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REVIEW ARTICLE

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Cyclin-dependent kinase 4/6 inhibitors in the treatment of advanced oestrogen receptor-positive breast cancer

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ABSTRACT

Breast cancer remains the most frequent cancer among women in Poland with malignancies, despite significant improvement in early detection and treatment. In oestrogen receptor-positive breast cancers activation of the CDK4/CDK6/E2F axis is very common, and one of the mechanisms of action of the endocrine therapies is the suppression of CDK4 and CDK6 activity. The inhibition of CDKs is an important target for novel agents. This article concentrates on two CDK4/6 inhibitors, which showed promising efficacy in recently published studies: palbociclib and ribociclib. The phase 3 studies with palbociclib and ribociclib produced practice-changing results, improving the progression-free survival in the first-line setting in ER-positive HER2-negative advanced breast cancer when added to standard endocrine therapy.

Key words: CDK4/6 inhibitor, breast cancer, palbociclib, ribociclib, abemaciclib

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Introduction

Breast cancer remains the most frequent cancer and the second cause of death among women with malignancies in Poland, despite significant improvement in early detection and treatment [1]. Our knowledge of molecular subtypes of the disease and its heterogeneity has expanded in recent years and led to the development of targeted therapies such as endocrine therapy for patients with oestrogen receptor and/or progesterone receptor-positive breast cancer, or anti-HER-2 receptor therapies. There are several molecular pathways that are targeted in the treatment of advanced breast cancer; some of them are shown in Figure 1. However, despite these advances, there are still a large number of patients who develop resistance to the above-mentioned targeted therapies. This resistance is a major clinical challenge, and its mechanisms have gained a lot of attention recently. Several studies [2–4] have shown that the signalling pathway crosstalk with different oestrogen receptors, and several mutations are fundamental in mediating resistance. In luminal breast cancers, activation of the CDK4/CDK6/E2F axis is very common. On the other hand, the reactivation of these kinases plays a major role in endocrine resistance. Cell division cycle (CDC) genes are key regulators of cell divisions [5], and a complex collaboration between cyclines and their associated cyclin-dependent kinases (CDK) drives the cell cycle (Figure 2). Alterations in cell cycle are typical for cancer, and several alterations in regulatory proteins have been described in breast cancer, including alterations in cyclins, RB gene product (pRB), and dysregulation of the cyclin D1:CDK4/6 axis [6–8]. CDK4/6 and cyclin D play a very important role in the regulation and transition from phase G1 to S in the cell cycle, and the inhibition of CDKs is an important target for novel agents. Results of the trials with first-generation, relatively nonselective CDK inhibitors were disappointing, but second-generation CDK inhibitors designed to target CDK4/6 pathway showed promising activity. Data from the preclinical studies identified kinases CD4 and CD6 as potential targets for the new anti-cancer agents [9, 10]. The amplification of the CDK4/6 gene is present in breast cancer, especially in ER-positive disease, and

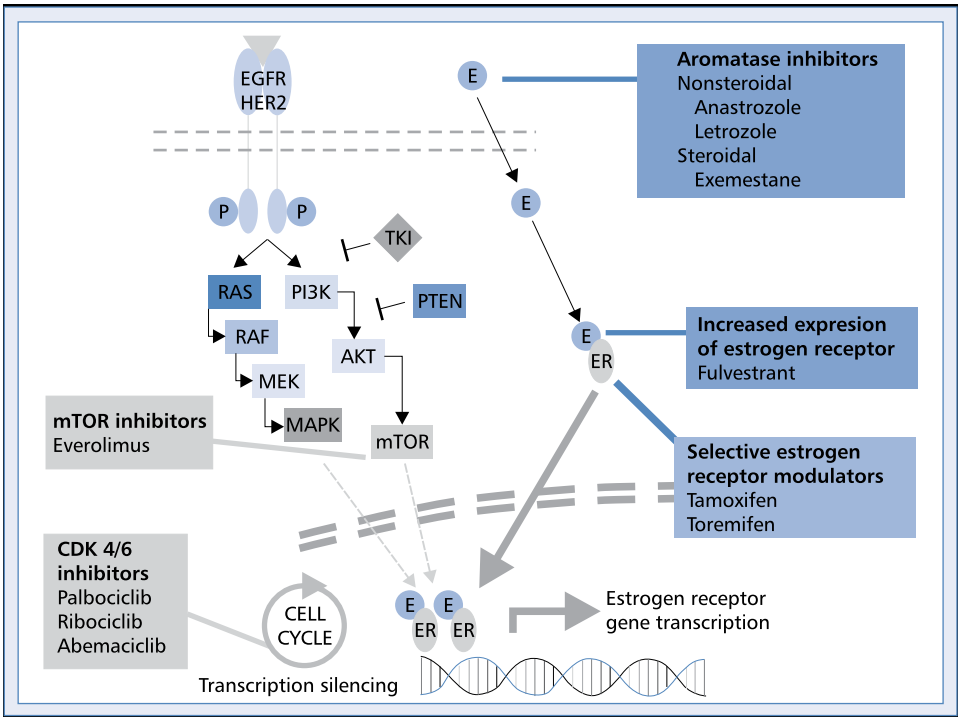

Figure 1. Molecular pathways and targets in breast cancer

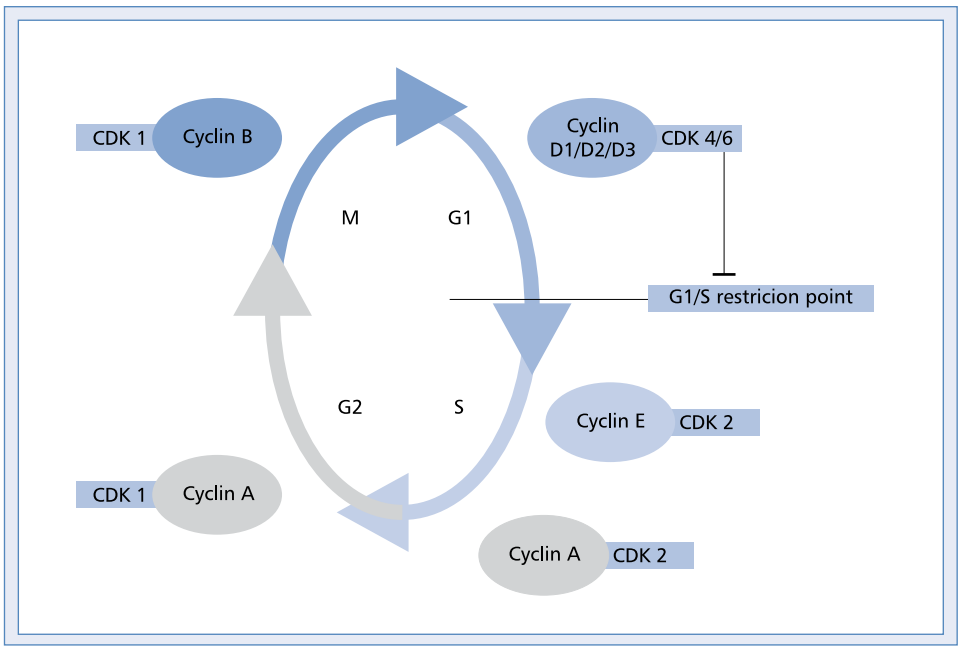

Figure 2. Cell division and a complex collaboration between cyclines and their associated cyclin-dependent kinases (CDK)

CDK4/6 inhibition is an alternative pathway of decreasing cell proliferation for patients resistant to endocrine therapy [11]. This article presents the mechanism of action of CDK4/6 inhibitors and the results of the most important clinical studies with these agents.

First-generation CDK inhibitors

Most of the first-generation CDK inhibitors are pan-CDK inhibitors, meaning they are not specific for any single cyclin-dependent kinase. These nonselec-

tive inhibitors showed limited activity in monotherapy [9] and are associated with severe toxicity caused by off-target interactions [12]. The most studied pan-CDK inhibitor is a synthetic flavonoid called flavopiridol, which showed in clinical phase I and II studies minimal efficacy as a single agent. The results of the therapy of flavopiridol combined with docetaxel in patients with metastatic breast cancer were also disappointing, and the use of this compound was associated with gastrointestinal toxicity and severe neutropenia [13–15]. Another pan-CDK inhibitor, dinaciclib, is considered to be superior to flavopiridol in inhibitory activity of Rb phosphorylation [9], but a phase II trial with dinaciclib versus capecitabine in 30 patients with advanced breast cancer was stopped prematurely after interim analysis showed inferiority of dinaciclib in the time to progression of the disease (2.7 *vs*. 4.2 months) [16].

Second-generation CDK inhibitors

The disappointing results of the first-generation CDK inhibitors were caused mainly by an unknown precise mechanism of action, low specificity toward the kinases, and lack of biomarkers to select an appropriate patient population. This led to the development of the more selective second-generation CDK inhibitors. This review will concentrate on two CDK4/6 inhibitors, which showed promising efficacy in recently published studies: palbociclib and ribociclib, and abemaciclib as an inhibitor under investigation.

Palbociclib

Palbociclib is an orally administered small molecule, a reversible, potent, and selective CDK4/6 inhibitor. In preclinical studies palbociclib exhibited strong inhibition of cell proliferation in ER+ or HER2-amplified cell lines [17, 18] and demonstrated an activity in a model of tamoxifen resistance, which led to the development of clinical studies with palbociclib combined with endocrine therapy. There are three randomised studies with palbociclib in advanced breast cancer: PALOMA-1 — phase II, open-label, randomised trial with palbociclib combined with letrozole versus letrozole alone [19]; PALOMA-2 — phase III study [20] designed to confirm the results of the previous one; and PALOMA-3 — a multicentre, double-blind, phase III study with palbociclib plus fulvestrant versus fulvestrant plus placebo [21]. In all three of them adding palbociclib to the hormonal therapy significantly improved progression-free survival.

PALOMA-1 was an open-label randomised phase 2 study in which postmenopausal women with oestrogen-positive and HER2-negative advanced breast cancer participated. Patients were divided into two cohorts: cohort 1 on the basis of oestrogen and HER-2 receptors status alone; and cohort 2 on the basis of required amplification of cyclin D1, loss of p16, or both. Patients were randomly assigned in a 1:1 ratio to receive 2.5 mg daily oral letrozole or 2.5 mg daily oral letrozole plus 125 mg oral palbociclib for three weeks in 28-day cycles. Due to the interim results analysis, the accrual to the cohort 2 was stopped and a combined analysis of the primary endpoint — progression-free survival (PFS) — was performed. In this study 165 patients were randomly assigned between December 2009 and May 2012, and the median follow-up was 27.9 months for the letrozole alone group and 29.6 months for the experimental arm. The groups were well balanced, and there were no major differences in patients' characteristics between the two groups. Median progression-free survival in the control arm was 10.2 months (95% CI 5.7–12.6) and in the palbociclib plus letrozole arm, 20.2 months (HR 0.488, 95% CI 0.319–0.748, $p = 0.0004$). There were many more grade 3 and 4 adverse events in the experimental arm, among them the most frequent were neutropaenia (54% of patients *vs.* 1% in the control arm) and leukopaenia. However, neutropaenia was not accompanied by serious outcomes such as febrile neutropaenia and/or severe infections. All adverse events were predictable and manageable.

Based on the positive and promising results of the PALOMA-1 study, a large phase 3 study was designed to confirm the efficacy and the safety profile of palbociclib in advanced oestrogen-positive HER2-negative breast cancer. The study (named PALOMA-2) was a double-blind trial, and the 666 patients participating in it were randomised in a 2:1 ratio to receive the treatment: palbociclib plus letrozole or letrozole plus placebo. The schema and dosage of the drugs were the same as in the PALOMA-1 study. Patients who received any prior treatment in the advanced setting were not allowed to take part in the study. The results of the study were presented during the annual meeting of the American Society of Clinical Oncology in Chicago in June 2016 and published in November 2016. Not surprisingly, in this study there was also a statistically significant improvement in the progression-free survival in the experimental arm: 24.8 months in the palbociclib and letrozole group and 14.5 months in the control arm (HR 0.58, 95% CI 0.46–0.72, $p < 0.001$). The objective response (OR) in the experimental arm was 42.1% (95% CI 37.5–46.9) and in the placebo and letrozole arm, 34.7% (95% CI 28.4–41.3). At the time of the analysis the data on overall survival was immature. The safety profile of the palbociclib-plus-letrozole arm was similar to the profile of the PALOMA-1 study: the most common adverse events were neutropaenia (occurred in 66.4% of the

patients in the experimental arm versus 1.4% of patients in the letrozole and placebo arm), leukopaenia (24.8% *vs*. 0%), anaemia (5.4% *vs*. 1.8%), and fatigue (1.8% *vs*. 0.5%). It is worth emphasising that neutropaenia is likely to be caused by CDK4/6 inhibition of the marrow progenitor cells, and therefore it is not accompanied by serious outcomes. In the PALOM-2 study febrile neutropaenia occurred only in 1.8% of patients in the experimental arm.

The third study with palbociclib in the metastatic setting was the PALOMA-3 study, in which this CDK4/6 inhibitor was combined with another endocrine therapy agent — fulvestrant, which is a complete oestrogen receptor antagonist with no agonist effects. It was also a large phase 3 multicentre and double-blind study on women with ER-positive, HER2-negative metastatic breast cancer, who had a disease relapse while on or within 12 months of completion of endocrine adjuvant therapy or progression of the disease while on or within one month of treatment of advanced disease. The protocol allowed one line of palliative chemotherapy before the start of the treatment, and among randomised patients 75% had such treatment. Patients were randomly assigned in a 2:1 ratio to receive oral palbociclib in a dose of 125 mg daily for three weeks in a 28-day cycle, combined with an intramuscular injection of fulvestrant in a dose of 500 mg on days 1 and 15 of cycle 1 and then on day 1 in a 28-day cycle or placebo plus fulvestrant. More than 500 (n = 521) patients participated in the study, and we have updated results on progression-free survival with the median follow-up of 8.9 months, published in April 2016 [22]. The overall survival follow-up is in progress. In the experimental arm median progression-free survival was 9.5 months (95% CI 9.2–11.0) and in the fulvestrant alone arm, 4.6 months (HR 0.46, 95% CI 0.36–0.59, $p < 0.001$). Objective response in the palbociclib and fulvestrant arm was 24.6% (95% CI 19.6–30.2) compared to 10.9% (95% CI 6.2–17.3) in the control arm. There was no statistically significant difference in the progression-free survival between patients with PIK3CA mutations and those in whom no mutations were detected: 5.8 months versus 9.2 months, respectively (HR 1.26, 95% CI 0.94–1.68, $p = 0.94$). The most common palbociclib toxicities were neutropaenia, anaemia, and leucopaenia, but they were manageable.

The three above-mentioned studies [19–22] proved that palbociclib is an effective compound, and based on these studies the drug was approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for the treatment of advanced hormone receptor (HR)-positive human epidermal growth factor receptor 2 (HER2)-negative breast cancer — in the first line combined with letrozole and in the combination with fulvestrant in patients with disease progression following endocrine therapy. Recently, in March 2017, the FDA approved ribociclib as an initial treatment for postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer.

Ribociclib

Another CDK4/6 inhibitor, which showed activity in the treatment of advanced breast cancer, is ribociclib, also known as LEE011. This oral selective CDK4/6 inhibitor showed an efficacy in preclinical studies as an inhibitor of RB-positive breast cancer cell lines [23]. Based on the results of the early phase studies [24, 25] many phase III clinical trials with this compound are ongoing and the results of the MONALEESA-2 study were shown during the European Society for Medical Oncology (ESMO) annual meeting in Copenhagen in October 2016, and they were published in the New England Journal of Medicine in November 2016 [26]. MONALEESA-2 was a large, randomised, placebo-controlled trial for the first-line treatment of postmenopausal women with oestrogen receptor-positive, HER2-negative advanced breast cancer. No prior systemic therapy for the metastatic disease was allowed, and the 668 patients participating in this study were randomly assigned to receive oral ribociclib in the dose 600 mg daily for three weeks in a 28-day cycle with oral letrozole in the dose 2.5 mg daily, or letrozole with placebo. The groups were well balanced with more than half of the patients in both groups receiving previous neoadjuvant or adjuvant endocrine therapy (52.4% in the ribociclib group and 51.4% in the placebo group). The study met its primary endpoint, which was progression-free survival. After 18 months of follow-up the progression-free survival rate in the ribociclib arm was 63% (95% CI 54.6–70.3) compared to 42.2% (95% CI 34.8–49.5) in the control arm. In the experimental arm the median duration of progression-free survival was not reached, and in the placebo group it was 14.7 months (HR 0.56, 95% CI 0.43–0.72, $p = 3.29 \times 10^{-6}$). There was also a statistically significant difference in the overall response rate favouring the experimental arm — 40.7% in the ribociclib group and 27.5% in the placebo group. The most common grade 3 or 4 adverse events were neutropaenia (in 59.3% of patients in the ribociclib group and 0.9% of patients in the placebo group) and leukopaenia (21% and 0.6% respectively). Febrile neutropaenia occurred only in five (1.5%) patients in the ribociclib group, and infections were reported in 50.3% of patients in the experimental arm and in 42.4% of patients in the control arm, but most of these infections were grade 1 or 2 and were manageable. This trial with a CDK4/6 inhibitor and letrozole for the first-line treatment of advanced

Table 1. Comparison between the two studies with CDK4/6 inhibitors in the first-line treatment of advanced ER--positive, HER2-negative breast cancer

	PALOMA-2 palb + letr *vs.* letr	MONALEESA-2 rib + letr *vs.* letr
PFS (months)	24.8 *vs.* 14.5	nr *vs.* 14.7
HR	0.58	0.56
p	$p < 0.001$	$p = 3.29 \times 10^{-6}$
OR		
ITT population	42.1% *vs.* 34.7%	40.7% *vs.* 27.5%
Measurable disease population	55.3% *vs.* 44.4%	52.7% *vs.* 37.1%
CB (ITT)	84.9% *vs.* 70.3%	79.6% *vs.* 72.8%

PFS — progression-free survival; HR — hazard ratio; nr — not reached; OR — overall response (complete and partial response); CB — clinical benefit (complete response, partial response and stable disease lasting 24 weeks or more); ITT — intention to treat population; palb — palbociclib; letr — letrozole; rib — ribociclib

ER-positive, HER2-negative breast cancer had a similar efficacy and tolerability to the PALOMA-2 trial with another CDK4/6 inhibitor — palbociclib. The comparison between those two studies is presented in Table 1.

Abemaciclib

The third small molecule CDK4/6 inhibitor currently under development and studies is abemaciclib (LY2835219). The results of the MONARCH 1 phase II study of abemaciclib in patients with hormone-receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer were presented at the 2016 American Society of Clinical Oncology (ASCO) annual meeting in Chicago [27]. There were 132 patients enrolled in this study, for whom endocrine therapy was no longer a suitable treatment option. They were given orally 200 mg of abemaciclib every 12 hours until disease progression. It is worth mentioning that patients participating in this study were heavily pretreated, having experienced progressive disease on or after prior endocrine therapy, and had received prior chemotherapy for metastatic disease. The primary objective of the trial was an investigator-assessed objective response (ORR), with secondary endpoints of durability of response (DoR), clinical benefit rate (CBR), and progression-free survival (PFS).

At the final analysis of response (minimum of 12 months follow-up), patients treated with abemaciclib achieved an ORR of 19.7% (95% CI 13.3–27.5), with a median duration of response of 8.6 months. The median progression-free survival was six months with a CBR of 42.4%. The treatment was well tolerated. The most common grade 3 non-laboratory treatment emergent adverse events (AEs) were diarrhoea (19.7%) and fatigue (12.9%), with no grade 4 non-laboratory events reported. The most common laboratory AEs were neutropaenia (22.3% grade 3, 4.6% grade 4) and leukopaenia (27.4% grade 3). Only 7.6% of patients discontinued treatment due to AEs, one due to diarrhoea. Based on this study we can say that abemaciclib as a single agent has shown promising activity in this population of pretreated patients. Phase III studies with abemaciclib combined with endocrine therapy are ongoing.

Conclusions and future directions

We are witnessing a new era of the treatment of oestrogen receptor-positive metastatic cancer. The translational research has identified a new relevant biologic target, the cyclin D/cyclin — dependent kinase (CDK)4/6/retinoblastoma (rb) pathway, and recent clinical studies have shown effective inhibitors of this target. The results of the phase 3 studies with palbociclib and ribociclib presented above are practice changing, substantially improving the progression-free survival in the first-line setting in ER-positive, HER2-negative advanced breast cancer when added to the standard endocrine therapy. The rates of the overall response were higher in the experimental arms favouring both CDK4/6 inhibitors over placebo arms. The safety profiles of these drugs is acceptable and the most common adverse events are manageable and reversible by dose interruptions and reductions. No predictive biomarkers have been identified up to date. Further analyses of the subgroups of patients are ongoing in order to select the patients who will benefit most from this treatment. Based on these positive results, there are also ongoing studies with CDK4/6 inhibitors in the neoadjuvant and adjuvant setting. We are also waiting for the results of the studies with a third drug — abemaciclib. Ongoing phase 3 studies with CDK4/6 inhibitors in hormonal receptor-positive and HER2-negtive breast cancer patients includes [28]: PALLAS — a randomised study of palbociclib with standard endocrine therapy versus standard endocrine therapy alone in early breast cancer; PEARL — a study of palbociclib in combination with exemestane *versus* capecitabine in advanced breast cancer patients with resistance to non-steroidal aromatase inhibitors; MONALEESA-7 — a randomised study of ribociclib or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor and goserelin for the treatment of the premenopausal women with advanced breast cancer; MONARCH-2 — a phase III study of abemaciclib combined with fulvestrant in women with hormone receptor-positive, HER2-negative breast cancer; MONARCH-3 — a study with

non-steroidal aromatase inhibitors (anastrozole or letrozole) plus abemaciclib or placebo as a first-line treatment in postmenopausal women with locoregionally recurrent or metastatic breast cancer. There are also interesting ongoing phase 1/2 triple therapy studies: a phase 1b/2 study with ribociclib, letrozole, and phosphatidylinositol 3-kinase (PI3K) inhibitor alpelisib and a phase 1b study with ribociclib, exemestane, and inhibitor of mammalian target of rapamycin (mTOR) everolimus. The results of all these studies will clarify the role of the above-mentioned agents in the treatment of breast cancer and will hopefully identify the subgroups of patients who will benefit the most.

References

1. Wojciechowska U, Olasek P, Czauderna K, Didkowska J. Nowotwory złośliwe w Polsce w 2014 roku, Ministerstwo Zdrowia, 2016; http://onkologia.org.pl/wp-content/uploads/Nowotwory2014.pdf.
2. Sanchez CG, Ma CX, Crowder RJ et al. Preclinical modeling of combined phosphatidylinositol-3-kinase inhibition with endocrine therapy for estrogen receptor-positive breast cancer. Breast Cancer Res 2011; 13: R21.
3. Toy W, Shen Y, Won H et al. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet 2013; 45: 1439–1445.
4. Pritchard KI. Endocrine therapy: is the first generation of targeted drugs the last? J Intern Med 2013; 274: 144–152.
5. Hartwell LH, Culotti J, Reid B. Genetic control of the cell-division cycle in yeast. I. Detection of mutants. Proc Natl Acad Sci USA 1970; 66: 352–359.
6. Arnold A, Papanikolaou A. Cyclin D1 in breast cancer pathogenesis. J Clin Oncol. 2005; 23: 4215–4224.
7. Yu Q, Sicinska E, Geng Y et al. Requirement for CDK4 kinase function in breast cancer. Cancer Cell 2006; 9: 23–32.
8. Landis MW, Pawlyk BS, Li T, Sicinski P, Hinds PW. Cyclin D1-dependent kinase activity in murine development and mammary tumorigenesis. Cancer Cell 2006; 9: 13–22.
9. Asghar U, Witkiewicz AK, Turner NC, Knudsen ES. The history and future of targeting cyclin-dependent kinases in cancer therapy. Nat Rev Drug Discovery 2015; 2: 130–146.
10. Cicenas J, Valius M. The CDK inhibitors in cancer research and therapy. J Cancer Res Clin Oncol 2011; 10: 1409–1418.
11. Heath EI, Bible K, Martell RE, Adelman DC, Lorusso PM. A phase 1 study of SNS-032 (formerly BMS-387032), a potent inhibitor of cyclin-dependent kinases 2, 7 and 9 administered as a single oral dose and weekly infusion in patients with meta- static refractory solid tumors. Invest New Drugs 2008; 1: 59–65.
12. Rizzolio F, Tuccinardi T, Caligiuri I, Lucchetti C, Giordano A. CDK inhibitors: from the bench to clinical trials. Curr Drug Targets 2010; 3: 279–290.
13. Jessen BA, Lee L, Koudriakova T et al. Peripheral white blood cell toxicity induced by broad spectrum cyclin- dependent kinase inhibitors. J Appl Toxicol. 2007; 133–142.
14. Fornier MN, Rathkopf D, Shah M et al. Phase I dose-finding study of weekly docetaxel followed by flavopiridol for patients with advanced solid tumors. Clin Cancer Res 2007; 13: 5841–5846.
15. Tan AR, Yang X, Berman A et al. Phase I trial of the cyclin-dependent kinase inhibitor flavopiridol in combination with docetaxel in patients with metastatic breast cancer. Clin Cancer Res 2004; 15: 5038–5047.
16. Mita MM, Joy AA, Mita A et al. Randomized phase II trial of the cyclin-dependent kinase inhibitor dinaciclib (MK-7965) versus capecitabine in patients with advanced breast cancer. Clin Breast Cancer 2014; 3: 169–176.
17. Fry DW, Harvey PJ, Keller PR et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Cancer Ther 2004; 1427–1438.
18. Finn RS, Crown JP, Lang I et al. Results of a randomized phase 2 study of PD 0332991, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with letrozole vs letrozole alone for first- line treatment of ER+/HER2- advanced breast cancer (BC). Cancer Res 2012; 72 (24 Suppl): S1–S6.
19. Finn RS, Crown JP, Lang I et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015; 16: 25–35.
20. Finn RS, Martin M, Rugo HS et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016; 375: 1925–1936.
21. Turner NC, Ro J, André F et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015; 373: 209–219.
22. Cristofanilli M, Turner NC, Bondarenko I et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016; 17: 425–439.
23. Kim S, Loo A, Chopra R et al. LEE011: an orally bioavailable, selective small molecule inhibitor of CDK4/6–Reactivat-ing Rb in cancer. Mol Cancer Ther 2013; 12 (Suppl 11): PR02. abstract.
24. Juric D, Munster P, Campone M et al. Ribociclib (LEE011) and letrozole in estrogen receptor-positive (ER+), HER2-negative (HER2–) advanced breast cancer (aBC): phase Ib safety, preliminary effi- cacy and molecular analysis. Presented at the 2016 annual meeting of the American Society of Clinical Oncology, Chicago, June 3–7, 2016 (poster).
25. Infante JR, Cassier PA, Gerecitano JF et al. A phase I study of the cyclin-depen- dent kinase 4/6 inhibitor ribociclib (LEE011) in patients with advanced solid tumors and lymphomas. Clin Cancer Res 2016; 22: 5696–5705.
26. Hortobagyi GN, Stemmer SM, Burris HA et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med 2016; 375: 1738–1748.
27. Dickler MN, Tolaney SM, Rugo HS et al. MONARCH1: Results from a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as monotherapy, in patients with HR+/HER2- breast cancer, after chemotherapy for advanced disease. J Clin Oncol 2016; 34 (suppl; abstr 510).
28. https://clinicaltrials.gov/.