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Integrating CDK4/6 inhibitors in the treatment of patients with early breast cancer☆

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ABSTRACT

CDK4/6 inhibitors have an established role in the treatment of hormone receptor positive HER2-negative advanced breast cancer. All studies conducted in metastatic breast cancer showed a benefit in delaying progression when added to standard endocrine therapy, regardless of therapy line, pretreatment, menopausal status, site of metastasis, CDK4/6 inhibitor used and associated endocrine therapy. A benefit in overall survival has also been demonstrated. In early breast cancer, only the MonarchE study has shown an improved invasive disease-free survival with abemaciclib taken for 2 years, whereas the Penelope-B did not meet the primary endpoint and the PALLAS study was terminated early for futility. Studies conducted in the neoadjuvant setting might help to explain the discordant results.

1. Mechanism of action of CDK4/6 inhibitors

Cyclin-dependent kinases (CDKs) are important regulators of cell division [1]. Both CDK4 and 6 control the cell transition from G1 phase into S phase and their activity is mostly regulated by the association with D-family cyclins. The expression of D cyclins is tissue-specific, with different pattern of cyclins able to promote the activation of CDK4 and 6 [2]. The best characterized is cyclin D1, which is also commonly dysregulated in breast cancer [3]. Several downstream signaling pathways converge on CDK4 and 6, leading to cell-cycle initiation. After activation, CDK4 and CDK6 selectively phosphorylate tumor suppressor retinoblastoma protein (RB) and the related proteins p107 and p130 [4]. The inhibition of E2F transcription factor by RB is suppressed and E2F is freed to regulate the expression of genes involved in the cell cycle control and mitotic progression (Fig. 1) [5]. Being essential for cell cycle entry, the CDK4/6-RB-E2F axis is often exploited by tumors to promote uncontrolled cell proliferation [6]. CDKs are therefore an appealing target for new treatment strategy in cancer. All agents inhibit the CDK4/6 pathway, but the currently available CDK4/6 inhibitors have differences in pharmacology and targets. Palbociclib and ribociclib are highly lipophilic agents [7]. Both agents have a large binding site and large substituents, which prevent the binding to CDKs other than CDK4/6 [8]. Due to its different structure, abemaciclib can react with other CDKs. However, it is much less potent against CDK1/2 than against CDK4/6 [9]. The presence of a histidine-100 residue on the binding site of both abemaciclib and the ligand, permits the creation of a potent molecular bridging between abemaciclib and CDK4/6 [8]. Abemaciclib is five times more potent against CDK4 compared to palbociclib and ribociclib. Palbociclib has similar potency against CDK4 and CDK6, whereas ribociclib is more potent against CDK4 [10]. All three drugs inhibit cell proliferation [9]. Abemaciclib is also cytotoxic, especially at higher doses [9]. Acquired mutations in RB1 might lead to treatment resistance against palbociclib and ribociclib. Abemaciclib seems to have RB1-independent activity which might explain the efficacy of abemaciclib in palbociclib and ribociclib resistant tumor cells [9].

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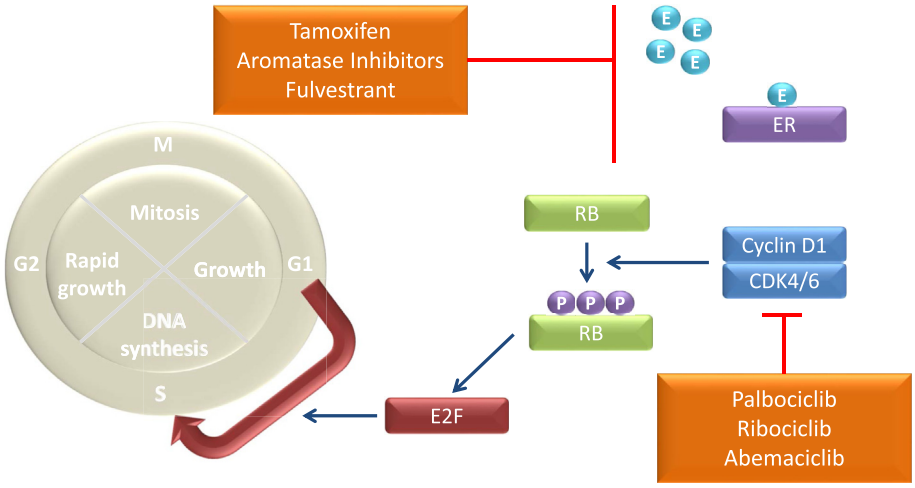

Fig. 1. Schematic overview of the mechanism of action of CDK4/6 inhibitors Abbreviations: CDK, cyclin kinase D; E2F, transcription factor E2F; E, estrogen; ER, estrogen receptor; p, phosphorylated; RB, Retinoblastoma tumor suppressor protein.

2. Overview of data on CDK4/6 inhibitors in the metastatic breast cancer setting

The concept of targeting CDKs was initially proposed in the 1990s [11,12]. However, only with the development of selective CDK4/6 inhibitors the first encouraging results have been achieved in advanced breast cancer [13]. The conduct of trials of CDK4/6 inhibitors in combination with endocrine therapy (ET) was justified by several preclinical observations. Firstly, palbociclib and ET showed a synergistic effect in estrogen receptor (ER)-positive breast cancer cell lines [14]. CDK4/6 inhibitors showed activity in ER-positive breast cancer models with acquired resistance to estrogen receptor antagonists [15]. Finally, endocrine resistance is driven by a dysregulation of proliferation genes induced by the CDK4/6-RB-E2F axis, which makes the use of this new class of drug a possible strategy to overcome ET resistance [16]. Several trials have shown the efficacy of palbociclib, ribociclib, and abemaciclib in advanced breast cancer (Table 1) [17–33]. The addition of CDK4/6 inhibitors led to a better progression-free survival (PFS) in the first and second-line compared to ET alone, which translated into an overall survival (OS) improvement [26,31–33]. Outcome could be improved irrespective of pretreatment, menopausal status, endocrine sensitivity and site of metastases [34]. On the basis of the PALOMA-2 [19,20] and PALOMA-3 [21,22] trials, palbociclib was approved for the treatment of HR-positive/HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or with fulvestrant in women who had received prior ET. The MONALEESA-2 [23,24], MONALEESA-3 [25,26,33], and MONALEESA-7 [27,28] studies led to the approval of ribociclib in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy or in women who have received prior ET. Similarly, based on the results of the MONARCH-2 [29] and MONARCH-3 [30] studies, abemaciclib was approved for the treatment of locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior ET. Abemaciclib also showed activity as monotherapy in patients who have been treated with at least one but no more than two lines of therapy for their metastatic breast cancer [35].

All seven pivotal trials were included in a metaanalysis conducted by the Food and Drug Administration (FDA), which included 4200 patients who received ET with or without a CDK4/6 inhibitor in the metastatic breast cancer setting [34]. The metaanalysis showed a hazard ratio of 0.59 (95% CI 0.54–0.64) for PFS with the addition of CDK4/6 inhibitors. A similar hazard ratio was observed irrespective of treatment line, ET backbone and pretreatment. The large number of patients included in the metaanalysis allowed the FDA to conduct subgroup analyses, confirming the efficacy of CDK4/6 inhibitors in metastatic breast cancer, regardless of progesterone-receptor status, lobular histology, disease-free interval of less than 12 months or patients with bone only disease. So far no biomarkers have been identified to select a subgroup with more or less benefit from CDK4/6 inhibitors. Data from the PALOMA-3 trial suggest that high cyclinE mRNA expression is associated with relative resistance to palbociclib. No significant interaction seems to be present between treatment and expression levels of CDK4, CDK6, cyclin D1, and RB1. Similarly, no significant interaction was found between luminal-A and luminal-B subtypes and treatment effect of palbociclib [36]. In a retrospective biomarker analysis of the MONALEESA studies, all PAM50-based subtypes demonstrated a benefit in terms of PFS with the addition of ribociclib to standard ET, with the exception of basal-like tumors. However, luminal-B patients derived a relative higher benefit from ribociclib (median PFS 22.2 vs 12.9 months, HR = 0.52, $p < 0.0001$) than luminal-A patients (median PFS 29.6 vs 19.5, HR = 0.63, $p = 0.0007$) [37].

The safety of all three drugs was extensively analyzed. The updated long-term 5-year pooled analysis confirmed the safety and feasibility of the addition of palbociclib to ET, with no cumulative or delayed toxicities [38]. Any-grade neutropenia and infections were more frequent with palbociclib plus ET (82.1% and 59.2%) than ET alone (5.1% and 39.5%). Febrile neutropenia was reported in 1.4% of patients receiving palbociclib plus ET. In a pooled long-term safety analysis of the PALOMA studies 36.9% of patients receiving palbociclib required a dose reduction, which was more frequent during the first 6 months, less frequent thereafter [39]. Palbociclib dose reduction led to a decrease in the frequency and severity of hematologic adverse events (AEs) [40], without compromising efficacy [41,42]. Ribociclib showed a similar safety profile, with all grade neutropenia reported in 69.6% of the patients (46.6% grade 3) and febrile neutropenia in 1% [25]. Prolongation of the QTcF interval was observed. Therefore, an electrocardiogram should be performed before start of ribociclib treatment, at day 14 and before cycle 2 together with appropriate monitoring of electrolytes throughout the treatment. As tamoxifen alone might lead to QTcF prolongation, the administration of ribociclib together with tamoxifen is not recommended [23,24]. Dose reduction was

Table 1
Overview of phase II and III clinical trials with CDK4/6 inhibitors in HR-positive metastatic breast cancer.

	Study	Phase	Treatment line	Menopausal status	CDK4/6 inhibitors	Endocrine therapy	Sample size	mFU	mPFS/OS (months) HR[a] (95% CI)
PALBOCICLIB	PALOMA-1	II	1	Post	Palbociclib 125 mg daily on days 1-21q 28 days	Letrozole	165	29.6	mPFS 20.2 vs 10.2 HR 0.49 (0.32–0.75) mOS 37.5 vs 34.5 HR 0.90 (0.62–1.29)
	PALOMA-2	III	1	Post	Palbociclib 125 mg daily on days 1-21q 28 days	Letrozole	666	37.6	mPFS 27.6 vs 14.5 HR 0.56 (0.46–0.69)
	PALOMA-3	III	1–2	Post and pre/peri	Palbociclib 125 mg daily on days 1-21q 28 days	Fulvestrant	521	15.8	mPFS 11.2 vs 4.6 HR 0.50 (0.40–0.62) mOS 34.9 vs 28.0 HR 0.81 (0.64–1.03)
	Young PEARL	II	1–2	Pre/peri	Palbociclib 125 mg daily on days 1-21q 28 days	Exemestane + leuprolide vs Capecitabine alone (2500 mg/m^2/day)	189	17.0	mPFS 20.1 vs 14.4 HR 0.66 (0.44–0.99)
	PEARL	III	After disease progression on AI	Post	Palbociclib 125 mg daily on days 1-21q 28 days	Cohort 1:[b] Exemestane vs Capecitabine alone (2500 mg/m^2/day) Cohort 2: Fulvestrant vs Capecitabine alone	601	13.5	Cohort 2: mPFS 7.5 vs 10.0 HR 1.13 (0.85–1.50) Cohort 1+2: mPFS 7.4 vs 9.4 HR 1.11 (0.92–1.34)
ABEMACICLIB	MONARCH-2	III	1–2	Post and pre/peri	Abemaciclib 150 mg twice daily continuous	Fulvestrant	669	47.7	mPFS 16.9 vs 9.3 HR 0.54 (0.45–0.65) mOS 46.7 vs 37.3 HR 0.76 (0.61–0.95)
	MONARCH-3	III	1	Post	Abemaciclib 150 mg twice daily continuous	Letrozole/Anastrozole	493	26.7	mPFS 28.2 vs 14.8 HR 0.54 (0.42–0.70)
	MONARCH plus	III	≥1	Post	Abemaciclib 150 mg twice daily continuous	Letrozole (Arm A)/Anastrozole vs Fulvestrant (Arm B)	463	16.0	Arm A: NR vs 14.7 HR 0.50 (0.35–0.72) Arm B: 38.5 vs 7.5 HR 0.38 (0.24–0.59)
RIBOCICLIB	MONALEESA-2	III	1	Post	Ribociclib 600 mg daily on days d1-21q 28 days	Letrozole	668	26.4	mPFS 25.3 vs 16.0 HR 0.67 (0.46–0.70) mOS 63.9 vs 30.1 HR 0.74 (0.62–0.89)
	MONALEESA-3	III	1–2	Post	Ribociclib 600 mg daily on days d1-21q 28 days	Fulvestrant	726	39.4	mPFS 33.6 vs 19.2 HR 0.55 (0.42–0.72) mOS not reached vs 40.0 HR 0.72 (0.57–0.92)
	MONALEESA-7	III	1–2	Pre/peri	Ribociclib 600 mg daily on days d1-21q 28 days	Tamoxifene/AI + Goserelin	672	19.2	mPFS 23.8 vs 13.0 HR 0.55 (0.44–0.69) mOS not reached vs 40.9 HR 0.71 (0.54–0.95)

Abbreviations: AI, aromatase inhibitor; CI, confidence interval; HR, hazard ratio; mPFS, median progression-free survival; post, postmenopausal; pre/peri, premenopausal/perimenopausal.
[a] ET plus CDK4/6 inhibitor vs ET alone.
[b] In Mai 2016 the protocol was amended, to treat patients with fulvestrant instead of exemestane. The decision was based on the observation that fulvestrant conversely to exemestane may be effective in patients with ESR1 mutation-positive tumors.

required for 41% of the patients in both MONALEESA-3 and -7 studies. However, this did not impact PFS [43] or OS [44]. In the pooled analysis of the MONARCH studies [45], the most frequent AE with abemaciclib was diarrhea grade ≥2 (42.8%), which occurred especially in the first cycles and was successfully managed with antidiarrheal medications and dose adjustment. Neutropenia grade ≥3 occurred in 25.4% of abemaciclib treated patients, febrile neutropenia in 0.7%. Interstitial lung disease/pneumonitis was experienced by 3.4% of the patients and was managed with corticosteroids and/or antibiotics. About 43% of the patients needed dose reductions due to AEs, mainly due to grade 2–3 diarrhea and grade ≥3 neutropenia. As for palbociclib and ribociclib, outcome was not negatively affected by dose reduction or toxicities [45].

The AEs observed with CDK4/6 inhibitors added to the known adverse events of ET, which is of major importance especially in the early setting [46]. However, in all of the studies described above, AEs were adequately managed with supportive treatment or dose adjustment, without compromising efficacy. Interestingly, arthralgia and hot flushes were reduced with the use of CDK4/6 inhibitors compared to ET alone [25,45]. The underlying reason is still unknown.

3. Adjuvant trials exploring the use of CDK4/6 inhibitors with endocrine therapy

CDK4/6 inhibitors have been investigated in early breast cancer in addition to ET compared to ET alone in 3 published trials, Penelope-B [47], PALLAS [48], and MonarchE [49,50] (Table 2). The NATALEE trial has completed accrual in March 2021 (Table 2) [51]. Some differences among the four trials need to be highlighted (Table 3). The PALLAS, MonarchE and NATALEE study enrolled more than 5000 patients each, whereas the Penelope-B study is smaller with only 1250 patients. However, Penelope-B has enrolled a very specific high-risk patient population, selected based on the CPS-EG score, which is prognostically more robust than the pathologic stage alone [52,53]. All patients had to have received neoadjuvant chemotherapy and had to be at high risk of relapse, defined as CPS-EG score ≥3 or 2 with involved lymph nodes after neoadjuvant chemotherapy. The Penelope-B study was the only placebo-controlled study, all other trials were open-label. The use of palbociclib or abemaciclib was the same as in the metastatic setting and in line with the approval. The NATALEE trial used a lower

Table 2
CDK4/6 inhibitor in early breast cancer: adjuvant studies.

	Study	Phase	Patient cohort	Sample size	Treatment arm	Primary Endpoint	mFU	Summary of results
PALBOCICLIB	**Penelope-B**	Phase 3 Randomized Placebo-controlled	High-risk (CPS-EG score ≥3 or 2 with ypN+)	1250	Palbociclib/placebo **125 mg/m^2 d 1–21 q28** (13 cycles) for **1 year** + at least 5 years ET	**iDFS**[a]	42.8	3-years iDFS 81.2% vs 77.7% HR 0.93 (0.74–1.17), p log-rank = 0.525
	PALLAS	Phase 3 Randomized Open label	Stage II-III	5600	**Palbociclib 125 mg/m^2 d 1–21 q28** (26 cycles) for **2 years** + at least 5 years ET total	**iDFS**[a]	23.7	3-years iDFS 88.2% vs 88.5% HR 0.93 (0.76–1.15), log-rank p = 0.51
ABEMACICLIB	**MonarchE**	Phase 3 Randomized Open label	High-risk	5637	Abemaciclib **150 mg continuous** (26 cycles) for **2 years** + at least 5 years ET total	**iDFS**[a]		2-years iDFS 92.3% vs 88.7 HR 0.75 (0.60–0.93), p = 0.01
RIBOCICLIB	**NATALEE**	Phase 3 (non) randomized Open label	Stage II-III	5000	**Ribociclib 400 mg day 1–21 q28 for 3 years** + at least 5 years ET	**iDFS**		Expected for December 2025

Abbreviations: CPS-EG, clinical-pathological stage, estrogen receptor, grade; iDFS, invasive disease-free survival; ypN+, nodal involvement after neoadjuvant chemotherapy.
[a] ET plus CDK4/6 inhibitor vs ET alone.

Table 3
Comparison of compliance/side effects of the CDK4/6 inhibitors adjuvant studies in the light of pretreatment.

	Penelope-B (%)	PALLAS (%)	MonarchE (%)
CDK4/6 inhibitor	PALBOCICLIB	PALBOCICLIB	ABEMACICLIB
Prior chemotherapy	100	88.0	95.0
Early discontinuation of CDK4/6 inhibitor (other than event)	14.9	42.2	23.0
Discontinuation due to AEs	5.2	27.1	16.6
Dose reduction	47.6 (at 1year)	49.0 (at 1year) 41.2 (overall)	41.0 (overall)
Any AE G3-4	79.0	72.9	45.9 (≥10%)
SAE	9.1	12.4	12.3
Selected toxicities			
Neutropenia (G3-4)	70.0	63.1 with CT vs 52.6 no CT	18.6
Anaemia	73.9	23.4	22.9
Thrombocytopenia	56.6	21.4	12.2
Fatigue	66.4	40.5	38.4
Hot flushes	43.8	24.3	14.1
Arthralgia	41.2		20.5
Nausea	23.7	19.1	27.9
Alopecia	14.7	17.5	9.1
Diarrhea	18.3	16.4	82.2
Interstitial lung disease	n.k.	0.5	2.7

Abbreviations: AE, adverse event; CT, chemotherapy; G, grade; SAE, severe adverse event.

ribociclib dose of 400 mg compared to the approved 600 mg dose for the metastatic breast cancer setting. Finally, treatment duration was 3 years in the NATALEE study, 2 years in the PALLAS and MonarchE, and 1 year in Penelope-B. All studies used a standard ET backbone including tamoxifen and tamoxifen plus LHRH, apart from the NATALEE study because the use of tamoxifen in combination with ribociclib led to an increased proportion of QT prolongation compared to an aromatase inhibitor combination. All had the same primary endpoint, invasive disease-free survival (iDFS).

The MonarchE [49] study randomized patients at high risk of relapse based on standard clinico-pathological factors, i.e. at least 4 involved lymph nodes or, in case of 1–3 involved lymph nodes, either grade 3 or with a tumor size ≥5 cm [49]. An additional cohort with slightly lower risk included patients with 1–3 metastatic lymph-nodes, with centrally assessed Ki67 ≥ 20% being the only additional risk factor. This should be considered a more intermediate risk population, as also patients with small tumors, 1 involved lymph node, and with Ki67 of 25% could be enrolled. Still, 95% of the patients received neoadjuvant or adjuvant chemotherapy. Patients were assigned to receive either abemaciclib continuously for 2 years together with ET or ET alone. At the final analysis, after a median follow-up of 19 months, patients who received abemaciclib had an improved iDFS compared to ET alone (Table 2). Results of the interim analysis after a shorter median follow-up of 15 months were thus confirmed [54]. Similarly, no difference between the interim and the final analysis were observed among subgroups. The majority of the subgroups benefit to the same extent as the overall cohort. However, patients older than 65 years do not seem to derive the largest benefit in this patients cohort. Similarly, the subgroup of patients with ECOG 1, that might include patients with more comorbidities or more toxicities after chemotherapy, seems to derive less benefit. This might indicate that less treatment was given in this group. The role of Ki67 was explored [50]. It was hypothesized that patients with tumors harboring higher Ki67 would benefit exclusively or much more from abemaciclib therapy than those with low Ki67. However, results did not confirm these hypotheses and both cohorts benefit to the same relative extent. In terms of absolute benefit, the difference in iDFS was larger in the high-risk population with Ki67 ≥ 20% (2-year iDFS Ki67 < 20% 94.7% vs 86.1%; Ki67 ≥ 20% 94.7% vs 92.0%) [50]. Even if about 95% of the whole cohort received chemotherapy, it is unclear, how many of the low Ki67 patients were not pretreated. Abemaciclib

discontinuation occurred due to AEs in 16.6% of the cases (dose reduction in 41.2%) with diarrhea, neutropenia and fatigue being the most common AEs. Over half of the early discontinuations due to AEs occurred within the first five months of treatment. Treatment discontinuation under ET alone occurred in 0.8% of the cases.

The PALLAS study [48] enrolled patients with stage II or III breast cancer who completed adjuvant or neoadjuvant chemotherapy and radiotherapy, if indicated, and underwent surgical tumor resection. Patients were randomized to receive palbociclib for 2 years with standard ET or ET alone. The trial was stopped early at the time of the second interim analysis due to futility [48]. After a median follow-up of 23.7 months, no difference was observed in the 3-year iDFS with the addition of palbociclib to ET (Table 2). However, we should consider that about 18% of the patients were at intermediate risk (stage I-IIA), resulting in overall 20% of the patients not previously treated with (neo)adjuvant chemotherapy. No clinicpathological subgroup appeared to benefit from the addition of palbociclib. Patients without previous chemotherapy showed a trend for benefit from palbociclib, but the interaction test was not positive. Patients who received previous chemotherapy seemed to not benefit at all by the addition of palbociclib. The cumulative incidence of early stopping of palbociclib was surprisingly high in this trial, about 42% of the patients had to stop treatment according to the rules of the study protocol either due to side effects, mainly neutropenia, or other reasons. In the phase II single-arm feasibility trial the discontinuation rate before 2 years was 37%, which is in the same range [55]. The lack of adequate exposure to palbociclib might have impacted the results. An exploratory analysis suggested that a longer duration of palbociclib treatment as well as exposure intensity correlate with improved iDFS [56]. The analysis of relative total dose intensity would help in providing a cut-off for drug exposure above which a benefit by adding the CDK4/6 inhibitor would be expected. Longer follow-up is needed especially for stage I patients and for patients without chemotherapy pretreatment.

Similar to the PALLAS trial, the Penelope-B study [47] did not meet the primary iDFS endpoint, even after a longer follow-up of 43 months. After 2 years there was a 4% absolute difference between treatment arms, which was lost with longer follow-up (Table 2). None of the subgroups seem to derive a benefit. With about 15%, treatment discontinuations were lower than in the PALLAS study. Dose reductions occurred more frequently within the first 6 months of therapy similar to observations in metastatic breast cancer. In the last treatment cycle about half of the patients were still receiving full doses.

The question arises, why the results of the trials in the adjuvant setting are so fundamentally different at this point in time, especially as data derived from the metastatic setting showed identical efficacy of all the three CDK4/6 inhibitors. The definition of high-risk population was defined differently across trials. However, all enrolled patients at high risk based on nodal involvement, high grade and large tumors. The control arm in the trials had a 2-year iDFS of 84.0% in Penelope-B, 88.5% in PALLAS, and 88.7% in MonarchE, reflecting the different risk profiles of the populations. At 2 years, the absolute difference in the MonarchE and in Penelope-B was similar (Fig. 2). Recently, data on the 3-year follow-up of the MonarchE study were published, showing the extent of the treatment benefit of abemaciclib beyond the 2-year treatment period [57]. The shape of the curves was different due to the higher risk population enrolled in the Penelope-B trial compared to the MonarchE trial, with half of the patients having more than 4 metastatic lymph nodes and 60% a CPS-EG score $\geq$3. Treatment adherence might have impacted the results, too. Early discontinuations other than an event were much higher in the PALLAS (42%) study compared to the MonarchE (16.6%), which can partly explain the results. The toxicity profile is especially important in the adjuvant setting. Therefore, the AE management is essential to maintain adequate dose intensity. The UNIRAD trial investigating the use of everolimus added to endocrine therapy in early breast cancer showed a high treatment discontinuation for everolimus in 53.4% and for the placebo group in 22.3% of the patients. This emphasizes the necessity of a drug to be of good tolerability when added to ET for a longer duration in early breast cancer [58]. For both abemaciclib and palbociclib no new safety concerns have arisen compared to the known safety profile explored in the metastatic setting. Neutropenia was much more common with palbociclib than abemaciclib, especially in the cohort of patients previously treated with chemotherapy. Similar trends could be observed with anemia and thrombocytopenia, arising the hypothesis that the addition of CDK4/6 inhibitors after chemotherapy and radiotherapy might lead to a higher toxicity rate. Among non-hematological toxicities, fatigue was high in all trials, especially in Penelope-B. Interestingly, as reported in the metastatic studies and in the neoadjuvant PALLET trial [11], arthralgia and hot flushes were reduced with the use of the CDK4/6 inhibitors compared to the control arm [49]. Diarrhea was more common with abemaciclib (7.6% of G3-4), which occurred early, was short-lived and manageable with supportive treatment. Another possible explanation for the contrasting results is that abemaciclib is more effective either due to the different mode of action or due to the continuous application compared to the other CDK4/6 inhibitors, but this assumption is not supported by studies in the metastatic setting. The CCTG MA38 trial examined the use of palbociclib 100 mg given continuously in comparison to the standard schedule of 125 mg 3 weeks on/1 week off. The continuous schedule was active, but associated with higher rates of grade 3/4 neutropenia (69% vs 53%) with consequent dose modifications (70% vs 40%) [59].

Based on the mainly anti-proliferative effect of palbociclib it can be argued that palbociclib might delay relapses rather than having a curative effect on breast cancer. Mainly because we are treating occult metastases, treatment duration should be longer than the 28 months median PFS under CDK4/6 inhibitor therapy in 1st line metastatic breast cancer [34]. Results of the NATALEE trial with ribociclib given for 3 years might clarify this aspect.

Tumor biology might have played an important role. The MonarchE study has enrolled mainly patients with luminal B-like tumors, which are more likely to have a higher risk of early recurrence [37,60]. Study patients with high Ki67 tumors derive a larger absolute benefit from the addition of abemaciclib than patients with low Ki67 tumors although the relative benefit is comparable.

Finally, the follow-up of the different trials is still too short to observe a late benefit for these drugs, as half of the recurrences in patients with HR-positive breast cancer are expected to occur beyond 5 years. Impact on overall survival is also questionable and needs to be awaited.

Based on the results of the MonarchE study [57], the German AGO guidelines 2021 have included the use of CDK4/6 inhibitors in patients with early breast cancer at high risk of relapse. Patients with characteristics similar to the MonarchE population might benefit by using abemaciclib for 2 years in combination with standard endocrine therapy (level of evidence 2b, AGO +/−). There are no data supporting the use of palbociclib in the adjuvant setting (level of evidence/AGO 2 years 2b/; 1 year 1b/-) [61]. The ESMO guidelines [62], updated in March 2020 [63] do not mention the use of CDK4/6 inhibitors for the treatment of early breast cancer but will be updated in 2022.

With the novel knowledge on the use of CDK4/6 inhibitors treatment in early breast cancer, we should define which the best place might be for this new agent class within the algorithm of treatment of early breast cancer. Burstein et al. proposed a decision

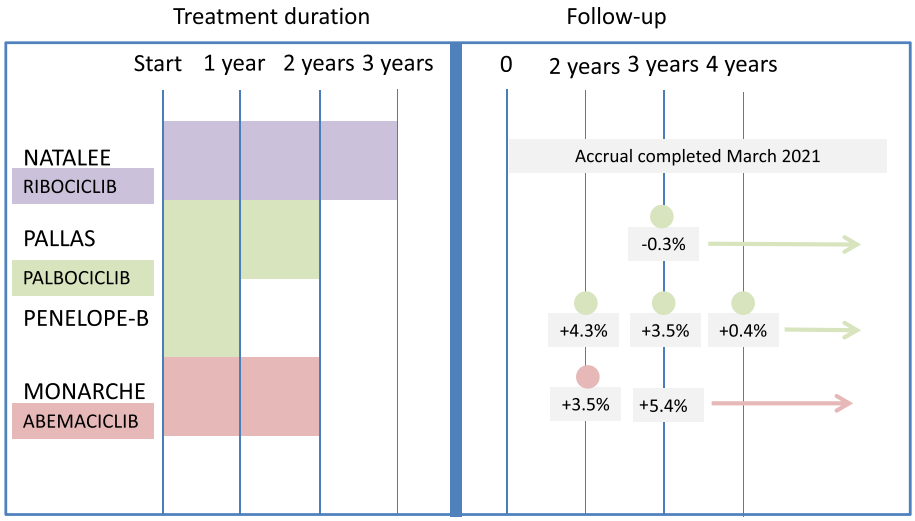

Fig. 2. Adjuvant studies with CDK4/6 inhibitors: treatment duration and invasive disease-free survival benefit.

making model based on anatomical risk and biological risk for patients with HR-positive breast cancer, helping to define the best adjuvant therapy [46]. With increasing risk, there is a greater absolute benefit from escalated ET, defined as longer duration of ET or addition of ovarian function suppression as well as chemotherapy. Currently abemaciclib can be added to ET after receiving (neo) adjuvant chemotherapy in patients being at high risk of relapse.

4. Neoadjuvant trials exploring the use of CDK4/6 inhibitors with endocrine therapy

Data derived from neoadjuvant studies might help in decrypting the different results derived from studies in the adjuvant setting (Table 4). The NeoPalAna study [64] was a phase II single-arm study assessing the anti-proliferative activity of palbociclib in patients with stage II/III early breast cancer together with anastrozole. The study included an initial 4-week period, where anastrozole was given alone together with goserelin for premenopausal women. Thereafter, palbociclib was added to ET. In case of Ki67 > 10% on tumor biopsy taken 15 days after palbociclib start, the patient went off study. Surgery was performed 3–5 weeks after end of palbociclib. Anastrozole was continued until surgery. After an amendment, patients with good recovery of the neutrophile count were treated with an additional 10–12 days of palbociclib (cycle 5) until surgery. The primary endpoint, complete cell cycle arrest, was more pronounced with the addition of palbociclib compared to ET alone. The effect was observed in luminal-A and B subtypes and regardless of the menopausal status or *PIK3CA* status. At surgery, Ki67 increased again in those patients who did not receive cycle 5, but remained low in patients treated up to surgery without a gap. Interestingly, most of the patients resistant to ET responded to the addition of palbociclib. The anti-proliferative effect of palbociclib was confirmed by the analysis of the PAM50 proliferation score [65]. The recovery of the proliferation score at surgery was inhibited by the additional administration of palbociclib. These results indicated that the anti-proliferative effect of palbociclib is reversible and the 7 days off, which is needed for neutrophils to recover, can have an adverse effect.

The NeoMONARCH study [66] with abemaciclib and anastrozole addressed a similar question. Abemaciclib alone or together with ET led to a higher decrease in Ki67 after two weeks of treatment compared to ET alone. Contrary to what has been observed in the metastatic setting, the combination therapy, even if effective, did not show a synergistic effect. The short treatment duration in this preoperative setting might have played a role. An exploratory analysis was conducted in patients who missed 4 days or less of abemaciclib treatment compared to those who missed more than 4 days. The Ki67 increase was observed in more than one third of the patients stopping therapy for more than 4 weeks compared to patients remaining on study therapy or who interrupted abemaciclib for more than 4 days. The data support the hypothesis that the continuous delivery of CDK4/6 inhibitors might be important.

The PALLET trial [67] is the largest trial investigating the use of CDK4/6 inhibitors in the neoadjuvant setting. The addition of palbociclib to letrozole significantly decreased cell proliferation after 14 weeks of treatment. Moreover, palbociclib led to a greater suppression of apoptosis as defined by the decline of c-PARP (log-fold change between baseline and end of treatment was −0.80, Interquartile range −1.35 to −0.29; $p < 0.001$), compared to ET alone (−0.42, Interquartile range −0.99 to −0.20). No improvement in the clinical response rate was observed. HR-positive tumors might need longer time to show tumor shrinkage, especially with the use of cytostatic drugs [68–70]. Results are in line with the observations derived from the metastatic setting, where the major impact seems to be in PFS rather than in response rate [20,23,30].

These studies show that most patients achieved a complete cell cycle arrest after a short period of therapy with CDK4/6 inhibitors alone or in combination with ET, supporting the importance of the antitumor activity of CDK4/6 inhibitors in HR-positive HER2-negative breast cancer. However, continuous treatment may be necessary to maintain cell-cycle inhibition. The suppression of apoptosis induced by CDK4/6 inhibitors might explain the absence of a modification in the tumor volume, defined by clinical response [67]. However, a suppression of Ki67 is more reliable compared to tumor response as a marker of treatment activity in patients receiving neoadjuvant ET [71,72] which also correlates with relapse-free survival in the post-neoadjuvant setting [73].

Two trials compared the use of an endocrine-based therapy with chemotherapy. The NeoPal study [74] looked at the use of palbociclib and letrozole in patients with stage II-III node-positive breast cancer. Most patients were classified as luminal-B by PAM50. The combination was associated with a poorer residual cancer burden 0–1, which doubled with the use of chemotherapy. However, Ki67 suppression was similar in both arms. This translated into a similar PEPI score [75] which correlates with breast cancer-specific survival and relapse-free survival. The CORALLEEN study

Table 4
CDK4/6 inhibitors in early breast cancer: neoadjuvant studies.

	Study	Phase	Sample size	Treatment arm	Primary Endpoint	Summary of results
PALBOCICLIB	**NeoPalAna**	II one-arm	50	Anastrozole cycle 0-4 Palbociclib (125 mg daily on days 1-21q 28 days) cycle 1 −4; cycle 5 after amendment	CCCA (Ki67 < 2.7%): change in Ki67 from cycle 1 day 1vs cycle 1 day 15	CCCA overall 87% vs 26%, p < 0.001 CCCA in selected subgroups: PIK3CA mutation 100% vs 25%, p < 0.001 PIK3CA wild type 79% vs 25%, p < 0.001 Luminal-A 100% vs 40%, p = 0.008 Luminal-B 75% vs 9%, p = 0.02 RR assessed by mammography (n = 41 patients receiving at least 3 cycles): 52%
	PALLET	II randomized	307	Arm A: letrozole for 14 weeks Arm B: letrozole for 2 weeks, than plus palbociclib (125 mg daily on days 1-21q 28) days to 14 weeks Arm C: palbociclib plus letrozole for 14 weeks	CCCA (Ki67 ≤ 2.7%): change in Ki67 between baseline and 14 weeks clinical response	CCCA: 90% vs 59%; p = 0.001 pCR + pPR54.3% vs 49.5%, p = 0.02 PD 3.2% vs 5.4% Median log-fold change in Ki67: 4.1 vs −2.2, p < 0.001
	NeoPAL	II randomized	106	Palbociclib (125 mg daily on days 1-21q 28 days) plus letrozole for 19 weeks FEC100 (5-fluorouracile 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) day 1 q21 days for 3 cycles followed by docetaxel 100 mg/m^2 day 1 q21 days for 3 cycles	RCB 0−1 rate after 19 weeks of treatment	RCB 0−1 7.7 vs15.7 RCB II-III 92.3 vs 84.3 PEPI (BCSS) score 0 17.6 vs 8.0 score 1−3 54.9 vs 36.0 score 4 and beyond 27.5 vs 56.0 PEPI (RFS) score 0 11.5 vs 16.0 score 1−3 59.6 vs 66.0 score 4 and beyond 28.9 vs 38.0
ABEMACICLIB	**NeoMONARCH**	II randomized	224	Lead-in: abemaciclib (150 mg orally twice daily) plus anastrozole or abemaciclib alone or anastrozole alone for 2 weeks followed by abemaciclib plus anastrozole for 14 weeks	CCCA: change in Ki67 from baseline to 2 weeks after treatment	CCCA overall: 68% vs 58% vs14%, p < 0.001 CCCA in selected subgroups: PIK3CA mutation 58% vs 70% vs 13%, A vs C p = 0.009, B vs C p = 0.007 PIK3CA wild type 71% vs 57% vs 15% A vs C p < 0.001, B vs C p = 0.001 Luminal-A 80% vs 60% vs 11% A vs C p = 0.023, B vs C p = 0.095 Luminal-B 50% vs 64% vs NE A vs C p = 0.286, B vs C p = 0.029 Radiologic ORR 46% (CR 5%, PR 42%) pCR overall 4%.
RIBOCICLIB	**CORALLEEN**	II randomized	106	Ribociclib (600 mg daily on days 1-21q 28 days) plus letrozole for 6 cycles Doxorubicin (60 mg/m^2 iv) and cyclophosphamide (600 mg/m^2 iv) day 1 q21 days for 4 cycles followed by weekly paclitaxel (80 mg/m^2 iv) for 12 weeks	PAM50 ROR at surgery	High ROR at baseline: 85% vs 89% Intermediate ROR at baseline: 15% vs 11% Low ROR at surgery: 46.9% vs 46.1% Conversion to luminal-A at surgery 87.8% vs 82.7%

Abbreviations: BCSS, breast cancer specific survival; CCCA, complete cell-cycle arrest, q, every; iv, intravenous; NE, not examined; pCR, pathologic complete response; pPR, pathologic partial response; RCB, residual cancer burden; RFS, relapse-free survival; ROR, risk of relapse; RR, response rate.

[76] enrolled patients with stage I-IIIA early breast cancer and luminal-B by PAM50. The study suggests that a high proportion of the patients with high-risk early stage breast cancer could achieve a molecular downstaging of the disease with the combination of ribociclib together with letrozole.

Taken together, these results suggest that the combination of CDK4/6 inhibitors and ET in early HR-positive breast cancer could have similar biological and clinical effects as chemotherapy, with a more favorable benefit–risk profile. However, in reality also patients receiving chemotherapy will be treated with an

ET±abemaciclib and do not only receive chemotherapy alone. Nevertheless, the chemotherapy-free strategy might be an additional treatment option especially in patients with early luminal-B breast cancer, not candidates for chemotherapy, e.g. elderly patients [46,77]. This is currently investigated in the Appalaches trial for elderly patients (NCT03609047) as well as the ADAPTcycle trial (NCT04055493) [78].

5. Which patients derive the greatest benefit by the addition of CDK4/6 inhibitors in early breast cancer?

In early breast cancer, toxicity of new therapies impacts on patient compliance and quality of life. Therefore, it is important to define a population with not only a relatively high but also an absolutely high benefit for the combination therapy. CDK4/6 inhibitors have the potential to overcome ET resistance. The results of the PALOMA-3 and MONARCH-2 trials in the hormone sensitive and non-sensitive cohort point into different directions [21,31]. In the PALOMA-3 study it seems that only patients with ET sensitive tumors derive a benefit from palbociclib in terms of improved OS, whereas in the MONARCH-2 trial there seems to be a benefit in patients with primary ET resistance. In none of the studies the interaction test was positive indicating these results are mainly driven by patient selection rather than biology. The combined analysis of the MONALEESA-3 and -7 studies demonstrated a consistent prolongation of overall survival with ribociclib in endocrine sensitive first-line patients as well as in patients with early relapse and in second-line meaning less endocrine sensitive or endocrine resistant tumors [32]. Similarly, in the MonarchE study, patients with a highly proliferative tumor, those being more chemotherapy sensitive and less ET sensitive, seem to derive the highest benefit by the addition of abemaciclib.

The neoadjuvant Neopalana study [64] suggested that there might be a difference between luminal-A and B patients. At baseline, luminal-B tumors had a higher Ki67 compared to luminal-A tumors. All luminal-A tumors achieved a decrease equal to no proliferation of Ki67 after 15 days of combination therapy, whereas this was not the case in patients with luminal-B tumors. Palbociclib showed efficacy in patients resistant to ET alone in both luminal-A and luminal-B tumors. However, there were some luminal-B tumors resistant to palbociclib. In the metastatic setting, patients with either luminal-A or luminal-B tumors enrolled in the MONALEESA studies obtained an improvement in PFS. However, luminal-B patients derived the highest degree of benefit [36]. These results underline that patients with high-risk HR-positive early breast cancer may be most likely to benefit from the addition of a CDK4/6 inhibitor. However, which patients might benefit the most from the combination therapy is not clear and should be further explored. The classification of a high-risk population should also be better defined. At the time of the analyses only 12.5% of the patients completed abemaciclib therapy in the MonarchE and 25% palbociclib therapy in the PALLAS study. Therefore, long-term data are urgently needed to answer all those open questions. Meanwhile, the FDA approved the adjuvant therapy with abemaciclib added to ET for patients with high-risk HR+/HER2-negative breast cancer and Ki67 > 20% as based on the inclusion criteria of the MonarchE study.

6. Conclusion

CDK4/6 inhibition represents a fundamental new treatment approach to improve endocrine therapy. While the role of CDK4/6 inhibitors is well established in metastatic breast cancer their use in early breast cancer is still less clear. Further studies investigating a longer treatment duration as well as data on long-term follow-up of the conducted studies are needed to define the place of the different substances in the treatment algorithm of early breast cancer and to define which high-risk patients might benefit the most.

Declaration of competing interest

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