDK4/6 inhibitor and is approximately five times more potent against CDK4 than CDK6, which leads to the expectation that abemaciclib exerts less hematological toxicity (Table 2) [34, 37, 49]. Preclinical drug-exposure experiments showed inhibition of CDK4 and CDK6 with half maximal inhibitory concentrations (IC_{50}) of 9–11 nM and 15 nM (ratio IC_{50} CDK4:CDK6 is 1:1.5) for palbociclib, 10 nM and 39 nM (1:4) for ribociclib, and 2 nM and 9.9 nM (1:5), for abemaciclib, respectively [50, 51]. In contrast to palbociclib and ribociclib, abemaciclib was shown to be a potent inhibitor of CDK9 as well [50]. CDK9 inhibition could potentially modify the cascade of glycogen synthase kinase 3 (GSK3)-mediated effects of abemaciclib leading to the specific intestinal toxicity observed [52, 53].

Table 2 (Pre)clinical pharmacodynamics and efficacy of palbociclib, ribociclib, and abemaciclib

	Palbociclib (Ibrance®) PD-0332991 [8, 11, 50, 55, 63, 119]	Ribociclib (Kisqali®) LEE011 [9, 13, 50, 119, 120]	Abemaciclib (Verzenios®) LY2835219 [10, 50, 58, 62, 119]
CDK4, IC_{50}	9–11 nM	10 nM	2 nM
CDK6, IC_{50}	15 nM	39 nM	9.9 nM
CDK9, IC_{50}	NR	NR	57 nM
Advanced setting			
Efficacy first line			
Median PFS vs aromatase inhibitor alone (mo)	24.8 vs 14.5 (HR 0.58; $p < 0.001$)	25.3 vs 16.0 (HR 0.56; $p < 0.001$)	Not reached vs 14.7 (HR 0.54; $p < 0.001$)
Median OS (mo)	NR	NR	NR
Efficacy second line			
Median PFS vs fulvestrant alone (mo)	9.5 vs 4.6 (HR 0.46; $p < 0.001$)	20.5 vs 12.8 (HR 0.59; $p < 0.001$)	16.4 vs 9.3 (HR 0.55; $p < 0.001$)
Median OS (mo)	34.9 vs 28.0 (HR 0.81; $p = 0.09$)	Not reached vs 40.0 (HR 0.72; $p = 0.005$)	46.7 vs 37.3 (HR 0.76; $p = 0.014$)
Toxicity advanced setting (all/grade 3–4) (%)	Neutropenia (80/66)	Neutropenia (75/60)	Neutropenia (41/22)
	Anemia (24/5)	Anemia (18/1)	Anemia (28/6)
	Thrombocytopenia (16/1)	Thrombocytopenia (29/1)	Thrombocytopenia (10/2)
	Diarrhea (26/1)	Diarrhea (35/1)	Diarrhea (81/9)
	Fatigue (37/2)	Fatigue (37/2)	Fatigue (46/3)
	ALT increased (43/2)	ALT increased (46/10)	ALT increased (48/6)
	Creatinine increased (NR/NR)	Creatinine increased (20/1)	Creatinine increased (98/2)
	Infections (60/7)	Infections (50/4)	Infections (39/5)
Dosing patterns advanced setting	Dose reduction: 36%	Dose reduction: 54%	Dose reduction: 43%
	Dose interruptions: 67%	Dose interruptions: 76%	Dose interruptions: 56%
	Permanent discontinuation: 7.4%	Permanent discontinuation: 7.5%	Permanent discontinuation: 20%
Adjuvant setting			
Efficacy adjuvant setting Proportion with IDFS event (%)	5.9% in the palbociclib arm vs 6.3% in control arm (HR 0.93; $p > 0.05$)	NR	4.8% in the abemaciclib arm vs 6.6% in control arm (HR 0.75; $p < 0.05$)
Toxicity adjuvant setting (all/grade 3–4) (%)	Neutropenia (83/61)	NR	Neutropenia (45/19)
	Anemia (23/1)		Anemia (23/2)
	Thrombocytopenia (21/1)		Thrombocytopenia (12/1)
	Diarrhea (17/1)		Diarrhea (82/8)
	Fatigue (41/2)		Fatigue (38/3)
	Upper respiratory infections (28/1)		Upper respiratory infections (10/0)
Dosing patterns adjuvant setting	Dose reduction: NR	NR	Dose reduction: 41%
	Discontinued prematurely: 42%		Discontinuation prematurely: 17%

HR hazard ratio, *mo* months, *NR* not reported, *IDFS* invasive disease free survival

4 Clinical Efficacy

4.1 Advanced Breast Cancer

The effects of the CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib in combination with non-steroidal aromatase inhibitors were studied in postmenopausal ER+, HER2− advanced breast cancer in the first-line setting in three large randomized phase III trials, PALOMA-2 (palbociclib), MONALEESA-2 (ribociclib), and MONARCH-3 (abemaciclib) [8–10]. All three CDK4/6 inhibitors significantly prolonged the progression free survival (PFS) with almost identical hazard ratios (HR) for PFS (Table 2). Overall survival (OS) data for these studies are not available yet. However, an OS benefit was found in the MONALEESA-7 trial, which investigated the addition of ribociclib to the gonadotropin-releasing hormone (GnRH) agonist goserelin with either tamoxifen or a non-steroidal aromatase inhibitor in pre- or perimenopausal women (HR 0.71; 95% CI 0.54–0.95) [54].

The effects of CDK4/6 inhibitors in addition to fulvestrant mainly during the second line of treatment in patients with HR+, HER2− advanced breast cancer were studied in the three large randomized phase III trials; PALOMA-3 (palbociclib), MONALEESA-3 (ribociclib), and MONARCH-2 (abemaciclib) [12, 13, 55]. All phase III trials showed prolongation of the PFS in the CDK4/6 inhibitor group as well as an OS benefit [56–58].

Based on the above described results, CDK4/6 inhibitors are registered for first- and second-line treatment in advanced HR+, HER2− breast cancer patients. Their most optimal position during treatment (i.e., first or second line) is a matter of debate (59–61), and is being investigated in the currently ongoing randomized phase III SONIA trial (ClinicalTrials.gov identifier NCT03425838) [61]. Due to the unique study design, this study will also allow for a head-to-head comparison of the three FDA-approved CDK4/6 inhibitors to identify the differences in clinical pharmacology.

4.2 Adjuvant Setting

The positive results in the advanced breast cancer setting raised interest in CDK4/6 inhibitors as potential treatments in the neo-adjuvant and adjuvant setting. For all three CDK4/6 inhibitors, large randomized phase III trials are currently ongoing to investigate the addition of a CDK4/6 inhibitor to standard adjuvant endocrine therapy (NCT03701334) [62, 63]. In the MonarchE trial, the addition of abemaciclib treatment for 2 years in postmenopausal, high risk HR+, HER2− early breast cancer

(EBC) patients is explored [62]. After a median follow-up of 15.5 months, 136 of the 2808 patients (4.8%) experienced recurrence of invasive disease in the abemaciclib arm compared with 187 of the 2829 patients (6.6%) in the control arm (HR 0.75; 95% CI 0.60–0.93) [62]. Almost all patients experienced adverse events in the abemaciclib arm (97.9%), with grade ≥ 3 adverse events reported in 45.9% of patients compared with 86.1% and 12.9% in the endocrine monotherapy group, respectively. In total, 463 patients (16.6%) discontinued abemaciclib due to these treatment-related adverse events. These results are in contrast with those of the PALLAS trial, which was terminated early following the interim analysis since no effect of additional palbociclib to adjuvant endocrine therapy was found. After a median follow-up of 23.7 months, 170 of the 2883 patients (5.9%) in the palbociclib arm experienced recurrence of invasive disease compared with 181 of the 2877 patients (6.3%) in the control arm (HR 0.93; 95% CI 0.75–1.14). A remarkably high premature discontinuation rate of 42% was observed in the palbociclib arm of this study, which was attributed to adverse events in 64% of these patients.

These contradictory results in effectiveness raise questions. One important difference between these two trials is the study population. Whereas the PALLAS study included all patients with stage 2–3 EBC, the MonarchE study specifically included patients with high-risk EBC, defined as patients with four or more positive pathologic lymph nodes or patients with one to three pathologic lymph nodes combined with either tumor size ≥ 5 cm, histologic grade 3, or centrally assessed Ki-67 proliferation index of ≥ 20%. Subgroup analyses of only patients with N2–N3 disease and patients with clinically high risk (≥ 4 nodes or 1–3 nodes with either T3–T4 and/or grade 3 disease) disease in the PALLAS trial still did not show a significant effect in recurrence rate with addition of palbociclib, suggesting differences in study population may not be the main cause for the difference in study outcome. However, cross-study comparison should be interpreted with caution. Furthermore, follow-up imaging for the presence of recurrence was not a protocol requirement, but was performed at the discretion of the treating medical oncologist. In combination with the open-label design of the MonarchE trial, this could introduce confounding by indication bias by a likely tendency to more often perform a scan in high-risk EBC patients in the placebo arm compared with the CDK4/6 inhibitor arm. This could lead to more frequently detected recurrences in patients in the placebo arm compared with patients in the abemaciclib arm.

Longer follow-up data of trials are needed to confirm the clinical benefit of CDK4/6 inhibitors in the adjuvant setting, including the impact on OS. Several other studies in the adjuvant setting are still ongoing. The NATALEE

trial (NCT03701334) is a study in the adjuvant setting in which ribociclib is added to endocrine treatment for 3 years. Recruitment is ongoing and no results are presented or published yet. The PENELOPE-B trial (NCT01864746) studies the addition of palbociclib to endocrine therapy for 1 year in patients with a high risk of recurrence based on the CPS-EG score, a risk score based on clinical stage before neoadjuvant treatment, pathological stage after neoadjuvant treatment, nuclear grade, and estrogen receptor status. The results are eagerly awaited as, when comparable effectivity is reached with additional palbociclib for 1 year compared with 2 years in the MonarchE trial, this would be advantageous to patients and decrease healthcare costs.

4.3 Neoadjuvant Setting

The addition of CDK4/6 inhibitors in the neoadjuvant setting could potentially increase antiproliferative effects on the primary tumor before surgery takes place and ultimately result in an improved OS. Although no long-term clinical outcomes have been published yet in the neoadjuvant setting, several studies have shown an increase in cell cycle arrest with the addition of a CDK4/6 inhibitor to neoadjuvant endocrine treatment. In the NeoPalAna trial, a complete cell cycle arrest, as determined by the Ki67 index, was reached in a significantly higher proportion of the patients who received palbociclib and anastrazole compared with patients who received anastrazole monotherapy [64]. The addition of ribociclib to letrozole during six cycles in the neoadjuvant setting was explored in the FELINE trial. It showed a higher number of patients with a complete cell cycle arrest after 2 weeks of treatment in the ribociclib group compared with the placebo group, although at surgery no difference in proportion of patients with complete cell cycle arrest was found [65]. The NeoMonarch trial showed a reduction in Ki67 when abemaciclib was added to anastrazole compared with anastrazole monotherapy after 2 weeks of treatment [66]. In all studies, the number patients with a complete cell cycle arrest decreased after discontinuation of the CDK4/6 inhibitor, which indicates the importance of continuation of CDK4/6 inhibition until surgery takes place.

5 Tolerability

The main side effects of CDK4/6 inhibitors are bone marrow suppression—such as neutropenia, anemia, and thrombopenia—and gastrointestinal toxicities. However, there seem to be some distinct differences between the three drugs. Interestingly, despite these differences in toxicity profiles, all three CDK4/6 inhibitors showed comparable EORTC QLQ-C30 quality-of-life scores [67–69]. Approximately 40–50% of patients treated in phase III trials needed a dose reduction

in cycle 1 or 2 (Table 2). Importantly, permanent discontinuation was reported more often with abemaciclib treatment (20%) compared with palbociclib and ribociclib (both 7.5%) [8–10]. The most common reasons for dose modification were myelosuppression for palbociclib and ribociclib and diarrhea for abemaciclib.

5.1 Neutropenia

Grade 3–4 neutropenia—scored by the common terminology criteria for adverse events (CTCAE)—was the most reported adverse event for palbociclib (66%) and ribociclib (60%) and was the second most reported adverse event in patients treated with abemaciclib (22%). Neutropenia is usually observed in the first cycles of both palbociclib and ribociclib. Median time from first dose to onset of first episode of neutropenia grade ≥ 3 is 28.0 (12–854) days with a median duration of 7 days [70]. Also, for abemaciclib, neutropenia often occurs in the first cycle, however in some cases a more delayed onset of neutropenia was observed in cycle 2 or later [10, 32, 71, 72]. Febrile neutropenia was observed at low frequency in patients treated with a CDK4/6 inhibitor (2% for both palbociclib and ribociclib and < 1% for abemaciclib) [8, 10, 13]. A pharmacokinetic and pharmacodynamic model suggested that higher palbociclib exposure was associated with lower absolute neutrophil counts [73]. However, in general, no clear correlation between race and toxicity was found in all phase III trials [8–11, 13, 58]. Therefore, more research is needed to identify pharmacokinetic targets for the three CDK4/6 inhibitors.

5.2 Gastrointestinal Toxicity

Grade 3 diarrhea (i.e., an increase of seven or more stools a day) was more frequently reported in patients treated with abemaciclib (9%) compared with palbociclib and ribociclib (both 1%) (Table 2) [8–10, 52, 74, 75]. Median time to onset of diarrhea was 6 days with a median duration of 6–8 days. The highest rate of diarrhea was noticed in the first cycle and decreased in following cycles [76]. Prevention of diarrhea is important, since this side effect can negatively impact drug absorption. A population pharmacokinetic and pharmacodynamic model demonstrated that administration of abemaciclib 200 mg twice daily resulted in proportionally less drug absorption than administration of 150 mg twice daily [77]. An explanation for this phenomenon is the increasing incidence of gastrointestinal toxicity and diarrhea at higher abemaciclib doses, resulting in decreased absorption as a consequence of disrupted intestinal endothelial cells [39, 77]. In most patients, this side effect does not lead to drug discontinuation. If there are no signs of infections, diarrhea can be treated with dietary modifications, hydration, and

loperamide or other antidiarrheal agents. After recovery, a dose reduction can be considered [31].

5.3 QTc Prolongation

Following ribociclib administration, the QTc interval might be prolonged, whereas the other two drugs are not associated with a clinically relevant QTc time prolongation (> 20 ms) at the recommended dosing schedules [31, 79]. Therefore, QTc prolongation seems to be rather drug specific, instead of a class effect of CDK4/6 inhibitors [80]. QTc prolongation (on average 22.9 ms) was mainly observed in the first cycle of ribociclib in combination with endocrine therapy. In the MONALEESA-2 trial, 11 patients (3.3%) were diagnosed with a QTc prolongation up to > 480 ms in combination with letrozole. In the MONALEESA-7 trial, a higher incidence of QTc prolongation (> 60 ms from baseline) was reported in patients receiving ribociclib in combination with tamoxifen (16%) compared with the combination of ribociclib and a nonsteroidal aromatase inhibitor (7%) [81]. Based on this, concomitant intake of ribociclib and drugs with a known potential for QTc prolongation—such as anti-arrhythmic drugs—should be avoided or closely monitored [80].

6 Future Perspectives

6.1 Refining CDK4/6 Inhibitor Therapy by Using Biomarkers

Despite the fact that many HR+, HER2− advanced BC patients respond well to CDK4/6 inhibitors in the first line of treatment, in subsequent lines the response period is evidently shorter and in the end all patients will develop resistance to CDK4/6 inhibitors. Consequently, predictive and prognostic biomarkers are needed to further refine CDK4/6 inhibitor treatment of advanced HR+/HER2− BC patients. In the large, randomized, controlled, phase III SONIA trial (NCT03425838), the optimal position of CDK4/6 inhibitors in HR+, HER2− advanced breast cancer in the first- or in second-line treatment setting will be determined. Important secondary aims of this phase III trial are to investigate the possible associations between pharmacokinetics, pharmacodynamics, and circulating tumor DNA (ctDNA) markers for each CDK4/6 inhibitor in relationship to clinical outcome [61]. The identification of biomarkers will be of importance both for selection of responsive patients and the optimization of the therapeutic response within a patient.

6.1.1 Biomarkers Reflecting Sensitivity or Resistance to CDK4/6 Inhibitors

Biomarkers reflecting increased activity of the CDK-RB1-E2F pathway in tumor cells could help to identify patients who are sensitive to CDK4/6 inhibitor treatment. However, within the PALOMA-1 trial, the use of *CCND1* amplification or p16 loss as additional biomarkers for patient selection did not result in an improved PFS compared with all ER+/HER2− patients [84]. Vice versa, identification of resistance mechanisms may yield biomarkers to identify tumors resistant to CDK4/6 inhibitors. Whole exome sequencing of CDK4/6 inhibitor-exposed breast cancer tissues identified eight potential resistance mechanisms, including *RB1* loss, activating alterations in *AKT1, RAS, AURKA, CCNE2, ERBB2*, and *FGFR2*, and loss of *ESR1* expression, together explaining 66% of the observed resistance [85]. In the PALOMA-3 trial, *RB1* mutations were acquired in 5% of patients after treatment with palbociclib, *RB1* deletions were observed more frequently but no evidence was found for selection of *RB1* deletion during treatment [87, 88]. Next to *RB1*, particularly the E-type cyclins, encoded by the *CCNE1* and *CCNE2* genes, appear to represent promising markers of resistance. High cyclin E expression was observed in preclinical models with acquired resistance to CDK4/6 inhibitors [88] and gene expression analyses of breast cancer tissues from the PALOMA-3 study showed that low expression of *CCNE1* before treatment start was associated with a longer PFS [89]. In the NeoPalAna trial described above, expression of *CCNE1*, *CCND3*, and *CDKN2D* genes remained elevated during treatment with CDK4/6 inhibitors only in non-responding patients [64]. Large clinical trials have to confirm this potential value of cyclin E proteins for identification of CDK4/6-resistant patients.

6.1.2 Biomarkers in Liquid Biopsies

Liquid biopsies, usually referring to detection of tumor-specific DNA fragments in a patient's blood, represent a promising means for real-time monitoring of treatment response. Targeted next-generation sequencing analyses on blood-derived cell-free DNA (cfDNA) from baseline samples were performed in the PALOMA-3 trial and showed that copy number gains of *FGFR1*, *CDK4*, *MYC*, *CCNE1*, and *MCL1* as well as *p53* mutations were associated with a decreased PFS in patients treated with fulvestrant and palbociclib. However, in multivariable analysis, *FGFR1* gain, *TP53* mutations, and estimated ctDNA tumor fraction were significantly associated with PFS, irrespective of treatment arm. Results of this study demonstrate that no specific alteration at baseline was associated with PFS specifically in the palbociclib group [85].

In the same cohort, *PIK3CA* and *ESR1* mutations were determined at baseline and after 2 weeks of treatment only in the palbociclib arm. Interestingly, a decrease in the level of detected mutant *PIK3CA* molecules, but not *ESR1* mutations, within the first 2 weeks of CDK4/6 inhibitor treatment was associated with a longer PFS. Although this phenomenon is probably not CDK4/6-inhibitor specific and is likely to reflect ctDNA tumor fraction (i.e., the amount of tumor-derived DNA in the blood), it could provide a potential tool for early monitoring of treatment response irrespective of treatment [86].

6.1.3 Therapeutic Drug Monitoring (TDM)

For many drugs, it has been shown that optimization of drug dosage by plasma concentration within a predefined therapeutic window—also known as therapeutic drug monitoring (TDM)—improves clinical outcome or reduces toxicity [92–94]. For CDK4/6 inhibitors, this represents an interesting concept as well. However, at present a minimal effective concentration has not been established for any of these three agents. On the other hand, the correlation between palbociclib exposure and toxicity suggests that we can improve the tolerability by dose reductions [42, 73]. Further research is needed to investigate whether the current practice of toxicity-guided dose adaptations can be further improved by implementing TDM.

6.2 Widening the Application of CDK4/6 Inhibitors

6.2.1 HER2+ Breast Cancer

Several studies have shown that a crosstalk exists between HER2 signaling and estrogen receptor pathways in a bidirectional way, which make CDK4/6 inhibitors an attractive therapeutic option in this breast cancer subtype [95]. In a preclinical study it has been shown that the CDK4/6 pathway could mediate resistance against HER2− targeted therapies [96]. A phase II randomized trial explored the safety and efficacy of the combination of abemaciclib plus fulvestrant with trastuzumab in HR+, HER2+ breast cancer patients [97]. Patients were included after at least two lines of therapy in the advanced setting. The experimental combination of trastuzumab plus abemaciclib and fulvestrant in comparison with trastuzumab plus standard-of-care chemotherapy of physician's choice showed a PFS of 8.3 months versus 5.7 months in the standard-of-care arm (HR 0.67; 95% CI 0.45–1.00). This study confirms preclinical data and is promising since a significant increase in PFS is present, even after two or more lines of treatment. However, results of phase III studies are needed to confirm this effectiveness.

6.2.2 Triple-Negative Breast Cancer

Triple-negative breast cancer (TNBC) is a heterogeneous and aggressive type of breast cancer with limited therapeutic options. Currently, CDK4/6 inhibitors do not play a role in the treatment since efficacy is expected to be limited. Several preclinical and clinical studies are examining a role for CDK4/6 inhibitors in TNBC with diverse biological rationales and hypotheses. TNBC can be divided into subgroups by gene expression profiling: luminal-AR, mesenchymal, basal-like immune-suppressed, and basal-like immune-activated [98]. Experiments in TNBC cell lines have shown that these subtypes differ in their sensitivity to CDK4/6 inhibition, with the luminal-AR subtype being more sensitive to CDK4/6 inhibitors, whereas the basal-like subtype is highly insensitive. These results indicate that patients with TNBC should be selected based on their subgroup for treatment with CDK4/6 inhibitors [99].

Research is ongoing into newly developed CDK4/6 inhibitors in combination with other drug modalities in breast cancer. A phase II trial explored the benefit of an addition of trilaciclib, a novel CDK4/6 inhibitor, to chemotherapy (gemcitabine and carboplatin) in patients with metastatic TNBC. An improvement of antitumor effect and in the tolerability of chemotherapy by myelopreservation was observed in patients who received additional trilaciclib [100]. One of the hypotheses to explain the observed effect is the enhancement of antitumor immunity by trilaciclib [101], an effect of CDK4/6 inhibitors that has recently raised more interest. Based on the foregoing information, phase III trials in which TNBC patients are selected based on their underlying subtype are needed to further explore the potential effects of adding CDK4/6 inhibitors to chemotherapy.

6.2.3 CDK4/6 Inhibitors and Chemotherapy

CDK4/6 inhibitors and chemotherapy target different phases of the cell cycle. CDK4/6 inhibitors induce cell cycle arrest in the G0–G1 phase, preventing cells from entering subsequent phases of the cell cycle. This antagonizes the effect of classic chemotherapeutics, of which the main mode of action takes place in these subsequent phases. Several preclinical studies in breast cancer explored the effect of treatment with CDK4/6 inhibitors followed by chemotherapy. Monotherapy was superior to the combination of these therapies [102, 103]. Interestingly, a preclinical study in pancreatic cancer showed that reversing the order of treatments by giving CDK4/6 inhibitors after chemotherapy could increase the effect of chemotherapy by repressive effects on homologous recombination proteins [104]. Based on these studies, sequence and timing of therapies seems to be essential to reach optimal antitumor effects. Further preclinical investigations potentially followed by clinical studies in breast

cancer are warranted to explore the implications for future clinical use of CDK4/6 inhibitors after DNA-damaging therapies.

6.2.4 HR+, HER2− Breast Cancer

Next to CDK4/6-RB1 signaling, PI3K/AKT/mTOR signaling is an important growth stimulatory pathway in HR+, HER2− metastatic breast cancer. One of the described mechanisms of resistance to CDK4/6 inhibition is the PI3K-dependent activation of the cyclin D1/CDK2 complex. This complex could phosphorylate pRb leading to S-phase entry independent of CDK4/6. Blocking the activation of cyclin D1 by inhibiting PIK3CA could be a strategy to overcome this resistance, which was effective in cell line experiments [88]. Similarly, mTORC1/2 inhibitors have shown potency to restore sensitivity to CDK4/6 inhibitors in resistant ER+ breast cancer cell lines [105]. Combining fulvestrant, a CDK4/6 inhibitor, and a PIK3CA inhibitor, as was explored in breast cancer patients with advanced disease in a phase I trial, results in promising efficacy and safety. A retrospective clinical trial found a limited effect of palbociclib when it was given after progression on everolimus, which suggests a role for mTOR inhibitors during or after CDK4/6 inhibitor treatment [106]. These studies imply that additional treatments that block the PI3K/AKT/mTOR signaling pathway could be of value in overcoming resistance and prolonging the anti-tumor effects of CDK4/6 inhibitors. Sequence and timing will be essential and biomarkers are needed to determine the optimal sequence and timing of treatment on the individual patient level.

6.2.5 Other Tumor Types

Since aberrations in the CDK-RB1-E2F pathway are frequently observed in many types of tumors, it is expected that CDK4/6 inhibitors have a wider applicability than in breast cancer alone. Amplification of cyclin D (*CCND1*), for example, is described in non-small lung cancer, melanoma, and endometrial cancer, among others. Several clinical trials in these tumor types are ongoing and the first encouraging results have been presented [39]. A recently performed phase II trial in patients with HR+ recurrent or advanced endometrial cancer showed a prolongation in PFS with the addition of palbociclib to letrozole [107].

In addition, several preclinical studies suggest other potential mechanisms of action of CDK4/6 inhibitors that could be of interest for the application in other types of tumors as well. For example, the ability of CDK4/6 inhibitors to increase the capacity of tumor cells to express antigens and enhance T cell infiltration was shown in vitro [108]. This suggests CDK4/6 in combination with immune checkpoint blockades could be of interest in specific tumor types.

However, possible applications first need to be explored further in clinical trials.

6.3 New Types of CDK4/6 Inhibitors

Research is ongoing into the novel CDK4/6 inhibitors lerociclib (NCT03455829; NCT02983071) and trilaciclib (NCT02978716; NCT03041311; NCT02514447) in combination with other targeted therapies or chemotherapy in lung and breast cancer. Preclinical work showed a different pharmacokinetic and pharmacodynamic profile for lerociclib compared with the other CDK4/6 inhibitors, since lerociclib accumulated in xenograft tumors but not in plasma [109]. This resulted in less inhibition of myeloid progenitor cells. A recently performed phase I/II trial of lerociclib in patients with HR+, HER2− metastatic breast cancer showed the potential clinical benefits of lerociclib since a low rate of both neutropenia grade 3 or 4 and gastrointestinal adverse events was seen compared with the other CDK4/6 inhibitors [110]. These results await confirmation in phase III trials. Trilaciclib differs from the clinically available CDK4/6 inhibitors since it is administered intravenously and is developed to be combined with chemotherapy, mainly to reduced side effects. As earlier described, the first phase I/II trial showed promising results in terms of efficacy.

7 Conclusions

CDK4/6 inhibitors—palbociclib, ribociclib, and abemaciclib—play an eminent role in the treatment of advanced breast cancer. The pharmacokinetics, pharmacodynamics, and efficacy of the three CDK4/6 inhibitors seem to be comparable, although there are also interesting differences such as ability for brain penetration, side effects, and dosing schedules. These differences between the three CDK4/6 inhibitors can be used to optimize selection of treatment for individual patients. Further research is needed to investigate the optimal treatment sequence of CDK4/6 inhibitors in different breast cancer settings and different subtypes and to develop (pharmacodynamic) biomarkers for selecting patients, predicting response, and to optimize the treatment schedule.

Declarations

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