



The role of CDK4/6 inhibitors in early breast cancer

Miguel Gil-Gil ^a, Emilio Alba ^b, Joaquín Gavilá ^c, Juan de la Haba-Rodríguez ^d,
Eva Ciruelos ^e, Pablo Tolosa ^e, Daniele Candini ^f, Antonio Llombart-Cussac ^{g,h,*}



^a Institut Català d'Oncologia IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

^b Department of Medical Oncology, Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain

^c Fundación Instituto Valenciano de Oncología, Valencia, Spain

^d Department of Medical Oncology, Hospital Universitario Reina Sofía, Instituto de Investigación Biomédica de Córdoba (IMIBIC), Córdoba, Spain

^e Department of Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain

^f Medical Department, Pfizer Oncology, Madrid, Spain

^g Department of Medical Oncology, Hospital Arnau de Vilanova, Valencia, Spain

^h FISABIO, Universidad Católica de Valencia, Spain

ARTICLE INFO

Article history:

Received 8 February 2021

Received in revised form

21 May 2021

Accepted 21 May 2021

Available online 25 May 2021

Keywords:

Early breast cancer

Cyclin-dependent kinase 4/6 inhibitors

Adjuvant therapy

Palbociclib

Abemaciclib

ABSTRACT

The use of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) has proven to be a successful strategy in the treatment of advanced hormone receptor-positive (HR⁺) and human epidermal growth factor receptor 2-negative (HER2⁻) breast cancer (BC), leading to a strong interest in their possible role in the treatment of early luminal BC. In this review we collect the most relevant and recent information on the use of CDK4/6i for the treatment of early BC in the neoadjuvant and adjuvant settings. Specifically, we evaluate the results of the large phase 3 adjuvant trials recently released, which have yielded apparently divergent results. We also examine the relevance of biomarkers as response predictive factors for CDK4/6i, the combination between radiotherapy and CDK4/6i, and provide a critical discussion on the evidence that we have so far and future directions of the role of these drugs in the treatment of early BC.

© 2021 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

1. Introduction	160
2. CDK4/6 inhibitors as neoadjuvant therapy for early BC	161
3. CDK4/6 inhibitors in adjuvant therapy for early BC	163
4. Predictors of efficacy and resistance to CDK4/6 inhibitors	163
5. Radiotherapy and CDK4/6 inhibitors	165
6. Discussion and conclusions	165
Funding	167
Declaration of competing interest	167
Acknowledgments	167
References	167

1. Introduction

Breast cancer (BC) is the most common invasive cancer in women. In developed countries, more than 90% of patients are diagnosed in an early-stage [1]. Approximately two-third of BC classifies as endocrine sensitive, defined by the presence of

* Corresponding author. Department of Medical Oncology, Hospital Arnau de Vilanova, Calle de Sant Clement 12, 46015 Valencia, Spain.

E-mail address: allombart1@yahoo.com (A. Llombart-Cussac).

Abbreviations			
AE	Adverse event	LHRH	Luteinizing hormone releasing hormone
AI	Aromatase inhibitor	NCT	Neoadjuvant chemotherapy
BC	Breast cancer	NET	Neoadjuvant endocrine therapy
CCCA	Complete cell cycle arrest	ORR	Objective response rate
CDK4/6i	Cyclin-dependent kinases 4/6 inhibitors	OS	Overall survival
CT	Chemotherapy	pCR	Pathological complete response
DFS	Disease-free survival	PEPI	Preoperative endocrine prognostic index
EFS	Event-free survival	PFS	Progression-free survival
EMA	European Medicines Agency	pRb	Retinoblastoma protein
ET	Endocrine therapy	RCB	Residual cancer burden
FDA	Food and Drug Administration	ROR	Risk of recurrence
FU	Follow up	RT	Radiation therapy
HER2 ⁻	Human epidermal growth factor receptor 2-negative	SAE	Serious adverse event
HR ⁺	Hormone receptor-positive	SERDs	Selective estrogen receptor degraders
IDFS	Invasive disease-free survival	SOC	Standard of care
IMC	Independent monitor committee	TK1	Thymidine kinase 1
		VTE	Vascular thrombo-embolic

hormone receptors (HR⁺) and the absence of human epidermal growth factor-2 receptor overexpression (HER2⁻) [2]. Despite available treatments for early HR⁺/HER2⁻ BC, up to 20% of patients will relapse within 10 years from diagnosis [3], and the likelihood rises in patients harboring genomic or clinical risk factors [4,5]. In recent years, novel therapies have been explored with the aim of minimizing the risk of distant relapse in patients with early HR⁺/HER2⁻ BC.

The cyclin-dependent kinases that regulate cell-cycle progression are involved in the development of resistance to endocrine therapy (ET), and therefore have been considered as promising targets for BC therapy [6,7]. The incorporation of cyclin-dependent kinases 4/6 inhibitors (CDK4/6i) into the treatment of HR⁺/HER2⁻ advanced BC was the main advance in decades, providing consistent benefits in progression-free survival (PFS), objective response rate (ORR), overall survival (OS) and quality of life [8]. Palbociclib was the first highly-selective oral CDK4/6i showing substantial PFS gains when combined with aromatase inhibitors (AI) or fulvestrant in both endocrine sensitive or resistant HR⁺/HER2⁻ advanced BC patients [9]. Palbociclib, as well as abemaciclib and ribociclib, two other CDK4/6i, received Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for the treatment of HR⁺/HER2⁻ advanced BC in combination with either AI or fulvestrant based on the pivotal PALOMA, MONARCH and MONALEESA registration programs that included a total of 8 randomized clinical trials [10–16]. Following on this success, a robust program of clinical research was developed to incorporate CDK4/6i for the treatment of HR⁺/HER2⁻ early BC, including window-of-opportunity, neoadjuvant and adjuvant strategies.

In this article we review the status of all studies with CDK4/6i associated with ET for the treatment of early BC, and especially those with published data. Since patient selection is critical for the application of these therapies, we also review our current understanding on biomarkers related to CDK4/6i and prognostic factors in the recruited populations and we offer some ideas about the possible interaction between CDK4/6i and radiotherapy (RT). Finally, we discuss the possible causes of conflicting results between studies and we make a reasoned and constructive critical assessment of the influence that trial designs may have had on the outcomes.

2. CDK4/6 inhibitors as neoadjuvant therapy for early BC

Neoadjuvant endocrine therapy (NET) was not broadly accepted until recently as an appropriate standard of care (SOC) in early BC. NET was mostly reserved for elderly patients or the ones carrying significant comorbidities. This decision was related to the molecular heterogeneity of HR⁺/HER2⁻ BC, and the lack of validated predictive and/or prognostic markers that could properly allocate patients to NET or neoadjuvant chemotherapy (NCT). However, nowadays the interest and use of NET in clinical practice is growing, especially for patients presenting tumors with high hormone receptor expression and low proliferative markers. The incorporation of CDK4/6i to NET, based on their described efficacy in metastatic disease, could accelerate these changes.

To date, the studies published on CDK4/6i as neoadjuvant treatment can be classified into two main groups (Table 1). Those which compared CDK4/6i + ET versus ET alone, and those that compared CDK4/6i + ET versus standard chemotherapy (CT). Most of them were randomized phase 2 studies and some of them focused on early or delayed biologic endpoints, such as changes on the proliferative marker Ki67 as a measure of complete cell cycle arrest (CCCA) or exploring potential markers of early or late resistance to ET and CDK4/6i. These include MONALEESA-1 and FELINE for ribociclib [17,18], PALLET for palbociclib [19], and NeoMONARCH for abemaciclib [20]. The decrease in Ki67 staining at 2–4 weeks from the start of NET is a robust and validated marker of efficacy [21]. CDK4/6i combinations showed the highest antiproliferative capacity in terms of CCCA rates defined as percentage of tumors with Ki67 values <2.7% confirmed at an early point as well as at surgery. However, the addition of a CDK4/6i induced no changes in the proportion of preoperative endocrine prognostic index (PEPI) score 0 or pathological complete response (pCR) at the time of surgery. Currently, none of the trials have reported results on event-free survival (EFS). Two important insights for future research derived from these studies, and especially from NeoPalAna: first, a group of patients (approximately 25%), did extremely well with ET alone; a second group clearly benefited from the addition of CDK4/6i, probably by reversing primary resistances to ET (60% of the total), and, finally, for a small proportion of patients the tumor showed to be resistant to both interventions [22]. A second aspect relates to the rebound effect observed on Ki67 values when the CDK4/6i is stopped: this effect may be particularly relevant for palbociclib and ribociclib as both requires a one week

Table 1
Randomized studies with CDK4/6 inhibitors plus ET in neoadjuvant therapy.

Reference	PALLET [19]	NeoPAL [24]	NeoPalAna [22]	FELINE [18]	CORALLEEN [25]	MONALEESA-1 [17]	NeoMONARCH [20]
Drug	Palbociclib 125 mg/d 3 wks on/1 wk off + letrozole	Palbociclib 125 mg qd 3 wks on/1 wk off + letrozole	Anastrozole 1 mg/d 4 wks (cycle 0; with goserelin if premenopausal), then palbociclib (125 mg/d on days 1–21) on cycle 1 day 1 for four 28-day cycles unless Ki67 >10% at day 15	Ribociclib 600 mg qd 3 wks on/1 wk off or Ribociclib 400 mg continuously + letrozole	Ribociclib 600 mg qd 3 wks on/1 wk off + letrozole	Ribociclib 400 mg/d 3 wks on/1 wk off or Ribociclib 600 mg/d 3 wks on/1 wk off + letrozole	Abemaciclib 150 mg c/12 bd continuously + anastrozole
Study design	Phase 2 randomized	Phase 2 randomized	Phase 2. Arm 1: PIK3CA wild type cohort Arm 2: Mutant PIK3CA cohort Arm 3: Endocrine resistant cohort	Phase 2 randomized, placebo-controlled	Phase 2 randomized	Phase 2 randomized, presurgical	Phase 2 randomized: Ana vs Abema vs Ana + Abema x 14 days follow by combination x 14 weeks
Population	HR+/HER2 ⁻ early BC ≥2 cm Postmenopausal	HR+/HER2 ⁻ early BC	HR+/HER2 ⁻ early BC	ER+>66%/HER2 ⁻ early BC ≥ 2 cm Postmenopausal	HR+/HER2 ⁻ early BC ≥ 2 cm Postmenopausal	HR+/HER2 ⁻ early BC	HR+/HER2 ⁻ early BC ≥ 1 cm Postmenopausal
N of patients	307	106	50	120	106	14	173
Control arm	Letrozole 2.5 mg	FEC x3 + Docetaxel x3		Letrozole 2.5 mg + Placebo	AC x4 + w paclitaxel x12	Letrozole	Anastrozole 1 mg
Key inclusion criteria	Stage II y III	Stage II y III luminal B by PAM50	Stage II/III	Stage II y III	Stage I-III A Luminal B by PAM50	T >1 cm Grade 2-3	Stage I-III B
1st endpoint	Change in Ki-67 CR	RCB 0-1	CCCA day 15	PEPI score 0	% ROR low risk	Rate of Ki-67 decrease	CCCA day 14
Secondary endpoints	pCR, %BCS, Apoptosis, Safety	CR, safety, PAM predictive valor, Ki-67 and PEPI		CCCA, Response Rate	CR, MRI Response, Ki-67, pCR, RCB, PEPI score	PK, safety and genetic profiling	CR; RR, pCR safety and Genes changes
CDK4/6i exposure Ki-67	14 weeks Median log-fold change (-4.1 vs -2.2 p <0.001 CCCA (90% v 59%; p <0.001)	19 weeks Decrease -0.95 vs -0.86		24 weeks CCCA at surgery (63.3% vs 75.7% vs 66.7% p = 0.42 CCCA on D14 (51.7% vs 97.1% vs 57.2% p = 0.0001) >10% on D14 (17.2% vs 2.8% vs 5.13% p = 0.025 71.4 vs 73.5 vs 77.8% p = 0.63 30.4% vs 50% vs 38.5% p = 0.25 22.6% vs 29.4% vs 26.5% p = 0.57	24 weeks	2 weeks 69% letrozole alone 96% Ribociclib 400 mg + letrozole 92% Ribociclib 600 mg + letrozole	14–16 weeks CCCA 14% vs 58% vs 68%
CR US Response MRI Response	54.3% vs 49.5%	74.5% vs 76%	80% (68%–90%) 41% (25%–58%) 52% (35%–68%)	71.4 vs 73.5 vs 77.8% p = 0.63 30.4% vs 50% vs 38.5% p = 0.25 22.6% vs 29.4% vs 26.5% p = 0.57	62.3% vs 53.9% 57.2% vs 78.8%	–	46%
pCR	3.3% vs 1.1% p = 0.43	–	CCCA rate 87% vs. 26%, p <0.001	–	2% vs 5.8%	–	4%
RCB 0–1	–	7.6% vs 15.7%		–	6.1% vs 11.8%	–	–
PEPI score 0	–	17.3% vs 8%		25.8% vs 29.7 vs 20.6% p = 0.96	22.4% vs 17.3%	–	–
AEs (CDK4/6 i vs control)	Any (99% vs 91%) G3 (50% vs 17%) G4 (4% vs 0%)	G3 43.4 vs 18.9% G4 1.9% vs 20.7%		AST/ALT G3 2.7% vs 31% vs 17% Neutropenia G3 0% vs 31.7% vs 7.3%	G3/4 neutropenia 43% vs 60% Febrile N 1% vs 13% G3/4 ALT 20% vs 10%	G3/4 0% in all arms	Any 96% G3 36% G4 2%
% dose reduction or CDK4/6i discontinuation	5% dose reduction 19% vs 15% (discontinuation)	18.9% vs 30.2% (dose reduction) 3.7 vs 13.2 (discontinuation)		–	–	–	–

AC, Adriamycin plus Cyclophosphamide; AEs, Adverse Events; BC, Breast Cancer; CCCA, Complete Cell-Cycle Arrest; CDK4/6, Cyclin-Dependent Kinases 4 or 6; CR, Clinical Response; HR, Hormone Receptor; MRI, Magnetic Resonance Image; pCR, pathological Complete Response; PK, pharmacokinetics; RCB, Residual Cancer Burden; RR, Radiological Response; US, Ultrasound.

of rest in every cycle in contrast with abemaciclib [22]. The rebound effect can be reversed by prolonged treatment with CDK4/6i, suggesting that extended exposure to these drugs could be needed to maintain their cytostatic effect [23].

A second approach compared CDK4/6i + NET with optimal CT schemes. These studies were NeOPAL for palbociclib [24], and CORALLEEN for ribociclib [25]. In these studies, the initial selection of patients focused on high-risk BC based on genomic platforms such as PAM50 risk of recurrence (ROR). Both studies showed that NCT is associated with a higher activity in terms of cell death and residual cancer burden (RCB) at the time of surgery, while CDK4/6i + NET showed a higher and faster antiproliferative effect based on Ki67 changes.

To confirm CDK4/6i + NET as a valid strategy, guidelines that define which patients can benefit and the optimal duration of treatment must be established. In this respect, the utility of genomic platforms needs to be validated with studies of extended follow-up. In coming years, we will have the results of studies with new designs and strategies, such as the combination with new selective estrogen receptor degraders (SERDs) and palbociclib (NCT04436744) or the search for new predictive and prognostic markers. The DxCARTEs study (NCT03819010) will assess the role of Oncotype DX Recurrence Score by measurement of molecular changes before and after 6 months of palbociclib and NET [26]. The CARABELA clinical trial (NCT04293393) investigates the role of 12-month treatment with abemaciclib and NET versus NCT based on anthracyclines and taxanes. Finally, whether letrozole and palbociclib before surgery offer a clinical benefit in patients with clinical residual disease after completing NCT is being explored in the PROMETEO II study (NCT04130152).

3. CDK4/6 inhibitors in adjuvant therapy for early BC

Four major trials have explored the role of CDK4/6i in the adjuvant setting. Three of them, PALLAS and PENELOPE-B for palbociclib, and MONARCH-E for abemaciclib have recently presented results from their interim or final analyses [27–30]. NATALEE (NCT03701334) for ribociclib is still ongoing [31].

PALLAS, MONARCH-E and NATALEE are 3 large, multicenter, randomized, open-label Phase III trials evaluating the efficacy in terms of invasive disease free survival (IDFS), of the addition of 2 years palbociclib, 2 years abemaciclib and 3 years ribociclib to standard adjuvant ET (Table 2).

The PALLAS study included pre- and postmenopausal women or men with stage II (stage IIA limited to a maximum of 1000 patients) or stage III early invasive BC [27]. A total of 5760 patients were recruited from September 2015 to November 2018. Patients were stratified according to stage, CT, age, and geographic region.

The MONARCH-E trial included pre- and postmenopausal women or men with high-risk early invasive breast cancer, defined as the presence of pathologic lymph node involvement and at least one of the following factors indicating a higher risk of recurrence: 4 or more positive axillary lymph nodes, tumor size of at least 5 cm, histologic grade 3, centrally tested Ki67 $\geq 20\%$ on untreated breast tissue. A total of 5637 patients were included in the trial, from July 2017 to August 2019 and stratified for prior CT, menopausal status and region [32].

The NATALEE trial is currently recruiting patients and the estimated sample size is around 5000 of pre- and postmenopausal women or men with anatomic stage II or III HR⁺/HER2⁻ early BC. Stage II was defined as N1 or N0 (T2-3, N0) with G2-3 and/or Ki67 $\geq 20\%$ (testing for Ki67 not mandatory), excluding G1 [31].

The PENELOPE-B trial included 1250 patients with HR⁺/HER2⁻ early BC with residual disease after NCT and considered at high risk by the clinical-pathological stage-estrogen/grade (CPS-EG score),

defined as CPS-EG score of ≥ 3 , or score 2 if nodal status at surgery is ypN⁺. Patients were randomized between February 2014 and December 2017 to receive 13 cycles (approximately 1 year) of palbociclib in combination with standard ET vs standard adjuvant ET alone and were stratified by nodal status at surgery, age at first diagnosis, centrally measured Ki67, global region of participating sites, and risk status [30].

In the PALLAS study, after a median follow-up (FU) of 23.7 months, palbociclib failed to demonstrate a statistically significant benefit in IDFS, with the IDFS rate at 3 years of 88.2% (palbociclib arm) vs 88.5% (control arm) with a HR = 0.93; 95% CI, 0.76–1.15 (p = 0.51) [27]. However, in the MONARCH-E study, after a median FU of 15.5 months, abemaciclib demonstrated to significantly reduce the risk of recurrence, with an absolute difference of 3.5% in the IDFS rate at 2 years being 92.2% (abemaciclib arm) vs 88.7% (control arm) with a HR = 0.75; 95% CI, 0.60–0.93 (p = 0.01) [29]. In the PENELOPE-B trial, at the time of final analysis, after a median FU of 42.8 months, 308 IDFS events had occurred and the study did not meet its primary endpoint: the addition of 1 year-palbociclib to SOC adjuvant therapy in women with HR⁺/HER2⁻ BC at high risk of relapse after NCT did not improve IDFS (HR = 0.93, 95% CI [0.74, 1.16]; p = 0.525) [30].

Other studies exploring palbociclib in the context of early BC are still on-going. Two examples are the phase III POLAR trial (NCT03820830) that is investigating the addition of 3 years of treatment with palbociclib to standard endocrine therapy in isolated loco-regional recurrence of early BC, and the phase II APPALACHES randomized trial (NCT03609047) evaluating adjuvant treatment with 2 years of palbociclib in combination to standard ET as an alternative to CT in elderly patients (age ≥ 70 years) with clinical high-risk HR⁺/HER2⁻ early BC.

In addition to these studies, some noteworthy on-going trials are also exploring CDK4/6i in settings which take into consideration data derived from genomic platforms. For example, the phase III ADAPTCycle (NCT04055493), now recruiting, will evaluate the role of ribociclib (600 mg) in combination with ET compared to SOC CT (followed by adjuvant ET) in patients with intermediate genomic risk as defined by Oncotype®. Similar design can be found in the phase III ADAPTlate (NCT04565054), where a population defined as high-risk of relapse by Oncotype® and that received SOC CT is now randomized to receive either abemaciclib + ET or ET alone.

It is also worth highlighting the phase 2 HIPEX study (NCT04247633), a Korean phase II, multi-center, single-arm trial that evaluates the efficacy of palbociclib with ET as adjuvant treatment in patients with clinical and genomic high risk (defined by The Breast Cancer Test [BCT] platform) HR⁺/HER2⁻ T1-2 N0-1 early BC.

Follow-up has been adapted with new techniques, such as circulating tumor DNA (ctDNA), which can detect molecular relapses. Examples of this innovative design are the phase II LEADER (NCT03285412) with ribociclib or the recently opened phase II DARE (NCT04567420) with palbociclib. PALLAS, MONARCH E and NATALEE have a translational research program that will analyze ctDNA and tissue samples, and the results will be published in coming years.

4. Predictors of efficacy and resistance to CDK4/6 inhibitors

Defining biological predictive markers would be highly valuable in the selection of patients to be treated with CDK4/6i in early BC. Common clinical and pathological criteria have been explored in early and advanced disease, with no relevant findings [11,20,33–40]. Similarly, the benefit of CDK4/6i is independent of the luminal subtype [22,33,41]. In fact, mechanisms of resistance are complex and still poorly understood in terms of underlying

Table 2
Phase 3 studies with CDK4/6 inhibitors plus ET in adjuvant therapy.

	PALLAS [27]	MONARCH-E [29]	PENELOPE-B [30]	NATALEE [31]
Drug	Palbociclib 125 mg qd, 3 wks on/1 wk off	Abemaciclib 150 mg c/12 bd continuously	Palbociclib 125 mg qd 3 wks on/1 wk off	Ribociclib 400 mg qd 3 wks on/1 wk off
Study design	Phase 3 randomized, not placebo-controlled	Phase 3 randomized, not placebo-controlled	Phase 3 randomized, placebo-controlled	Phase 3 randomized, not placebo-controlled
Population	HR ⁺ /HER2 ⁻ early BC	HR ⁺ /HER2 ⁻ early BC	HR ⁺ /HER2 ⁻ early BC, high risk after neoadjuvant CT	HR ⁺ /HER2 ⁻ early BC
Number of patients	5760	5637	1250	Estimated 5000
Patients ≥ N2 or N1 if G3 or T3/4	58.7%	100% (includes Ki67 ≥ 20% in N1)	50.4%	–
Start Date/LPFV	September 2015–November 2018	July 2017–August 2019	February 2014–December 2017	December 2018/Ongoing
Patients with prior CT	82.4–82.7%	95.3–95.5%	100%	–
Key inclusion criteria	Stage II y III	4 or more positive lymph nodes 1–3 lymph nodes and also T ≥ 5 cm, G3, or Ki67 ≥ 20	RID post-neoadjuvant CT. CPS-EG score ≥ 3, or score 2 if nodal status at surgery is ypN+	Stage II (if N1 or N0 (T2–3, N0) with G2–3 and/or Ki67 ≥ 20%) or stage III
Primary endpoint	IDFS	IDFS	IDFS	IDFS
Secondary endpoints	DRFS, LRRFS, OS and safety	DRFS, OS, safety, PK and PROs	IDFS excluding second non-BC, DRFS, OS, IDFS by molecular subtype, safety, PK and QoLQ	RFS, DDFS, OS, PROs, PK, safety and tolerability
CDK4/6i exposure	2 years	2 years	1 year	3 years
Median Follow Up	23.7 months	15.5 months	42.8 months	–
IDFS events	351 events; 170 (palbociclib) vs 181 (control), p = 0.51	323 events; 136 (abemaciclib) vs 187 (control), p = 0.026	308 events; 152 (palbociclib) vs 156 (control), p = 0.525	–
IDFS rate	88.25% (palbociclib) vs 88.5% (control) HR = 0.93; 95% CI, 0.76–1.15 (p = 0.51) at 3 years	92.2% (abemaciclib) vs 88.7% (control) HR = 0.75; 95% CI, 0.60–0.93 (p = 0.01) at 2 years	81.2% (palbociclib) vs 77.7% (control) HR = 0.93; 95% CI, 0.74–1.17 (p = 0.525) at 3 years	–
DRFS rate	89.3% (palbociclib) vs 90.7% (control) HR = 1; 95% CI, 0.79–1.27 (p = 0.9997)	93.6% (abemaciclib) vs 90.3% (control) HR = 0.72; 95% CI 0.56–0.96 (p = 0.01)	–	–
OS	Not mature	Not mature	HR = 0.87, 95% CI, 0.61–1.22 (p = 0.420)	–
AEs (CDK4/6i vs control)	Any grade (99.4% vs 88.6%) G3 (66.8% vs 13.8%) G4 (5.6% vs 0.8%)	Any grade (97.9% vs 86.1%) G3 (43.0% vs 12.0%) G4 (2.5% vs 0.7%)	Any grade (99.8% vs 99.8%) Hematological G3/4 (73.1% vs 1.3%) Non-hematological G3/4 (19.9% vs 19.5%)	–
% of dose reduction and discontinuation of CDK4/6i	55.4% (dose reduction) and 42.2% (discontinuation) 27.1% (discontinuation due to AEs)	42.7% (dose reduction) and 27.7% (discontinuation) 17.2% (discontinuation due to AEs)	47.6% (dose reduction) and 20% (discontinuation) 5% (discontinuation due to AEs)	–
SAEs	12.4% vs 7.6%	12.3% vs 7.2%	9.3% vs 8.7%	–
CDK4/6i relevant toxicity	G3–4 neutropenia, 61.3%	Any VTE 2.3% (1.2% G 3–4) and any ILD 2.7% (0.3% G3–4)	–	–

AEs, Adverse Events; BC, Breast Cancer; CDK4/6i, Cyclin-Dependent Kinases 4 or 6 inhibitors; CI, Confidence Interval; LPFV, last patient first visit; CPS-EG, Clinical-Pathologic Stage - Estrogen/Grade; CT, chemotherapy; DRFS, Distant Relapse-Free Survival; HR, Hormone Receptor; IDFS, invasive Disease-Free Survival; ILD, Interstitial Lung Disease; LRRFS, Loco-Regional Recurrences-Free Survival; OS, Overall Survival; PK, pharmacokinetics; PROs, Patients Reported Outcomes; QoLQ, Quality of Life Questionnaire; RID, Residual Invasive Disease; VTE, Venous Thromboembolic Event; wk, week; SAEs, Serious Adverse Events.

biological processes. Many biomarkers have been explored in samples from the large phase-III studies in advanced disease: most of them analyzing metastatic, endocrine pretreated tumors, limiting their value in early disease.

PIK3CA and *ESR1*, two of the most prevalent mutated genes in metastatic HR⁺/HER2⁻ BC, did not significantly affect the response to CDK4/6i treatment in the metastatic stage [13,14,42]. *PIK3CA* mutations in neoadjuvant studies did not significantly affect proliferation changes [20,22].

The retinoblastoma gene (*RB*) is central to the mechanism of action of CDK4/6i. Preclinical models have shown that the absence of a functional *RB1* acts as a mechanism of resistance to CDK4/6i. In a retrospective study on 348 patients with advanced HR⁺/HER2⁻ BC treated with CDK4/6i plus ET, patients with baseline loss of *RB1* showed a PFS of 3.6 months compared with 10.1 months of those with functional *RB1* (p = 0.0004). However, only 2.5% of the samples presented alterations in *RB1* [43]. In a pooled analysis of MONALEESA-2, -3, and -7, evaluating the baseline ctDNA of 1503 patients, patients with wild-type *RB1* had a numerically longer PFS with ribociclib compared to the mutant *RB1* patients (1.7% of all tumors) [44]. Neoadjuvant studies confirm the low prevalence of basal mutant *RB1* as well as tumors with low *RB1* expression, but

also suggest that the loss of *RB1* activity induces primary resistance to CDK4/6 [20,22].

A whole exome sequencing of 59 tumor samples from CDK4/6i treated patients focused on alterations enriched in the resistant versus sensitive tumors. The biallelic disruption of *RB1* as well as activating alterations in *AKT1*, *RAS*, *AURKA*, *CCNE2*, *ERBB2*, and *FGFR2* were identified [45]. *In vitro* experiments confirmed that these alterations conferred CDK4/6i resistance.

In the PALOMA-3 study, baseline *TP53* mutations on ctDNA were significantly associated with shorter PFS, as were baseline *FGFR1* amplification, identifying patients at risk of early progression [46]. Similarly, ctDNA from patients enrolled in MONALEESA-2 showed that those with *FGFR1* amplification (5% of all patients) exhibited a shorter PFS compared to patients with *FGFR1* wild-type tumors [47]. In contrast, a benefit of ribociclib was observed independently of the alterations of *TP53* and *FGFR1* found in the baseline ctDNA in MONALEESA-3 [48]. The MONALEESA-2 study also demonstrated that ribociclib prolonged PFS regardless of *TP53* mutational status [49].

Proteins involved in the CDK4/6 signaling cascade have been analyzed. In a preclinical study, phosphorylated CDK4 was detected in all palbociclib-sensitive cell lines and was not detected in any of

the resistant cell lines [36]. However, the PALOMA-1 and PALOMA-2 studies failed to demonstrate a relationship between baseline gene expression levels of *CCND1*, *CCNE1/2*, *CDK2/6* and *CDKN2A* and benefit with the addition of palbociclib to letrozole treatment [33].

Increased CDK6 activity has been implicated in *de novo* and acquired resistance to CDK4/6i in several preclinical studies with palbociclib, ribociclib, and abemaciclib [36,37,40]. However, the clinical validation of cyclin D-CDK4/6 complex as a predictive biomarker has failed in most pivotal studies [11,46,49]. *FAT1* loss increases CDK6 levels *in vitro* and *in vivo*. This is mediated by the accumulation of YAP and TAZ transcription factors (key effectors of the Hippo pathway) on the CDK6 promoter. Indeed, genomic alterations of the Hippo pathway components have been found to promote CDK4/6i resistance [43].

Preclinical data suggest that overexpression and amplification of cyclin E1 is predictor of acquired CDK4/6i resistance [50]. In PALOMA-3, *CCNE1* was shown to be highly predictive when evaluated in metastatic biopsies, but only marginal in simple primary biopsies [41]. But in the MONALEESA-3 and PALOMA-2 studies, a similar benefit was observed regardless of levels of expression of *CCNE1* [33,51]. *CCNE1* amplification was also an adverse predictor in the NeoPalAna trial [52], and high *CCNE1* mRNA expression was associated with a worse prognosis in both MONALEESA-2 [36] and in the preoperative phase II POP study [34]. Similarly, in the neo-Monarch study, resistant tumors showed higher expression of *CCNE1* than sensitive tumors, although this was not statistically significant [20]. These data would support the hypothesis that *CCNE1* could be a marker of resistance to CDK4/6i. The correlation between *CCNE1* and *RB1* is still unclear. In the NeoPalAna, the *CCNE1/RB1* ratio discriminated better than *CCNE1* or *RB1* alone between palbociclib sensitive and resistant patients [50].

Thymidine kinase-1 (TK1) plays a key role in DNA replication and is regulated by the transcription factor E2F pathway. In NeoPalAna, TK1 was measured in plasma samples from patients receiving palbociclib in monotherapy or palbociclib plus ET. While baseline TK1 was not prognostic, after one month of treatment patients with increased TK1 had a worse outcome compared to those with decreased or stable activity. This represented the first evidence to suggest that the dynamics of TK1 on CDK4/6i might serve as an early marker of resistance [53].

In conclusion, although there have been some promising results, the attempts to identify a subgroup of patients more likely to benefit from CDK4/6i have been unsuccessful. More robust clinical studies are needed to validate whether all those potential biomarkers can discriminate early CDK4/6i sensitivity or resistance. Vast translational research programs are underway in all three adjuvant studies, including integration of molecular platforms, and will undoubtedly contribute to the knowledge of the biology behind CDK4/6i activity in early ER⁺/HER2⁻ BC.

5. Radiotherapy and CDK4/6 inhibitors

The combination of CDK4/6i and RT has been considered of risk as it may exacerbate known CDK4/6i toxicities, particularly neutropenia and leukopenia. However, pre-clinical data indicate that CDK4/6i may enhance the therapeutic effects of RT [54,55]. Specifically, palbociclib may act as an inhibitor of double-stranded DNA repair [56], and abemaciclib as a multi-functional radiation modifier [57]. In pre-clinical models, CDK4/6 inhibition may exert a protective effect on RT-induced gastrointestinal toxicity [58]. Palbociclib may also have a radio-sensitizing effect by interacting with the p53-ATM signaling axis [59].

In the context of metastatic BC, some series have analyzed the possible association of palliative RT with concomitant CDK4/6i regimens. With the bias from retrospective analyses, no potentially

harmful interactions were identified, nor increase in hematological, skin, neurological or gastrointestinal toxicity were observed when combining CDK4/6i and radiotherapy compared to CDK4/6i alone [60–64]. The largest case series reported on concomitant or sequential treatment with RT and CDK4/6i regimens included 85 patients with palbociclib or ribociclib, confirming that treatment with RT palliative did not impact on CDK4/6i inhibitors dose reduction or discontinuation due to exacerbation of adverse events [64]. These results should be confirmed in larger, controlled studies with greater FU to allow for extrapolation of these data in the context of early BC, where RT doses are higher, and toxicities could be exacerbated in a different way.

Unfortunately, a great number of questions remains unsolved regarding RT and CDK4/6i interactions in early BC. All principal trials in early BC allowed concomitant treatment with CDK4/6i and RT, but the timelines between the end of RT and the start of adjuvant treatment varied among studies. Patients with prior CT reported higher hematological toxicities on PALLAS, but no report has been presented for prior RT. Could RT have played a role in the discontinuations of CDK4/6i observed in these randomized trials?

More questions are opened and more clinical trials with a concomitant or sequential use of adjuvant RT and CDK4/6i are required to better understand if this combination is feasible and whether there is a synergism between CDK4/6i and RT to be explored. Relevant examples of on-going studies are presented in Table 3.

6. Discussion and conclusions

Based on survival gains and outstanding tolerability, the CDK4/6i have become the new SOC for patients with advanced HR⁺/HER2⁻ BC. Vast research programs have been undertaken to translate benefits to early-stage BC patients. Studies in the neo-adjuvant setting had provided consistent safety and efficacy results. However, in line with studies of the advanced disease, no reliable predictive biomarker has been identified to guide patient selection. The first-generation CDK4/6i adjuvant trials selected patients harboring “classical” prognostic high-risk clinic-pathological characteristics. Results from PALLAS, PENELOPE-B and MONARCH-E trials have been recently published [27,29,30,32], generating considerable debate. The three trials, with IDFS as primary objective, provided diverging results. PALLAS at a median FU of 23.7 months showed that the addition of 2 years of palbociclib to SOC adjuvant ET provided no IDFS benefits (HR = 0.93, p = 0.51). PENELOPE-B, at a median FU of 42.83 months, also offered no significant benefit from the addition of one year 13 months of palbociclib to ET (HR = 0.93, p = 0.53). In contrast, MONARCH-E, with a median FU of 15.5 months reported a statistically significant benefit with 2 years of abemaciclib + SOC adjuvant ET (HR = 0.75; p = 0.0092).

The three studies presented relevant differences, particularly in the definition of high-risk patients and the uses of previous CT. PENELOPE-B required residual invasive disease at surgery following adequate neoadjuvant CT. MONARCH-E required node-positive disease, and one additional risk factor for N1, histologic grade 3, Ki-67 ≥20%, or tumor size ≥5 cm. PALLAS study included stage II–III HR⁺/HER2⁻ BC patients, and up to 13% were node-negative. Previous use of CT was quite different, 100% in PENELOPE-B, 95% in MONARCH-E and 83% in PALLAS. The three studies had a median age population of 50–52 years; however, the use of luteinizing hormone releasing hormone (LHRH) agonists was in the range of 20% in all 3 studies. The better prognosis suggested for patients in PALLAS was also supported by the indirect comparison of the control arms; at 2-years the IDFS was 84% in PENELOPE-B, 89% in MONARCH-E, and in the range of 93% for PALLAS.

Table 3
On-going clinical trials in breast cancer with CDK4/6i in combination with RT.

Study name	NCT	Phase n	Status	Type of RT	Arm	Primary Outcome
ASPIRE	NCT03691493	II	42 Recruiting	Palliative RT at bone metastases	Palbociclib + ET + RT	Response rate
PALATINE	NCT03870919	NA	200 Recruiting	Locoregional RT in <i>de novo</i> Stage IV	Palbociclib + Letrozole + locoregional treatment (Cx ± RT or RT)	OS
SRS with CDK4/6i in brain metastases	NCT04585724	I	25 Recruiting	SRS in Brain Metastases	Abemaciclib, Ribociclib or Palbociclib + RT	grade ≥ 3 RT CNS toxicity
Combined Immunotherapies in metastatic ER ⁺ BC	NCT04563507	II	102 Not yet recruiting	SBRT (50 Gy in 5 fractions) to each metastatic lesion	Palbociclib + Letrozole + RT	PFS

NCT, number of clinical trial; RT, radiation therapy; ET, endocrine therapy; NA, not applicable; OS, overall survival; SRS, stereotactic radiosurgery; CDK4/6i, Cyclin-Dependent Kinases 4 or 6 inhibitors; CNS, central nervous system; ER⁺, positive for endocrine receptors; SBRT, stereotactic body radiation therapy; Gy, Gray; PFS, progression-free survival.

The proportion of patients discontinuing therapy is another factor to be analyzed. In the PALLAS study, 42% of patients stopped palbociclib prematurely; and 27% of them due to an adverse event, mainly grade 3 neutropenia [65]. The PALOMA-2 trial in the first-line advanced BC setting, patients faced a similar palbociclib regimen and schedule, and the discontinuation rate was as low as 9% [9,10,13]. However toxicities and severe adverse events reported in PALLAS were similar in kind and incidence to the PALOMA-2 and PALOMA-3 [27]. The only difference between these trials is related to the management of neutropenia, as repeated grade 3 asymptomatic neutropenia required permanent treatment discontinuation. In contrast, the CDK4/6i total discontinuation rate in PENELOPE-B and MONARCH-E were much lower, 19.5% and 21.7% respectively. However, in MONARCH-E discontinuation rates may still increase, as the median FU was short (19.15 months) and many patients were still under treatment [29,66]. Adherence to treatment is of utmost importance in the efficacy of prolonged oral therapies. The symptoms and side effects derived from the treatment are the main causes for an early discontinuation of adjuvant ET [67], and lack of adherence may be the cause of an increase in the rate of recurrence and mortality [68,69]. When considering the incorporation of CDK4/6i into adjuvant ET, the duration of treatment and toxicity can be decisive in adherence and in the selection between the different therapeutic options. It is possible that symptomatic toxicities due to CDK4/6i, such as asthenia, diarrhea, nausea, abdominal pain, arthralgias and alopecia, are likely to limit adherence to treatment. When selecting the best therapeutic option, probably it would be advisable consider the dropout rates from the ongoing studies, the toxicity profile of each CDK4/6i, and the patient characteristics.

The toxicity profile of CDK4/6i in early stage was not dissimilar to the previously reported in advanced disease, but the relevance may be different. In the palbociclib trials, and excluding the well-known neutropenia–leukopenia effect, other severe events were quite infrequent. In PALLAS, fatigue (2%), arthralgia (1%), or upper respiratory tract infections (1%) were the most frequent grade 3 toxicities. The type and incidence of AEs in MONARCH-E were in line to the ones reported in advanced BC. Diarrhea (7%), fatigue (3%), and abdominal pain (1%) were the most common grade 3 toxicities for abemaciclib. However, the vascular thrombo-embolic (VTE) disorders (2%) and particularly pulmonary embolism (1%), although already reported in the metastatic scenario, should be carefully analyzed. In fact, the incidence of pulmonary embolism may be underestimated in MONARCH-E at this moment; FU is still short, and many patients remain on treatment. Moreover, a higher incidence of VTE was identified in the MONALEESA-7 trial for the combination of ribociclib, LHRH-agonists, and tamoxifen in premenopausal patients, so a third factor that needs to be explored is the potential interaction with tamoxifen.

PALLAS and MONARCH-E achieved the predefined number of

IDFS events for interim analyses within 23.8 and 15.5 months of median FU respectively. In summary, many events occurred within the first two years of ET in both studies. International guidelines categorize progressions within the first 2 years of adjuvant ET as primary endocrine resistant, where endocrine sensitivity in advanced disease is clearly compromised. With this very short FU in MONARCH-E, abemaciclib somehow prevented endocrine-resistant events. In the advanced setting indirect analysis suggest a different activity profile for abemaciclib and the other two CDK4/6i. Although non statistically significant, the OS gain in MONARCH-2 was relevant for patients with primary endocrine resistant criteria (HR 0.69). PALOMA-3 OS analysis identified a benefit for patients with endocrine sensitivity to the prior ET line (HR = 0.7, $p = 0.008$) but not for non-sensitive patients (HR = 1.1, $p = 0.29$). A meta-analysis of the MONARCH-2 and -3 trials showed that abemaciclib was more efficient among tumors with aggressive profiles, including short disease-free interval, high grade, or high Ki-67 [70].

Does abemaciclib have underlying mechanisms that may explain differences in early stages but not necessarily for advanced disease? Neoadjuvant studies identified that the one week of CDK4/6i rest is enough to observe an increase in cell proliferation measured by Ki-67 [17–19,24,25,71]. This effect has not been seen with abemaciclib as it does not require a one-week off between cycles. It is unlikely that the small differences in the pharmacokinetics of the three drugs could explain this effect. All three CDK4/6i have a similar absorption, distribution, and metabolism by CYP3A4. Maximum concentration (C_{max}) is achieved within hours in all cases and the half-life within two days. Only for abemaciclib the saturation of drug absorption supported a twice-daily dosing regimen [72].

The three CDK4/6i display subtle differences in kinase selectivity. Abemaciclib is about 14 times more potent inhibitor of CDK4 than of CDK6 and is also a potent inhibitor of CDK9. For ribociclib and palbociclib the IC50 ratio between CDK4 and CDK6 ranges 1.6 to 0.4. As CDK4 is more prevalent in hematological cell lines, neutropenia is the dose-limiting toxicity for both palbociclib and ribociclib. Both drugs require a week of rest between cycles to grant full hematological recovery. Abemaciclib exerts less hematological toxicity, and it does not require dose interruptions, being gastrointestinal the most common dose-limiting toxicity [73,74]. Pre-clinical studies have shown that continuous administration of abemaciclib reduced tumor growth more efficiently compared with an intermittent schedule [72]. Abemaciclib also induces high senescence in BC cell lines. In fact, the continuous regimen for abemaciclib may be crucial when treating micro-metastatic residual disease but not so relevant for controlling advanced disease [73].

Will a longer FU reveal differences in both trials? If palbociclib endorses activity in endocrine sensitive tumors, longer FU will be required to show benefits. Indeed, trials comparing different

endocrine agents or strategies in early BC commonly failed to show differences in the first few years. The SOFT trial in high-risk premenopausal patients required up to 8 years of median FU to demonstrate that the addition of an LHRH agonist to tamoxifen increased the recurrence-free survival (HR = 0.76, $p = 0.009$). Similar observations can be addressed for the adjuvant studies of aromatase inhibitors vs. tamoxifen in postmenopausal patients. PALLAS was designed to capture information up to 10 years and may identify late changes on the pattern of IDFS. Although results will be jeopardized by the early trial interruption and the high discontinuation rates.

The PENELOPE-B results, with 42.8 3-months follow-up, shed new light on this debate. Although patients received just one year of palbociclib (13 cycles), patients were definitively high-risk by clinical-pathological criteria, and the discontinuation rates were reasonable. Differences in IDFS were observed at two years (88.3% vs 84.0% IDFS for palbociclib and placebo respectively), but the effect diluted over time, and at 4-years the IDFS rates were similar (72.4% and 73.0% for palbociclib and placebo respectively). These findings suggest that one-year treatment with palbociclib was able to delay relapses but eventually not prevent them. The IDFS differences at 2-years for the CDK4/6i in MONARCH-E and PENELOPE-B are very similar (3.5% and 4.3% absolute differences respectively). If the effect of CDK4/6i could vanish over time, more mature FU is required from MONARCH-E to rule out this phenomenon.

The decision process defining prognosis and establishing optimal systemic therapy in early ER⁺/HER2⁻ BC is a complex decision. Two molecular platforms, MammaPrint and Oncotype-Dx, have demonstrated to be efficient identifying the lack of benefit from CT in node-negative and node-positive (up to 3 lymph-nodes) and have become standard in clinical practice, but unfortunately the MONARCH-E defined molecular risk by Ki-67 status. Future studies should address the benefits of CDK4/6i in both high and low risk patients by molecular platforms. Several ongoing studies will help establish the value of the CDK4/6i in different early BC populations. The ADAPTCycle is the first to explore ribociclib in patients with genomic intermediate risk and the ADAPTlate is the first to explore abemaciclib in patients with clinical or genomic high risk.

In conclusion, the three adjuvant CDK4/6i trials present relevant differences on patient characteristics, CDK4/6i schedule, treatment duration, and discontinuations rates that may have contributed to the different trial outcomes. However, the activity of abemaciclib in MONARCH-E is remarkable, with a significant 2-year IDFS rate reduction that is mostly related to the prevention of distant recurrences (93.6 vs 90.3%, HR = 0.717, $p = 0.0085$). Mature data are needed to consolidate the early IDFS benefits observed in MONARCH-E and establish the safety profile. Also, a late benefit of palbociclib in more hormone-sensitive tumors cannot be ruled out.

Funding

This review was sponsored by Pfizer Inc.

Declaration of competing interest

MGG reports consulting fees and honoraria from Pfizer, Agendia, and Kern; advisory roles for AstraZeneca and Daiichi-Sankyo; travel grants from Pfizer, Roche, Novartis, and Kern.

EA reports advisory roles for Roche, Novartis, Pfizer, Eli Lilly, BMS, AstraZeneca, Genomic Health, and Nanostring; travel grants from Celgene; research grants from Roche, Pfizer, Sysmex, MSD, and Nanostring.

JG reports consulting fees and honoraria from Novartis, Pfizer, AstraZeneca and Daiichi-Sankyo; advisory roles for Novartis, Pfizer, Eli Lilly and AstraZeneca.

JdIH-R reports consulting fees and honoraria from Pfizer, Novartis, and Agendia; advisory roles for AstraZeneca, Daiichi-Sankyo, Pfizer, Novartis and Roche; travel grants from AstraZeneca, Pfizer, Roche and Novartis.

EC reports consulting fees from Pfizer, Eli Lilly, Roche, Novartis, AstraZeneca and MSD; participating as a speaker for Roche, Pfizer and Eli Lilly; travel grants from Roche and Pfizer.

PT reports personal fees from AstraZeneca and honoraria for participation in advisory boards from Amgen, AstraZeneca, MSD, Roche, Pfizer and Eisai.

DC is an employee of and may own stock in Pfizer Inc.

AL-C reports owing stock, patents and intellectual property with MedSIR; consultant for AstraZeneca, Daiichi-Sanyo, MSD, Novartis, Pfizer, Roche and Eli Lilly; research funding from Eisai, Daiichi-Sanyo, Roche, Pfizer, Eli Lilly, MSD, Genomic-Health, Agendia and Pierre Fabre; travel grants from Roche, Pfizer and Eli Lilly; providing expert testimony for AstraZeneca.

Acknowledgments

Editorial support was provided by Francisco López de Saro (Trialance SCCL), funded by Pfizer Inc.

References

- [1] Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin* 2020;70:7–30. <https://doi.org/10.3322/caac.21590>. 2020.
- [2] Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst* 2014;106. <https://doi.org/10.1093/jnci/dju055>.
- [3] Early Breast Cancer Trialists' Collaborative Group (eBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015;386:1341–52. [https://doi.org/10.1016/S0140-6736\(15\)61074-1](https://doi.org/10.1016/S0140-6736(15)61074-1).
- [4] Mamounas EP, Tang G, Paik S, Baehner FL, Liu Q, Jeong JH, et al. 21-Gene Recurrence Score for prognosis and prediction of taxane benefit after adjuvant chemotherapy plus endocrine therapy: results from NSABP B-28/NRG Oncology. *Breast Canc Res Treat* 2018;168:69–77. <https://doi.org/10.1007/s10549-017-4550-8>.
- [5] Early Breast Cancer Trialists' Collaborative Group (eBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378:771–84. [https://doi.org/10.1016/S0140-6736\(11\)60993-8](https://doi.org/10.1016/S0140-6736(11)60993-8).
- [6] Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. *Breast Cancer Res* 2016;18:17. <https://doi.org/10.1186/s13058-015-0661-5>.
- [7] Sobhani N, D'Angelo A, Pittacolo M, Roviello G, Miccoli A, Corona SP, et al. Updates on the CDK4/6 inhibitory strategy and combinations in breast cancer. *Cells* 2019;8. <https://doi.org/10.3390/cells8040321>.
- [8] Gao JJ, Cheng J, Bloomquist E, Sanchez J, Wedam SB, Singh H, et al. CDK4/6 inhibitor treatment for patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer: a US Food and Drug Administration pooled analysis. *Lancet Oncol* 2020;21:250–60. [https://doi.org/10.1016/S1470-2045\(19\)30804-6](https://doi.org/10.1016/S1470-2045(19)30804-6).
- [9] Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016;375:1925–36. <https://doi.org/10.1056/NEJMoa1607303>.
- [10] Turner NC, Ro J, Andre F, Loi S, Verma S, Iwata H, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015;373:209–19. <https://doi.org/10.1056/NEJMoa1505270>.
- [11] Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, 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. [https://doi.org/10.1016/S1470-2045\(14\)71159-3](https://doi.org/10.1016/S1470-2045(14)71159-3).
- [12] Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016;375:1738–48. <https://doi.org/10.1056/NEJMoa1609709>.
- [13] Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, 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;17:425–39. [https://doi.org/10.1016/S1470-2045\(15\)00613-0](https://doi.org/10.1016/S1470-2045(15)00613-0).
- [14] Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivov X, 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;35:2875–84. <https://doi.org/10.1200/JCO.2017.73.7585>.
- [15] Johnston S, Martin M, Di Leo A, Im SA, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Canc* 2019;5:5. <https://doi.org/10.1038/s41523-018-0097-z>.
- [16] Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, 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;36:2465–72. <https://doi.org/10.1200/JCO.2018.78.9909>.
- [17] Curigliano G, Gomez Pardo P, Meric-Bernstam F, Conte P, Lolkema MP, Beck JT, et al. Ribociclib plus letrozole in early breast cancer: a presurgical, window-of-opportunity study. *Breast* 2016;28:191–8. <https://doi.org/10.1016/j.breast.2016.06.008>.
- [18] Khan QJ, O'Dea A, Bardia A, Kalinsky K, Wisinski KB, O'Regan R, et al. Letrozole + ribociclib versus letrozole + placebo as neoadjuvant therapy for ER+ breast cancer (FELINE trial). *J Clin Oncol* 2020;38. https://doi.org/10.1200/JCO.2020.38.15_suppl.505. 505–505.
- [19] Johnston S, Puhalla S, Wheatley D, Ring A, Barry P, Holcombe C, et al. Randomized phase II study evaluating palbociclib in addition to letrozole as neoadjuvant therapy in estrogen receptor-positive early breast cancer: PALLET trial. *J Clin Oncol* 2019;37:178–89. <https://doi.org/10.1200/JCO.18.01624>.
- [20] Hurvitz SA, Martin M, Press MF, Chan D, Fernandez-Abad M, Petru E, et al. Potent cell-cycle inhibition and upregulation of immune response with abemaciclib and anastrozole in neoMONARCH, phase II neoadjuvant study in HR(+)/HER2(-) breast cancer. *Clin Canc Res* 2020;26:566–80. <https://doi.org/10.1158/1078-0432.CCR-19-1425>.
- [21] Smith I, Robertson J, Kilburn L, Wilcox M, Evans A, Holcombe C, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol* 2020;21:1443–54. [https://doi.org/10.1016/S1470-2045\(20\)30458-7](https://doi.org/10.1016/S1470-2045(20)30458-7).
- [22] Ma CX, Gao F, Luo J, Northfelt DW, Goetz M, Forero A, et al. NeoPalAna: neoadjuvant palbociclib, a cyclin-dependent kinase 4/6 inhibitor, and anastrozole for clinical stage 2 or 3 estrogen receptor-positive breast cancer. *Clin Canc Res* 2017;23:4055–65. <https://doi.org/10.1158/1078-0432.CCR-16-3206>.
- [23] Rocca A, Schirone A, Maltoni R, Bravaccini S, Ceconnetto L, Farolfi A, et al. Progress with palbociclib in breast cancer: latest evidence and clinical considerations. *Ther Adv Med Oncol* 2017;9:83–105. <https://doi.org/10.1177/1758834016677961>.
- [24] Cottu P, D'Hondt V, Dureau S, Lerebours F, Desmoulins I, Heudel PE, et al. Letrozole and palbociclib versus chemotherapy as neoadjuvant therapy of high-risk luminal breast cancer. *Ann Oncol* 2018;29:2334–40. <https://doi.org/10.1093/annonc/mdy448>.
- [25] Prat A, Saura C, Pascual T, Hernando C, Munoz M, Pare L, et al. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol* 2020;21:33–43. [https://doi.org/10.1016/S1470-2045\(19\)30786-7](https://doi.org/10.1016/S1470-2045(19)30786-7).
- [26] Llombart Cussac A, Pérez-García J, Guerrero Á, Bermejo B, Gil M, Carañana V, et al. Abstract CT219: neoadjuvant letrozole and palbociclib in stage II-IIIb HR [+]/HER2[-] breast cancer with Oncotype DX Recurrence Score ® (RS) 18-25 or 26-100. Analysis of RS changes at surgery (DxCARTES trial). In: *Clin. Trials. American Association for Cancer Research*; 2019. <https://doi.org/10.1158/1538-7445.AM2019-CT219>. CT219–CT219.
- [27] Mayer EL, Dueck AC, Martin M, Rubovszky G, Burstein HJ, Bellet-Ezquerria M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2021;22:212–22. [https://doi.org/10.1016/S1470-2045\(20\)30642-2](https://doi.org/10.1016/S1470-2045(20)30642-2).
- [28] von Minckwitz G, Bear H, Bonnefoi H, Colleoni M, Gelmon K, Gnant M, et al. Abstract OT2-6-11: PENELOPE: phase III study evaluating palbociclib (PD-0332991), a cyclin-dependent kinase (CDK) 4/6 inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy (GBG-78/BIG1-13). *Canc Res* 2013;73. <https://doi.org/10.1158/0008-5472.sabcs13-ot2-6-11>. OT2-6-11-013–11.
- [29] Johnston SRD, Harbeck N, Hegg R, Toi M, Martin M, Shao ZM, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol* 2020;38:3987–98. <https://doi.org/10.1200/JCO.20.02514>.
- [30] Loibl S, Marmé F, Martin M, Untch M, Bonnefoi H, Kim S-B, et al. Palbociclib for residual high-risk invasive HR-positive and HER2-negative early breast cancer—the penelope-B trial. *J Clin Oncol Off J Am Soc Clin Oncol* 2021; JCO2003639. <https://doi.org/10.1200/JCO.20.03639>.
- [31] Slamon DJ, Fasching PA, Patel R, Verma S, Hurvitz SA, Stephen K, Chia L, et al. NATALEE: phase III study of ribociclib (RIBO) + endocrine therapy (ET) as adjuvant treatment in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) early breast cancer (EBC). *J Clin Oncol* 2019;vol. 37. https://doi.org/10.1200/JCO.2019.37.15_suppl.TPS597. TPS597–TPS597.
- [32] Mayer EL, Gnant M, DeMichele A, Martin M, Burstein H, Prat A, et al. PALLAS: a randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer. *Ann Oncol* 2020;31(suppl.4):S1142–215. <https://doi.org/10.1016/annonc/annonc325>.
- [33] Finn RS, Liu Y, Zhu Z, Martin M, Rugo HS, Dieras V, et al. Biomarker analyses of response to cyclin-dependent kinase 4/6 inhibition and endocrine therapy in women with treatment-naïve metastatic breast cancer. *Clin Canc Res* 2020;26:110–21. <https://doi.org/10.1158/1078-0432.CCR-19-0751>.
- [34] Arnedos M, Bayar MA, Cheaib B, Scott V, Bouakka I, Valent A, et al. Modulation of Rb phosphorylation and antiproliferative response to palbociclib: the preoperative-palbociclib (POP) randomized clinical trial. *Ann Oncol* 2018;29:1755–62. [https://doi.org/S0923-7534\(19\)34123-7](https://doi.org/S0923-7534(19)34123-7) [pii].
- [35] Iida M, Nakamura M, Tokuda E, Toyosawa D, Niwa T, Ohuchi N, et al. The p21 levels have the potential to be a monitoring marker for ribociclib in breast cancer. *Oncotarget* 2019;10:4907–18. <https://doi.org/10.18632/oncotarget.27127>.
- [36] Raspé E, Coulouval K, Pita JM, Paternot S, Rothe F, Twyffels L, et al. CDK4 phosphorylation status and a linked gene expression profile predict sensitivity to palbociclib. *EMBO Mol Med* 2017;9:1052–66. <https://doi.org/10.15252/emmm.201607084>.
- [37] Gong X, Litchfield LM, Webster Y, Chio LC, Wong SS, Stewart TR, et al. Genomic aberrations that activate D-type cyclins are associated with enhanced sensitivity to the CDK4 and CDK6 inhibitor abemaciclib. *Canc Cell* 2017;32:761–776 e6. <https://doi.org/10.1016/j.ccell.2017.11.006>.
- [38] Herrera-Abreu MT, Palafox M, Asghar U, Rivas MA, Cutts RJ, García-Murillas I, et al. Early adaptation and acquired resistance to CDK4/6 inhibition in estrogen receptor-positive breast cancer. *Canc Res* 2016;76:2301–13. <https://doi.org/10.1158/0008-5472.CAN-15-0728>.
- [39] Wang H, Nicolay BN, Chick JM, Gao X, Geng Y, Ren H, et al. The metabolic function of cyclin D3-CDK6 kinase in cancer cell survival. *Nature* 2017;546:426–30. <https://doi.org/10.1038/nature22797>.
- [40] Yang C, Li Z, Bhatt T, Dickler M, Giri D, Scaltriti M, et al. Acquired CDK6 amplification promotes breast cancer resistance to CDK4/6 inhibitors and loss of ER signaling and dependence. *Oncogene* 2017;36:2255–64. <https://doi.org/10.1038/onc.2016.379>.
- [41] Turner NC, Liu Y, Zhu Z, Loi S, Colleoni M, Loibl S, et al. Cyclin E1 expression and palbociclib efficacy in previously treated hormone receptor-positive metastatic breast cancer. *J Clin Oncol* 2019;37:1169–78. <https://doi.org/10.1200/JCO.18.00925>.
- [42] Tolane SM, Toi M, Neven P, Sohn J, Grischke E-M, Llombart-Cussac A, et al. Abstract 4458: clinical significance of PIK3CA and ESR1 mutations in ctDNA and FFPE samples from the MONARCH 2 study of abemaciclib plus fulvestrant. *Clin. Res. Clin. Trials, Am Assoc Canc Res* 2019. <https://doi.org/10.1158/1538-7445.AM2019-4458>. 4458–4458.
- [43] Li Z, Razavi P, Li Q, Toy W, Liu B, Ping C, et al. Loss of the FAT1 tumor suppressor promotes resistance to CDK4/6 inhibitors via the Hippo pathway. *Canc Cell* 2018;34:893–905. <https://doi.org/10.1016/j.ccell.2018.11.006>. e8.
- [44] Andre F, Su F, Solovieff N, Arteaga CL, Hortobagyi GN, Chia SKL, et al. Pooled ctDNA analysis of the MONALEESA (ML) phase III advanced breast cancer (ABC) trials. *J Clin Oncol* 2020;38. https://doi.org/10.1200/JCO.2020.38.15_suppl.1009. 1009–1009.
- [45] Wander SA, Cohen O, Gong X, Johnson GN, Buendia-Buendia JE, Lloyd MR, et al. The genomic landscape of intrinsic and acquired resistance to cyclin-dependent kinase 4/6 inhibitors in patients with hormone receptor-positive metastatic breast cancer. *Canc Discov* 2020;10:1174–93. <https://doi.org/10.1158/2159-8290.CD-19-1390>.
- [46] O'Leary B, Cutts RJ, Liu Y, Hrebien S, Huang X, Fenwick K, et al. The genetic landscape and clonal evolution of breast cancer resistance to palbociclib plus fulvestrant in the PALOMA-3 trial. *Canc Discov* 2018;8:1390–403. <https://doi.org/10.1158/2159-8290.CD-18-0264>.
- [47] Formisano L, Lu Y, Servetto A, Hanker AB, Jansen VM, Bauer JA, et al. Aberrant FGFR signaling mediates resistance to CDK4/6 inhibitors in ER+ breast cancer. *Nat Commun* 2019;10:1373. <https://doi.org/10.1038/s41467-019-09068-2>.
- [48] Neven P, Petrakova K, Val Bianchi G, De la Cruz-Merino L, Jerusalem G, Sonke G, et al. Abstract PD2-05: biomarker analysis by baseline circulating tumor DNA alterations in the MONALEESA-3 study. In: *Poster discuss. Abstr., American association for cancer research*; 2019. PD2. <https://doi.org/10.1158/1538-7445.SABCS18-PD2-05>. 05-PD2-05.
- [49] Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol* 2018;29:1541–7. <https://doi.org/10.1093/annonc/mdy155>.
- [50] Guarducci C, Bonechi M, Benelli M, Biagioni C, Boccagni G, Romagnoli D, et al. Cyclin E1 and Rb modulation as common events at time of resistance to palbociclib in hormone receptor-positive breast cancer. *NPJ Breast Canc* 2018;4:38. <https://doi.org/10.1038/s41523-018-0092-4>.
- [51] Chia S, Su F, Neven P, Im S-A, Petrakova K, Bianchi GV, et al. Abstract PD2-08: gene expression analysis and association with treatment response in postmenopausal patients with hormone receptor-positive, HER2-negative advanced breast cancer in the MONALEESA-3 study. In: *Poster spotlight sess. Abstr., American association for cancer research*; 2020. PD2. <https://doi.org/10.1158/1538-7445.SABCS19-PD2-08>. 08-PD2-08.
- [52] Martin L-A, Pancholi S, Ribas R, Gao Q, Simigdala N, Nikitorowicz-Buniak J,

- et al. Abstract P3-03-09: resistance to palbociclib depends on multiple targetable mechanisms highlighting the potential of drug holidays and drug switching to improve therapeutic outcome. *Canc Res* 2017;77. <https://doi.org/10.1158/1538-7445.sabcs16-p3-03-09>. P3-03-09-P3-03-9.
- [53] McCartney A, Bonechi M, De Luca F, Biagioni C, Curigliano G, Moretti E, et al. Plasma thymidine kinase activity as a biomarker in patients with luminal metastatic breast cancer treated with palbociclib within the TRENd trial. *Clin Canc Res* 2020;26:2131–9. <https://doi.org/10.1158/1078-0432.CCR-19-3271>.
- [54] Whiteway SL, Harris PS, Venkataraman S, Alimova I, Birks DK, Donson AM, et al. Inhibition of cyclin-dependent kinase 6 suppresses cell proliferation and enhances radiation sensitivity in medulloblastoma cells. *J Neuro Oncol* 2013;111:113–21. <https://doi.org/10.1007/s11060-012-1000-7>.
- [55] Yang Y, Luo J, Chen X, Yang Z, Mei X, Ma J, et al. CDK4/6 inhibitors: a novel strategy for tumor radiosensitization. *J Exp Clin Cancer Res* 2020;39:188. <https://doi.org/10.1186/s13046-020-01693-w>.
- [56] Huang CY, Hsieh FS, Wang CY, Chen LJ, Chang SS, Tsai MH, et al. Palbociclib enhances radiosensitivity of hepatocellular carcinoma and cholangiocarcinoma via inhibiting ataxia telangiectasia-mutated kinase-mediated DNA damage response. *Eur J Canc* 2018;102:10–22. <https://doi.org/10.1016/j.ejca.2018.07.010>.
- [57] Naz S, Cook JA, Mitchell JB. Abemaciclib: a multi-functional radiation modifier. *Oncotarget* 2019;10:1230–2. <https://doi.org/10.18632/oncotarget.26652>.
- [58] Wei L, Leibowitz BJ, Wang X, Epperly M, Greenberger J, Zhang L, et al. Inhibition of CDK4/6 protects against radiation-induced intestinal injury in mice. *J Clin Invest* 2016;126:4076–87. <https://doi.org/10.1172/JCI88410>.
- [59] Fernández-Aroca DM, Roche O, Sabater S, Pascual-Serra R, Ortega-Muelas M, Sánchez Pérez I, et al. P53 pathway is a major determinant in the radio-sensitizing effect of Palbociclib: implication in cancer therapy. *Canc Lett* 2019;451:23–33. <https://doi.org/10.1016/j.canlet.2019.02.049>.
- [60] Chowdhary M, Sen N, Chowdhary A, Usha L, Cobleigh MA, Wang D, et al. Safety and efficacy of palbociclib and radiation therapy in patients with metastatic breast cancer: initial results of a novel combination. *Adv Radiat Oncol* 2019;4:453–7. <https://doi.org/10.1016/j.adro.2019.03.011>.
- [61] Hans S, Cottu P, Kirova YM. Preliminary results of the association of Palbociclib and radiotherapy in metastatic breast cancer patients. *Radiother Oncol* 2018;126:181. <https://doi.org/10.1016/j.radonc.2017.09.010>.
- [62] Ippolito E, Greco C, Silipigni S, Dell'Aquila E, Petrianni GM, Tonini G, et al. Concurrent radiotherapy with palbociclib or ribociclib for metastatic breast cancer patients: preliminary assessment of toxicity. *Breast* 2019;46:70–4. <https://doi.org/10.1016/j.breast.2019.05.001>.
- [63] Meattini I, Desideri I, Scotti V, Simontacchi G, Livi L. Ribociclib plus letrozole and concomitant palliative radiotherapy for metastatic breast cancer. *Breast* 2018;42:1–2. <https://doi.org/10.1016/j.breast.2018.08.096>.
- [64] Meattini I, Scoccimarro E, Saieva C, Desideri I, Visani V, Luca Dominici, et al. Impact of metastases directed radiation therapy on CDK4/6 inhibitors dose reduction and treatment discontinuation for metastatic HR+/HER2- breast cancer (MBC). *J Clin Oncol* 2020;38. <https://doi.org/10.1200/JCO.2020.38.15-suppl.562>. 562–562.
- [65] Mayer EL, Fesl C, Dueck A, Martin M, Burstein H, Prat A, et al. Treatment exposure and discontinuation in the PALLAS trial: PALbociclib CoLLaborative Adjuvant Study of palbociclib with adjuvant endocrine therapy for HR+/HER2- early breast cancer. In: San Antonio breast cancer symp. Virtual; 2020. Abstract PD2-03.
- [66] O'Shaughnessy J, Johnston S, Harbeck N, Toi M, Im YH, Reinisch M, et al. Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib combined with adjuvant endocrine therapy for high risk early breast cancer. In: San Antonio breast cancer symp. Virtual; 2020. Abstract GS1-01.
- [67] Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Canc Res Treat* 2012;134:459–78. <https://doi.org/10.1007/s10549-012-2114-5>.
- [68] Brier MJ, Chambless DL, Chen J, Mao JJ. Ageing perceptions and non-adherence to aromatase inhibitors among breast cancer survivors. *Eur J Canc* 2018;91:145–52. <https://doi.org/10.1016/j.ejca.2017.12.006>.
- [69] Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Canc Res Treat* 2011;126:529–37. <https://doi.org/10.1007/s10549-010-1132-4>.
- [70] Di Leo A, O'Shaughnessy J, Sledge GW, Martin M, Lin Y, Frenzel M, et al. Prognostic characteristics in hormone receptor-positive advanced breast cancer and characterization of abemaciclib efficacy. *Npj Breast Canc* 2018;4:41. <https://doi.org/10.1038/s41523-018-0094-2>.
- [71] Martin M, Hurvitz S, Chan D, Fernandez-Abad M, Petru E, Rostorfer R, et al. Abstract PD5-01: final results of Neomonarch: a phase 2 neoadjuvant study of abemaciclib in postmenopausal women with hormone receptor positive (HR+), HER2 negative breast cancer (BC). Poster Discuss Abstr 2018. <https://doi.org/10.1158/1538-7445.SABCS17-PD5-01>. PD5-01-PD5-01.
- [72] Braal CL, Jongbloed EM, Wilting SM, Mathijssen RHJ, Koolen SLW, Jager A. Inhibiting CDK4/6 in breast cancer with palbociclib, ribociclib, and abemaciclib: similarities and differences. *Drugs* 2021;81:317–31. <https://doi.org/10.1007/s40265-020-01461-2>.
- [73] Torres-Guzmán R, Calsina B, Hermoso A, Baquero C, Alvarez B, Amat J, et al. Preclinical characterization of abemaciclib in hormone receptor positive breast cancer. *Oncotarget* 2017;8:69493–507. <https://doi.org/10.18632/oncotarget.17778>.
- [74] Marra A, Curigliano G. Are all cyclin-dependent kinases 4/6 inhibitors created equal? *NPJ Breast Canc* 2019;5:27. <https://doi.org/10.1038/s41523-019-0121-y>.