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Clinical use of cyclin-dependent kinase (CDK) 4/6 inhibitors in patients with breast cancer — literature review

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ABSTRACT

Luminal subtype predominates in patients diagnosed with breast cancer — the incidence in developed countries is up to 80% of all cases. Hormonal therapy is an important part of the treatment; this is used as adjuvant treatment after radical surgery, and is also the preferred option of palliative systemic treatment. Unfortunately, during adjuvant hormonal treatment as well as palliative therapy, primary or secondary resistance may appear. To prevent and overcome these phenomena a strategy of combined pharmacological treatment was developed. In many clinical trials the effectiveness of doublets composed of hormonal and molecularly targeted drugs was assessed. So far, combination of hormonal therapy with cyclin-dependent kinase 4 and 6 inhibitors appears to be the most successful. Such a combination used in the first or further lines of palliative treatment prolongs progression-free survival. Moreover, its toxicity is relatively low and manageable. Until now, three drugs have been approved for treatment of breast cancer: palbociclib, ribociclib, and abemaciclib. This review describes the mechanism of action of cyclin-dependent kinase 4 and 6 inhibitors and summarises the most relevant trials, which have become the basis of these drugs' approval.

Key words: CDK 4 and 6 inhibitors, palbociclib, ribociclib, abemaciclib, hormone therapy, breast cancer, cyclin-dependent kinase

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Introduction

Breast cancer is a heterogeneous disease, which includes tumours of different biology and different clinical course, drug sensitivity, and prognosis. According to molecular classification based on gene expression analysis, hormone receptors (HRs), HER2 and Ki67 — four subtypes of breast cancer were identified based on immunohistochemistry: luminal A, luminal B, HER2-dependent, and triple negative. It is estimated that in western countries tumours expressing hormonal receptors account for about 80% of cases of breast cancer [1]. An indispensable element of systemic treatment of patients with such cancers is hormone therapy. It is used for both radical and palliative treatment. It is the first-choice treatment for patients with advanced HER2-negative breast cancer, except when the disease is extremely dynamic and is associated with the risk of critical organ failure. Adjuvant hormone therapy in breast cancer patients includes: tamoxifen (selective estrogen receptor modulators — SERMs), luteinising-hormone-releasing hormone (LHRH) analogues, aromatase inhibitors (AIs), steroid (exemestane), as well as non-steroidal aromatase inhibitors (anastrozole, letrozole). In addition, fulvestrant (selective ER down-regulator — SERD), megestrol acetate, and medroxyprogesterone are also used in metastatic disease. AIs and fulvestrant can be used only in patients with hormonally inactive ovaries, either by natural or artificially induced menopause [2, 3].

A significant problem associated with hormonal therapy is drug resistance emerging at various time points. Based on the results of Early Breast Cancer Trialists' Collaborative Group meta-analysis [4], approx. 15% of patients experience disease recurrence during

five years of adjuvant hormone therapy with tamoxifen. However, relapses are also observed many years after treatment cessation: after 10 years the relapse rate increases to 25%, and after 15 years to 33%. Approx. 50–70% of patients with metastatic breast cancer have clinical benefit from the first-line of hormonal therapy, and the remaining patients experience primary resistance to hormone therapy [5]. In general, all patients treated with palliative treatment develop resistance, and the duration of response is reduced along the next hormonal therapy lines. Primary hormonal resistance is defined as relapse within the first two years of adjuvant hormonal therapy or disease progression within six months since introduction of palliative hormonal treatment. Secondary hormone-resistance is defined in case of recurrence diagnosed during adjuvant hormonal therapy, but more than two years after it starts or after its completion, or progression occurs during palliative treatment, six months after its introduction [6].

In order to prevent the development of resistance to hormonal therapy, attempts have been made to combine hormone therapy with molecularly targeted therapies:
- mammalian target of rapamycin (mTOR) kinase inhibitors: everolimus with exemestane [5], temsirolimus with letrozole [7], everolimus with tamoxifen [8];
- anti-HER2 drugs: trastuzumab with AIs [9–11], lapatinib with letrozole [12], lapatinib with fulvestrant [13];
- phosphoinositide 3-kinase (PI3K) inhibitors: pictilisib with fulvestrant [14], buparlisib with fulvestrant [15];
- 26S proteasome inhibitor: bortezomib with fulvestrant [16];
- histone deacetylase inhibitor: entinostat with exemestane [17].

However, most of the aforementioned trials failed, and these drugs (except everolimus) did not enter clinical practice.

The greatest success so far has been the combination of hormones with cyclin-dependent kinase (CDK) 4/6 inhibitors. Such therapy not only significantly prolongs progression-free survival (PFS) compared to hormone therapy alone, but is also associated with relatively low toxicity. This is a review of the literature on the use of CDK 4 and 6 inhibitors — palbociclib, ribociclib, and abemaciclib — in breast cancer patients, with a special focus on the activity of these drugs in patients with advanced HR-positive/HER2-negative disease.

Mechanism of action of CDK 4/6 inhibitors

Cancer cells are characterised by loss of proliferation and aging control, resulting from dysfunction of so-called cell cycle checkpoints. One of them is G1 phase checkpoint in which, after checking for the potential presence of DNA damage, the cell enters the division phase or is stopped in resting phase G0. Passing through this point and cell cycle progression also depend on the presence of favourable metabolic conditions and many signals promoting and inhibiting cellular growth, also extracellular. After crossing this checkpoint, the cell continues the division cycle regardless of the presence of growth factors, so it is also called the restriction point [18]. The direct regulator of G1 phase checkpoint, which incorporates the aforementioned signals, is the mechanism in which retinoblastoma protein (RB) plays a central role. Non-phosphorylated RB protein inhibits cell cycle progression. On the other hand, its phosphorylation by the complex the complex of cyclin-dependent kinases 4 and 6 (CKD4 and CDK6) and cyclin D allows the cycle to pass to the next phase [19, 20]. This is a target for CKD 4 and 6 inhibitors, which prevent the phosphorylation of RB protein and cell cycle progression. This mechanism is shown in Figure 1. Preclinical studies have shown that short-term inhibition of CDK 4 and 6 kinases causes a temporary stop of the cell cycle at G1 phase checkpoint, followed by a cell cycle progression. In the case of long-term inhibition of CDK 4 and 6, cell cycle inhibition is maintained, followed by apoptosis or aging of the cell [21]. Studies on the inhibition of cyclin-dependent kinase activity in neoplastic cells have been initiated from compounds being non-selective inhibitors of these enzymes, such as alvociclib (CDK1, CDK2, CDK4, CDK6, CDK7, and CDK9 inhibitor) or seliciclib (CDK1, CDK2, CDK7, and CDK9 inhibitor) [19]. Unfortunately, the activity of these substances on tumour cells is limited, with high toxicity, especially myelotoxicity.

A breakthrough in these studies was the development of selective CDK 4 and 6 inhibitors. Among them three compounds have shown particularly promising properties and have been successfully moved into the next phases of clinical trials. Palbociclib (Ibrance, PD-0332991; Pfizer), ribociclib (LEE011; Novartis), and abemaciclib (LY2835219; Eli Lilly & Company) are potent, selective inhibitors of CDK 4 and 6 and do not inhibit other cyclin-dependent kinases at all or to a very small extent (palbociclib inhibits CDK1 activity 1000 times less, abemaciclib — at least 160 times less, and ribociclib — more than 1000 times less). These drugs are competitive inhibitors — they compete with ATP molecules for binding to the active site of kinases [20]. Importantly, these medicines are given orally. Palbociclib and ribociclib have a very similar chemical structure, abemaciclib is different in structure and there are reports that it has a greater ability to cross the blood-brain barrier than the other two inhibitors, particularly palbociclib [22].

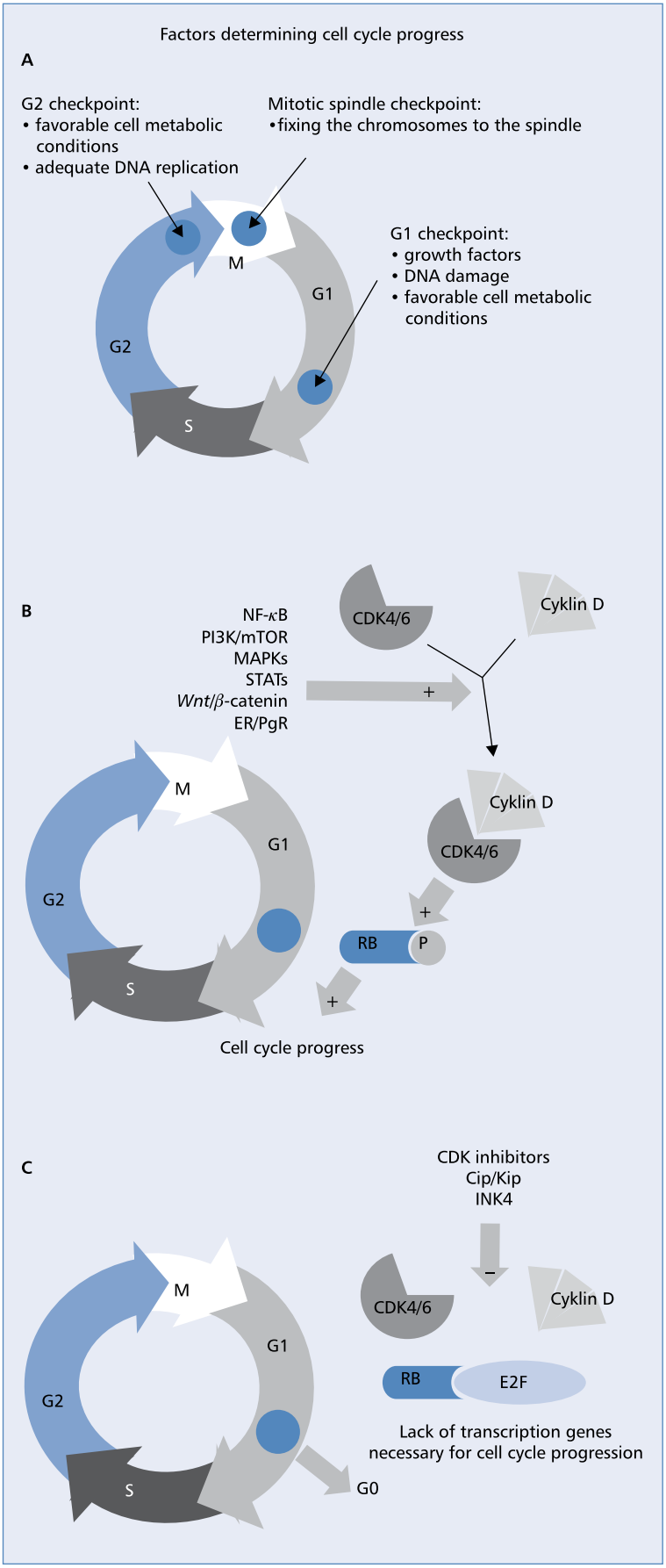

Figure 1A. Factors determining the passing of a cell cycle through the checkpoints; **B.** Cell cycle progression through the checkpoint in case of inactive 4/6: complex of serine/threonine-protein kinase consisting of cyclin-dependent kinase 4 and 6 and their activating subunits — cyclins D1, D2, and D3 phosphorylates RB protein and related proteins P107 and 130. This prevents sequestration of transcription factors from E2F family, which results in the expression of genes responsible for cell cycle progression. Cell cycle progress through this mechanism is promoted by multiple signalling pathways and growth factors (NF-κB, PI3K/mTOR, MAPKs, STATs, Wnt/β-catenin, ER/PgR); **C.** Cell cycle arrest at checkpoint after cyclin-dependent kinases inhibition: RB protein in hypophosphorylation state binds transcriptional factors from E2F family and prevents the expression of genes involved in cell cycle transition from G1 to S phase. Intracellular natural non-specific cyclin-dependent kinase inhibitors are proteins from Cip-Kip family, while proteins from INK4 family specifically inhibit CDK4 and 6. CDK 4/6 — cyclin-dependent kinases 4/6; mTOR — mammalian target of rapamycin kinase; NF-κB — nuclear factor kappa-light-chain-enhancer of activated B cells; MAPKs — mitogen-activated protein kinases; STATs — signal transducers and activators of transcription; ER — oestrogen receptor; PgR — progesterone receptor; Wnt — signal glycoprotein; PI3K — phosphoinositide 3-kinase

As with other cytostatics, the antitumor properties of CDK inhibitors can be strengthened by combination with drugs from other groups. Of note, by inhibiting cell cycle in G1 phase, CDK 4 and 6 inhibitors may exhibit antagonistic properties to drugs targeting synthesis phase or mitosis, and even to ionising radiation [23, 24]. The solution to this problem could be administration of additional medicines at fixed points in time to synchronise the cell cycle and to sensitise different cell populations to their action [20, 24]. In theory, inhibitors of CDKs 4 and 6 may antagonise the effects of immune checkpoint inhibitors because activated T lymphocytes require the efficient functioning of cyclin-dependent kinases.

Dean et al. investigated the inhibition effect of CDK 4 and 6 activity on cell lines undergoing gamma-irradiation [24]. Significant shift of DNA double strand break repair from homologous recombination mechanism (providing repair relatively error-free) was observed toward the mechanism of non-homologous end joining (NHEJ). This mechanism is fraught with more errors, which can cause genomic instability and generate or accelerate carcinogenesis. Hence careful planning should be undertaken to assess the association of CDK inhibitors with chemotherapy, particularly in the context of radical treatment.

These concerns seem not to apply to the combination of CDK 4 and 6 inhibitors with hormone drugs. First of all, theoretically the effects of estrogens as stimulators for cell growth and proliferation are driven by a cyclin D-dependent mechanism, cyclin-dependent kinase, and RB protein. Secondly, cell and animal models have shown a strong association between oestrogen and stimulation of this mechanism: activated estrogen receptors (ERs) as transcription factors increase expression of cyclin D, and in ER+ breast cancer cells CDK 4 and 6 are strongly activated through these receptors and other signalling pathways involved in oncogenesis [20]. In addition, permanently increased cyclin D1 activity and RB phosphorylation are likely to be associated with the development of hormonal resistance of breast cancer cells [25]. CDK 4 and 6 inhibitors exhibit activity in RB protein-expressing cells, and it was revealed that this characterises over 90% of ER+ breast cancers [26]. In breast cancer patients there was also an increase in the activity of the remaining proteins involved in the mechanism based on the RB protein. Amplification of *CCND1* gene encoding cyclin D1 was reported in 38% of patients with breast cancer with HER2 hyperexpression, 58% of patients with luminal B breast cancer, and 29% of patients with luminal A breast cancer; however, increasing the number of copies of *CDK4* — in 24%, 25%, and 14% of patients, respectively [27].

The theoretical assumption that CDK 4 and 6 inhibitors should exhibit anti-tumour effects on ER-positive breast cancer cells and synergism with hormone therapy have been confirmed in studies on cell lines [28], animal models [29, 30], and in phase 1 clinical trials [28, 29]. Their positive results have become the starting point for further phase clinical studies.

Palbociclib — pivotal studies

Palbociclib is a pyridopyrimidine derivative. The drug also exhibits activity against HER2-positive breast cancer cells, especially when accompanied by ER expression [28]. The half-life of the drug is about 26 hours, the recommended daily dose is 125 mg, given in a 3/1 schedule (the drug is taken daily for three weeks, followed by a one week break). At this dosage, nadir neutrophil and platelet counts are usually observed during the week when the drug is not taken, with an increase in the number of blood cells thereafter [20]. Haematological adverse reactions are most commonly seen, but others include fatigue, diarrhoea, nausea, and constipation, which usually are not severe.

The efficacy of palbociclib used in monotherapy in patients with advanced breast cancer was assessed in a phase 2 clinical study published by DeMichele et al. [31]. The study included 37 breast cancer patients with immunohistochemically confirmed expression of RB protein. In 31 patients the receptor profile was ER+/HER2–, in two — ER+/HER2+, and in four — ER–/HER2–. In total, 24 patients had at least two lines of previous hormone therapy, and 28 had at least two lines of chemotherapy. The primary endpoints were direct response and treatment tolerance, secondary endpoints included PFS and assessment of potential predictive biomarkers (RB expression/localisation, Ki67 expression, protein loss, and *CCND1* amplification). Clinical benefit [partial response (PR) and stable disease (SD) for at least 6 months] were reported in 19% of all patients and median PFS was 3.7 months. These results were numerically better in patients with ER expression and in those who received prior hormone therapy. Unfortunately, the predictive value of biomarkers was not demonstrated. The results of the study confirmed the efficacy of the drug in patients with advanced breast cancer and once again highlighted the group of patients with ER expression as specific beneficiaries of this therapy. Palbociclib monotherapy in this group of patients made it possible to achieve PFS similar to the hormone therapy results of consecutive lines.

Studies on efficacy of palbociclib combined with hormone therapy in subsequent palliative treatment lines had acronym PALOMA (Palbociclib: Ongoing Trials in the Management of Breast Cancer).

PALOMA-1 study

The PALOMA-1/TRIO-18 phase 2 study included postmenopausal patients with ER+/HER2– receptor

profile, who had not received prior palliative systemic treatment [32]. Patients were consecutively assigned to two cohorts: recruitment to the first cohort was based only on the mentioned receptor profile, allocation to the second cohort as well as ER+/HER2– feature, required the presence of amplification of the cyclin D1 coding gene (*CCND1*), loss of the P16 protein gene (*INK4A*/*CDKN2A*), or both. Patients from both cohorts were assigned to two study arms: they received either letrozole (standard dosage) or letrozole in combination with palbociclib (dosage as above). The primary endpoint of the study was PFS as assessed by the investigator. Recruitment to cohort 2 was stopped after unplanned interim analysis of the results in cohort 1, which showed a significantly higher efficacy of combination therapy. Investigators concluded that further recruitment of patients based on molecular criteria would not improve the screening of patients compared to ER/HER2 assessment alone. A combined PFS analysis in both cohorts was also allowed. In total 165 patients were included in the study. After approx. 28–29 months of follow-up, median PFS was 10.2 and 20.2 months for patients treated with letrozole and both drugs, respectively (HR 0.488, 95% CI 0.319–0.748, p = 0.0004). In cohort 1, including 66 patients, median PFS was 5.7 and 26.1 months, respectively (HR 0.299; 95% CI 0.156–0.572; p < 0.0001), and in cohort 2, involving 99 patients, it was 11.1 and 18.1 months, respectively (HR 0.508; 95% CI 0.303–0.853; p = 0.0046).

Based on these findings, the US Food and Drug Administration (FDA) in February 2015 granted accelerated approval for palbociclib in this indication. In March 2017, the drug was registered in the standard procedure in combination with aromatase inhibitor in the first-line palliative treatment of postmenopausal patients with HRs+/HER2– breast cancer.

This was possible by confirmation of the impressive results of the PALOMA-1 study in the PALOMA-2 phase 3 trial for patients previously not systematically treated for advanced disease.

PALOMA-2 study

The inclusion criteria in the PALOMA-2 study were as in cohort 1 of the PALOMA-1 study discussed above. Patients were similarly assigned in a 2:1 ratio to two arms — experimental (palbociclib and letrozole) and standard treatment (letrozole) [33]. The study protocol did not allow crossover. The primary endpoint was PFS assessed by the investigator, and secondary endpoints included overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR), patient reported outcome, pharmacokinetics, and safety. The study involved 666 patients. Almost half of them had metastases to the parenchymal organs, 37% of patients had newly diagnosed metastatic breast cancer, 63% of patients received prior systemic treatment as part of radical treatment: almost half of all patients had chemotherapy, and 56% had hormone therapy (including 46% with tamoxifen and 21% with NSAI). Median PFS was 24.8 and 14.5 months, respectively (HR 0.58, 95% CI 0.46–0.72, p <0.001). Subgroup analysis showed greater efficacy of combination therapy regardless of age (< 65 years *vs*. ≥ 65 years), race (white *vs.* Asian), metastases location (visceral *vs.* other), previous adjuvant hormone therapy or chemotherapy, the type of the last hormone drug (AI *vs.* anti-estrogen) or histological subtype (ductal *vs.* lobular carcinoma) — confirming the results of the PALOMA-1 study [34]. The quality of life (QoL) of patients included in the study was assessed based on FACT-B (Functional Assessment of Cancer Therapy — Breast) questionnaire, which included a general assessment of QoL (FACT-General, FACT-G) and breast cancer-related QoL (Breast Cancer-Specific Subscale — BCS). The questionnaire evaluated five aspects of patient welfare: physical, social, emotional, functional, and disease related (BCS). No statistically significant differences were found in the QoL of patients treated with palbociclib and letrozole compared to hormone therapy alone. The authors conclude that combination therapy as well as standard first-line hormone therapy can help maintain health-related QoL (HRQOL) [35].

In both studies, at the time of publication of the above-mentioned articles, no overall survival results were achieved. Such data from the PALOMA-1/TRIO-18 study were presented at this year's Annual ASCO Meeting (2017). By December 2016, 116 deaths had been reported. Median OS was 37.5 and 34.5 months, respectively, and the difference in mortality was not significant [HR = 0.897 (95% CI 0.623–1.24), p = 0.281] [36]. No differences were found when analysing separately the survival of patients in both study cohorts. These disappointing data the authors tried to explain, among others, by the fact that the phase 2 study was not adequately designed to assess OS, slightly more patients treated with standard therapy received further antineoplastic treatment (86 *vs*. 79%), and more received at least three palliative treatment lines (37% *vs*. 18%). On the other hand, less than 3% of patients were treated with CDK 4 and 6 inhibitor beyond progression. Hence, the results of the PALOMA-2 study regarding OS are even more impatiently awaited, albeit with slightly less optimism.

PALOMA-3 study

The clinical value of palbociclib was also assessed in patients previously treated with palliative hormone therapy. This was a goal of the phase 3 PALOMA-3 study, which compared the combination of palbociclib (standard dosage) and fulvestrant (500 mg, standard dosage)

with fulvestrant monotherapy in randomly assigned (2:1) patients [37, 38]. The study involved 521 patients with advanced HRs+/HER2– breast cancer, who had previously received hormone therapy: 40% of patients had AI, 14% tamoxifen, and 46% had both. 33% of patients received palliative chemotherapy. 37% of patients received at least two lines of any pharmacological palliative treatment. Importantly, 21% of patients included in the study were premenopausal — they underwent pharmacological suppression of ovarian function. The median follow-up time was over 15 months. Combination therapy was more effective with respect to PFS, which was the primary endpoint. Median PFS was 11.2 and 4.6 months, respectively (HR 0.50, 95% CI 0.40–0.62, $p < 0.0001$). The secondary endpoints of the study were, among others, overall survival, ORR, patient-reported outcomes, pharmacokinetics, treatment safety, and biomarker evaluation of tumour tissue [*PIK3CA* gene mutations, quantitative assessment of estrogen and progesterone receptor (PgR) expression] [38]. At the time of publication of the first results of the study, mature data on OS was not yet available, but the study protocol did not permit crossover, which allows us to expect reliable data. Patient-reported outcomes included a HRQoL assessment as measured by the EQ-5D questionnaire (EuroQol Group 5-Dimension Self-Report Questionnaire), QLQ-C30 [European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core Module], and QLQ-BR23 (EORTC Breast Cancer Module). Combination therapy has enabled patients to maintain overall QoL, while in patients treated with fulvestrant and placebo it was significantly impaired ($p = 0.03$). Experimental treatment also enabled patients to improve emotional function as compared to placebo ($p = 0.002$) [37]. Unfortunately, it was not possible to identify biomarkers with predictive value for experimental treatment. *PIK3CA* gene mutations in circulating tumour DNA were detected in 33% out of 395 patients included in the study. No association between *PIK3CA* gene status and efficacy was found. No association was also found for level of hormone receptor expression or for the type of hormone therapy used or for the response to it [38].

Adverse events during palbociclib treatment

The most commonly observed grade 3/4 adverse events in the above-mentioned studies were haematological disorders. Neutropaenia was reported in 54% of patients treated with palbociclib and letrozole [32] and 65% of patients treated with palbociclib and fulvestrant [37]. For comparison, after the hormonal treatment alone, the figure was 1%.

Leukopaenia was reported in 19% and 28% of patients treated with the above-mentioned combination therapies, respectively. Despite such frequent neutropaenia, patients treated with palbociclib rarely experienced febrile neutropaenia — no such cases were reported in the PALOMA-1 study, whilst in the PALOMA-2 and PALOMA-3 studies these episodes occurred in eight (1.8%) and three patients (1%), respectively [32, 33, 37]. Serious adverse events in the PALOMA-2 and PALOMA-3 studies occurred in 20% and 13% of patients treated in experimental arm and in 10% and 14% of patients receiving standard treatment, respectively. Non-haematological adverse events grade 3/4 reported in both studies in at least 1% of patients included fatigue, anaemia, thrombocytopaenia, and dyspnoea. In both studies the treatment was discontinued due to adverse events in the experimental and standard treatment group in 9.7 and 5.9% of patients, respectively, and 2.6 and 1.7%, respectively. Thus, the addition of palbociclib to palliative hormone therapy in the first or further line has proven to be not only effective but also a safe and relatively well-tolerated therapeutic option.

The results of the above-mentioned PALOMA-3 study enabled the FDA to register the drug in February 2016 in combination with fulvestrant for the treatment of patients with HRs+/HER2– breast cancer after failure of prior hormone therapy.

According to the European registration of palbociclib, the drug can be given to both pre- and postmenopausal patients in the first or subsequent treatment line. Registration of palbociclib in the first-line hormone therapy in combination with AI in premenopausal patients has not been directly confirmed in a phase 3 clinical trial. In premenopausal patients, hormone therapy should be combined with an LHRH analogue.

Palbociclib — ongoing clinical trials in breast cancer patients

Although palbociclib has already been registered in two indications in breast cancer patients, currently more than 50 clinical trials of various phases are ongoing regarding its efficacy in groups of patients with this diagnosis [39]. In patients with advanced HRs+/HER2– breast cancer the combination of CDK 4/6 inhibitor with tamoxifen or fulvestrant is assessed in the first-line treatment. Very interesting results may be provided by the PEARL phase 3 study, in which patients after disease progression during IA treatment receive palbociclib combined with exemestane/fulvestrant or chemotherapy with capecitabine. Researchers also paid attention to premenopausal patients. In the FATIMA study the efficacy of palbociclib, exemestane, and suppression of ovarian function was compared to hormone

therapy alone. In another study a combination of palbociclib with HT was compared to chemotherapy with capecitabine in this group of patients. Other interesting studies, although phase 1b/2, assessed a combination of palbociclib with new drugs from the SERD group, showing oral bioavailability (SAR439859 and GDC0810). There is also a phase 1/2 study that evaluates the efficacy of combination of palbociclib with hormone therapy (anastrozole) and anti-HER2 drugs (trastuzumab with pertuzumab) in first-line treatment in patients with advanced HRs+/HER2+ breast cancer. Patients with the same diagnosis are included in the phase 3 PATINA study, specifically patients after initial chemotherapy with trastuzumab and pertuzumab for maintenance therapy with both antibodies and hormone therapy with possible combination with palbociclib. Activity of palbociclib in HER2+ breast cancer patients with brain metastases is also clinically evaluated. In patients with advanced breast cancer with androgen receptor (AR) expression the efficacy of combination of palbociclib with bicalutamide is assessed. There are early stage clinical studies that evaluate a combination of palbociclib with mTOR (everolimus, AZD2014) or PI3K (gedatolisyb, kopanlisyb) inhibitors. Finally, palbociclib in combination with hormone therapy and optionally with immune checkpoint inhibitors (avelumab, pembrolizumab) was also evaluated in patients already being treated with CDK 4/6 inhibitor.

Palbociclib is also evaluated in preoperative treatment in combination with hormone therapy in patients with HRs+/HER2– breast cancer (PELOPS, PALLET). Also very interesting is the design of the NEOPAL study, which involves patients diagnosed with luminal subtype of breast cancer with a small and medium risk assessed on the basis of PAM50 gene signature. In this group of patients, the efficacy of palbociclib combined with letrozole is compared with chemotherapy 3 × FEC → 3 × docetaxel. The PREDIXLumB study was designed based on a similar idea, although the subtype of breast cancer was evaluated based on expression of ER, PgR, and Ki67. Patients with luminal B or luminal A subtype of breast cancer with metastatic lymph nodes or age under 40 years are assigned to two arms: either paclitaxel-based chemotherapy or hormone therapy combined with palbociclib. On the other hand, in the PREDIXLumA study the allocation to particular therapeutic groups depends on preliminary tumour response to hormone treatment (change in Ki67 expression). The study involved patients with luminal A subtype, over 40 years of age, and with the feature N0. Patients with good response to initial hormone therapy are randomised to two arms: continuation of hormone therapy or combination with palbociclib; in the absence of response patients receive combination therapy. There are also ongoing studies with preoperative treatment in HRs+/HER2+ patients; in the PALTAM and NA-PHER2 studies a combination of palbociclib with hormone therapy and trastuzumab or double blockade (trastuzumab + pertuzumab) is evaluated.

The clinical value of palbociclib is also evaluated in an adjuvant setting. In the PALLAS study a standard hormone therapy alone is compared to combination with two-year treatment with palbociclib. The PENELOPE-B study is dedicated to high-risk patients who have not achieved pathologic complete response (pCR) after preoperative chemotherapy — they are assigned to standard hormone therapy alone or in combination with one-year treatment with palbociclib.

Ribociclib — pivotal studies

Preclinical studies indicate that the mechanism of action of ribociclib is based not only on CDK 4 and 6 inhibition, but also on interfering with ER, PI3K, and HER2 signalling pathways. In addition, animal models have demonstrated the anti-tumour activity of ribociclib in melanomas with *BRAF* or *NRAS* activating mutations [20]. The combination of this drug with anti-estrogens inhibits the growth of breast tumours, whilst in combination with PI3K inhibitor it causes a dynamic regression of such tumours [30]. Hence, this led to premises for testing the combinations of these drugs in clinical trials. The dose of ribociclib determined in phase 1 clinical studies with this drug used in monotherapy [40] is 600 mg (three tablets); the drug is administered once daily for three weeks with a one week break (four-week cycle) and meal intake does not affect the bioavailability. The half-life of ribociclib is about 30 hours [41]. Ribociclib elimination may be impaired by cytochrome CYP3A4 inhibitors or activators, while the drug inhibits CYP3A4, CYP1A2, and BSEP with a dose-related pattern [20]. Like palbociclib, adverse reactions observed in early phases of clinical trials were haematological disorders, but also nausea and fatigue, and, importantly, asymptomatic prolongation of QT interval. The MONALEESA-1 study [41] assessed among others pharmacodynamic parameters of ribociclib administered in combination with letrozole for 14 days prior to radical surgery in 14 postmenopausal patients with early HRs+/HER2– breast cancer. Combination therapy compared with monotherapy with letrozole has been shown to have a greater effect on the reduction of Ki67 index in cancer cells. In addition, ribociclib treatment resulted in decreased expression of phosphorylated RB protein and decreased expression of *CDK4*, *CDK6*, *CCND2*, *CCND3*, and *CCNE1* genes that are involved in the D-CDK4/6-INK4-RB cyclin signalling pathway.

MONALEESA-2 study

MONALEESA-2 was a study that led to registration of ribociclib in breast cancer patients [42]. In this randomised phase 3 study the efficacy of ribociclib combined with letrozole was compared with placebo with letrozole (dosage of ribociclib as previously described, standard dosage of letrozole) in first-line palliative treatment in postmenopausal patients with HRs+/HER2– breast cancer. The primary endpoint of the study was PFS as assessed by the investigator, and secondary endpoints included: OS, ORR, safety, QoL, pharmacokinetics, and biomarkers of response to the treatment. The study did not allow crossover. In total 668 patients were included; 43% received tamoxifen for radical treatment, and 29% received AI [in those patients, disease-free survival (DFS) had to be at least 12 months]. At the time of preparation of the first publication median follow-up was 15.3 months, and patients receiving experimental treatment did not achieve median PFS, whilst in patients with standard treatment it was 14.7 months, representing a 44% reduction in risk of progression (HR 0.56; 95% CI 0.43–0.72; $p = 3.29 \times 10^{-6}$ for superiority testing). In patients with baseline measurable disease, objective response rates were 53 and 37%, respectively ($p < 0.001$). Updated results of the study were presented at this year's Annual ASCO Meeting (2017) [43]. At the time of the next analysis after more than 26 months of follow-up, the survival data were still insufficient, although a trend towards reducing the death rate was observed in the experimental arm (15 *vs*. 20%, HR 0.75; $p = 0.059$). Median PFS was 25.3 and 16 months, respectively (HR 0.57; $p = 9.63 \times 10^{-8}$). Greater benefit of combination therapy was reported in all subgroups of patients: regardless of age (< 65 years, ≥ 65 years), race (Asian, non-Asian), PgR expression, liver or lung metastases, diagnosis of primary metastatic breast cancer, type of previous hormone therapy, or earlier use of chemotherapy. However, for patients with metastases localised only in bone, the difference in PFS was not statistically significant.

During this congress, the results of QoL analysis of patients included in the MONALEESA-2 study were also presented [44]. The EORTC QLQ-C30, QLQ-BR23, and EQ-5D-5L questionnaires were used. It has been shown that during treatment the QoL was maintained and consistent regardless of the treatment used. There were no statistically or clinically significant differences in the symptoms reported by patients such as fatigue, nausea, or vomiting, but the authors underlined the clinically important difference in the reduction of pain in favour of ribociclib.

The most common adverse events grade 3/4 in experimental and standard treatment arms were neutropaenia (59% *vs*. 0.9%, respectively) and leukopaenia (21% *vs*. 0.6%, respectively). Non-haematological adverse events grade 3/4 were increased ALAT (9% *vs*. 1%) and ASPAT (6% *vs*. 1%) level, infections (4.2% *vs*. 2.4%), fatigue (2.4% *vs*. 1%), diarrhoea (1.2% *vs*. 0.9%), vomiting (3.6% *vs.* 0.9%), constipation (1.2% *vs*. 0%), and back pain (2.1% *vs.* 0.3%). Treatment was discontinued due to adverse events in 7.5% and 2.1% of patients, respectively. The risk of neutropaenia grade ≥ 2 increased along with ribociclib plasma concentration. Although this was the most common complication of treatment with ribociclib, it was the reason for therapy discontinuation in less than 1% of patients. Febrile neutropaenia occurred in 1.5% of patients and was not associated with the need for treatment discontinuation. On the other hand, neutropaenia resulted in breaks in treatment and reduced dose of ribociclib, which allowed the incidence of this complication to diminish as treatment progressed. A new adverse event reported in patients treated with ribociclib was the prolongation of QT interval. It was reported in 3.3 and 0.3% of patients in the MONALEESA-2 study, respectively. Among them, three patients had a break in a treatment, but only in one patient QT interval prolongation was a direct cause of treatment discontinuation [45]. These results indicate that the combination of ribociclib with letrozole is a safe therapeutic option and the side effects of treatment can be avoided by modifying the dosage.

The result of the MONALEESA-2 study became a basis for FDA registration of ribociclib in March 2017 in combination with AI for the first-line treatment of postmenopausal patients with advanced HRs+/ /HER2– breast cancer. In August 2017 ribociclib was also registered in Europe.

Ribociclib — ongoing clinical trials in breast cancer patients

The abovementioned study was a part of the MONALEESA (Mammary Oncology Assessment of LEE011's Efficacy and Safety) clinical trial program. It also includes two phase 3 studies dedicated to patients with advanced breast cancer. The MONALEESA-3 study evaluated the efficacy of ribociclib in combination with fulvestrant as compared to fulvestrant monotherapy in men and postmenopausal women with advanced HRs+/ /HER2– breast cancer, not previously receiving hormone therapy or treated with one hormone therapy line. In the MONALEESA-7 study a combination of ribociclib with tamoxifen or NSAI and goserelin was compared to hormone therapy in premenopausal patients with HRs+/ /HER2– 1 breast cancer in the first-line of palliative treatment. In addition, many studies dedicated to clinical assessment of ribociclib in patients with different stages

of breast cancer are just enrolling [39]: in combination with hormone therapy in preoperative treatment as compared to chemotherapy (CORALLEEN), in adjuvant treatment in combination with hormone, palliative treatment in combination with fulvestrant in patients previously treated with CDK 4 and 6 inhibitor and IA (MAINTAIN), in combination with anti-HER2 agents in patients with HER2+ breast cancer, in combination with bicalutamide in patients with so-called "triple negative" breast cancer with expression of androgen receptors, or in combination with paclitaxel in patients with immunohistochemically confirmed RB protein expression in tumour cells. Interestingly, several projects are devoted to patients with advanced cancer who have undergone several lines of palliative pharmacotherapy, including use of molecular targeted drugs such as CDK 4 and 6 inhibitors or mTOR inhibitors. In these studies, ribociclib is combined with other molecular targeted drugs (PI3K inhibitors, mTOR inhibitors). The high antitumor activity of such drug combinations was observed in preclinical studies, as discussed above. It is worth mentioning two reports from the San Antonio Breast Cancer Symposium 2015 by Juric et al. [46] and Bardia et al. [47]. Only partial results from both phase 1b/2 studies were presented. The first trial assessed a combination of ribociclib, the PI3K inhibitor alpelisib, and letrozole, and the second one a combination of ribociclib, everolimus, and exemestane. In both cases, the researchers assessed triple therapy as active in previously treated breast cancer patients with acceptable toxicity profile and indicated the need to continue the studies with such combinations in subsequent phases. In addition, Bardia et al. indicate amplification of the cyclin D gene as a potential predictor for combination therapy with ribociclib and mTOR inhibitor.

Abemaciclib — pivotal studies

As mentioned above, abemaciclib is structurally distinct from the inhibitors discussed previously. Its activity against CDK 4 and 6 is 14-fold higher as compared to the aforementioned preparations. Abemaciclib also exhibits antitumor activity against HRs+/ /HER2+ breast cancer, non-small cell lung cancer (NSCLC), melanoma, glioblastoma multiforme (GBM), or lymphoma [29]. In addition, it crosses the blood-brain barrier and exhibits antitumor activity against cerebral metastases, which was preliminarily observed in animal models and confirmed in clinical studies [29, 48]. Serum concentration increases with dose, and the half-life is between 17 and 38 hours [29]. When used alone, the dose of abemaciclib is 200 mg twice daily, but in combination with hormone therapy the established dose is 150 mg twice daily. The drug is administered continuously. Abemaciclib used in preoperative treatment of patients with early HRs+/ /HER2– breast cancer, either in combination with AI or in monotherapy, caused a greater reduction in Ki67 expression as compared to AI [49].

The activity of abemaciclib in monotherapy in patients with advanced breast cancer was confirmed in the phase 2 MONARCH-1 study [50]. This study included 132 patients with advanced HRs+/HER2– breast cancer, with documented resistance to previous hormone therapy: 64% of patients received previously at least two lines of palliative hormone therapy. Patients also underwent one or two palliative chemotherapy regimens, and 28% of them were previously treated with everolimus. The median number of previous treatment lines was three (range 1–8). Abemaciclib was administered at a dose of 200 mg twice daily. The primary endpoint of the study was ORR, and secondary endpoints included, among others, the percentage of patients with clinical benefit (CBR), PFS, OS, and treatment safety.

Objective response rate (ORR) was nearly 20%, clinical benefit rate was 42%, median PFS was six months, and median OS was almost 18 months. The most commonly observed grade 3/4 adverse events were: diarrhoea (20%), fatigue (13%), nausea (4.5%), neutropaenia (27%), leukopaenia (28%), thrombocytopaenia (2.3%), and elevated ALAT activity (1.5%). However, treatment was discontinued due to adverse events in less than 8% of patients. So, monotherapy with abemaciclib is a relatively safe therapeutic option for patients with advanced breast cancer, previously treated with multiple lines of palliative pharmacotherapy, and the antitumor activity of this drug appears to be at least as high as cytostatics or hormone therapies available in this indication. Based on the results of the MONARCH-1 study, in September 2017 FDA registered abemaciclib in monotherapy for the treatment of women and men with advanced HRs+/HER2– breast cancer with disease progression after previous palliative hormone therapy and chemotherapy.

MONARCH-2 study

At the same time abemaciclib has also been registered in combination with fulvestrant for the treatment of patients with advanced HRs+/HER2– breast cancer, who have experienced progression after previous hormone therapy. This approval was granted based on the phase 3 MONARCH-2 study, comparing the efficacy of a combination of fulvestrant with abemaciclib to fulvestrant monotherapy [51]. The study involved 669 patients with advanced HRs+/HER2– breast cancer, with disease progression during neoadjuvant or adjuvant hormone therapy within 12 months of completion of

adjuvant hormone therapy or during first-line palliative hormone treatment. Palliative chemotherapy was one of the exclusion criteria from the study. Patients were assigned to two study arms in a 2:1 ratio: they received abemaciclib (150 mg twice daily, every day) in combination with fulvestrant (standard dosage) or placebo and fulvestrant. The primary endpoint of the study was PFS as assessed by the investigator, and secondary endpoints included among others: OS, ORR, CBR, QoL, and treatment safety. In total 17% of patients included in the study were premenopausal; they also received a gonadotropin analogue. 38% of patients received previously one line of palliative hormone therapy, and 70% had previous AI. A two-drug regimen was more effective with respect to PFS — median was 16.4 *vs.* 9.3 months, respectively (HR 0.553; 95% CI 0.449–0.618, p = 0.001), ORR (48 *vs*. 21%, p < 0.001), and CBR (72 *vs*. 56%, p < 0.001). PFS improvement was consistently demonstrated for all analysed subgroups (age, primary or secondary hormone resistance, PgR expression, metastatic location, menopausal status). At the time of publication preparation OS data was immature, and QoL data was not presented. The spectrum of adverse drug reactions in the MONARCH-2 study was similar to that observed in the abovementioned MONARCH-1 study. The most common grade 3/4 adverse events were diarrhoea (13% *vs*. 0.4%), neutropaenia (27% *vs.* 2%), nausea (2.7% *vs*. 1%), fatigue (2.7% *vs.* 0.4%), abdominal pain (2.5% *vs*. 1%), anaemia (7% *vs.* 1%), leukopaenia (9% *vs.* 0%), increased ALAT (4% *vs*. 2%), and ASPAT (2% *vs*. 3%) activity. Despite the high incidence of neutropaenia in patients treated with abemaciclib, febrile neutropaenia occurred in only four patients. Patients treated with experimental therapy were more likely to have infections, but those grade 3/4 concerned 7% and 4% of the patients receiving experimental and standard treatment, respectively.

Diarrhoea of any intensity occurred in 86% of patients treated with abemaciclib (25% in the fulvestrant treated group). In patients receiving CDK 4/6 inhibitor diarrhoea usually appeared during the first treatment cycle (approximately day 6 of therapy) and resolved after symptomatic treatment and modification of abemaciclib dose, which was required in 30% of patients. In 12% of patients treated with inhibitor, elevated serum creatinine concentration (1% — in grade 3) was observed because the drug inhibits creatinine secretion in renal tubules.

Three deaths associated with the use of abemaciclib were reported in the study.

MONARCH-3 study

At the ESMO 2017 Congress the results of another important study evaluating the combination of abemaciclib with hormone therapy in the first line of palliative treatment were presented. The publication was published shortly after presentation of study results [52]. The phase 3 MONARCH-3 study included 493 postmenopausal patients with advanced HRs+/ /HER2– breast cancer, not yet receiving a palliative treatment. Patients were assigned to therapeutic arms in a 2:1 ratio — they received abemaciclib at the dose 150 mg twice daily everyday with NSAI (anastrozole or letrozole) or placebo with NSAI. The primary endpoint of the study was PFS as assessed by the investigator, and secondary endpoints included, among others, ORR and treatment safety. The median follow-up at the time of analysis was 18 months. In total 40% of the patients included in the study were diagnosed with newly disseminated cancer; the remaining patients had disease relapse at least 12 months after completion of neoadjuvant or adjuvant hormone therapy. Almost half of the patients received prior hormone therapy as part of radical treatment, and 27% of patients received AI. Almost 22% of all patients had "bone-only disease/metastases". In the group of patients treated experimentally the PFS median was not achieved, and in standard treatment group it was 15 months (HR 0.543; 95% CI 0.409–0.723, p = 0.000021). Objective response rate was 48% *vs.* 34%, respectively (p = 0.002). At the time of analysis, OS data was missing. Interestingly, exploratory analysis has shown that a clinical variable, e.g. treatment-free interval (TFI), may have a certain predictive value for the treatment of CDK 4 and 6 inhibitor. For patients with TFI < 36 months, median PFS was not achieved with abemaciclib and was nine months in the placebo group (HR 0.48; 95% CI 0.25–0.91). For patients with TFI ≥ 36 months, the difference in PFS was not statistically significant (HR 0.83, 95% CI 0.46–1.52). In addition, the two-drug regimen was particularly beneficial in patients with liver metastases (HR 0.47; 95% CI 0.25–0.87). Adverse events reported in the MONARCH-3 study were similar to those observed in the abovementioned studies [52]. Thus, abemaciclib has joined the CDK 4 and 6 inhibitors group, members of which have proven to be effective and relatively well tolerated in the first line of palliative treatment in combination with AI in patients with HRs+/HER2– breast cancer.

Abemaciclib — ongoing clinical trials in breast cancer patients

The clinical value of abemaciclib in breast cancer patients is still being evaluated in numerous ongoing and currently recruiting clinical trials [39]. In palliative treatment, the combination of abemaciclib with tamoxifen is compared to monotherapy with abemaciclib, and the combination of abemaciclib with trastuzumab ± fulvestrant is compared to standard chemotherapy with

trastuzumab in patients with HRs+/HER2+ breast cancer (MONARCHER); abemaciclib activity is also evaluated in "triple negative" breast cancer with immunohistochemically confirmed RB protein expression. Very interesting results may provide a study in which abemaciclib is used in patients with breast cancer, NSCLC and melanoma with brain metastases. The pharmacodynamic and clinical effects of abemaciclib alone or in combination with AI are evaluated in the neoMONARCH study, which includes patients with early HRs+/HER2– breast cancer. For 14 weeks prior to surgery patients receive abemaciclib (150 mg twice daily) with anastrozole, abemaciclib alone, or anastrozole alone. Loperamide is additionally given in primary prophylaxis of diarrhoea in patients treated with CDK 4 and 6 inhibitor. The primary endpoint of the study is a change in Ki67 expression (these results are already available, and cited above), secondary endpoints include: treatment safety, clinical and radiological response, and change in gene expression associated with proliferation. Abemaciclib is also being studied in adjuvant treatment. The phase 3 MONARCH-E study includes patients with early breast cancer who are receiving standard adjuvant hormone therapy or in combination with abemaciclib.

Summary

Introduction of CDK 4 and 6 inhibitors to clinical practice is an excellent illustration of the progress made in the area of cancer treatment. These drugs have increased the number of preparations available for the treatment of patients with the most common subtype of breast cancer in advanced stage and are an important advance in the prevention and reversal of hormone resistance. In other words, these drugs provide the opportunity for quite comfortable, effective, and long-lasting treatment of this incurable disease. Although they represent a modest progression in medicine, their introduction also faces serious problems, which mainly come down to limited budgets for the financing of antineoplastic treatment, as with many other medical procedures. Clinical studies published so far have provided a wealth of knowledge about these drugs; however, there are still many questions regarding their practical use, which still need to be resolved. It is already known that these preparations, in combination with hormone therapy in patients with HRs+/HER2– receptor profiles, provide significant prolongation of PFS, regardless of whether they are used in first or subsequent lines. Unfortunately, there are still lacking data on their effects on OS, and the initial results of the PALOMA-1 study do not generate much enthusiasm in this regard. These drugs are relatively well tolerated and the toxicity of treatment can be controlled adequately by monitoring the therapy and by modifying the dose. Of note, the profiles of their side effects are slightly different. Clinical trials of CDK 4 and 6 inhibitors have included careful assessment of patients' QoL, which is crucial during long-term hormone therapy. It is well known already that the use of palbociclib and ribociclib in the first-line of treatment does not compromise the QoL as compared to hormone therapy alone, and the addition of palbociclib to second-line treatment even improves it. Unfortunately, the data for abemaciclib have not yet been published — they are expected to be of interest because the drug differs slightly in dosage, shows a slightly different clinical effect, allows a higher objective response rate, and penetrates to the CNS, but regarding the undesirable effects, it is also characterised by quite a high percentage of patients affected by diarrhoea. An important problem associated with the clinical use of CDK 4 and 6 inhibitors is lack of biomarkers, enabling rational selection of patients who would benefit from therapy. For the time being it seems that the benefit from adding of CDK 4 and 6 inhibitors to first-line hormone therapy may be lesser for patients with long treatment-free interval (TFI ≥ 3 years). Thus, this new therapeutic option requires rational development that takes into account the real needs of patients and financial possibilities. A summary of the most important data regarding use of CDK 4 and 6 inhibitors is presented in Table 1.

Table 1. Summary of key clinical data on CDK 4 and 6 inhibitors registered for the treatment of patients with advanced HRs+/HER2– breast cancer

	Palbociclib	Ribociclib	Abemaciclib
Half-life	26 hr.	30 hr.	17–38 hr.
Dosage	125 mg once daily for 3 weeks, followed by 1 week break	600 mg once daily for 3 weeks, followed by 1 week break	Monotherapy: 200 mg twice daily (BID) every day In combination with HT: 150 mg BID every day
Toxicity	Adverse events grade 3/4: — neutropaenia 54–65% — leukopaenia 19–28% — FN 1–1.8% — fatigue 2%	Adverse events grade 3/4: — neutropaenia 59% — leukopaenia 21% — increased ALAT activity 9% — increased ASPAT activity 6% — FN 1.5% — fatigue 2% — diarrhoea 1% grade 1/2: — **QTc prolongation 3.3%**	Adverse events grade 3/4: — **diarrhea 13–20%** — neutropaenia 27% — leukopaenia 9–28% — nausea 3–5% — increased ALAT activity 1.5–4% — fatigue 1–3%
Efficacy in monotherapy in previously treated patients	Study of De Michele et al. 2014 — RB+ patients — PR 2/37 — SD 5/37 — mPFS 3.7 months — HR+/HER2– patients — CBR 29%	Study of Infante et al. 2014 — PR 1/18 — SD 6/18	MONARCH-1 — ORR 20% — CBR 42% — mPFS 6 months — mOS 18 months
Efficacy of combination with HT in first line treatment	PALOMA-1, PALOMA-2 P + L *vs*. L mPFS 25 *vs.* 14.5 months ORR 42% *vs*. 35% mOS 38 *vs*. 35 months, NS (PALOMA-1) Comparable maintain of quality of life	MONALEESA-2 R+L *vs*. L mPFS 25 *vs*. 16 months ORR 53% *vs*. 37% Comparable maintain of quality of life	MONARCH-3 A+L/Ana *vs.* L/Ana mPFS NR *vs*. 15 months ORR 48% *vs*. 34%
Efficacy of combination with HT in second and subsequent lines treatment	PALOMA-3 P+F *vs*. F mPFS 11 *vs*. 5 months ORR 10% *vs*. 6% Longer maintain of quality of life	MONALEESA-3 Ongoing	MONARCH-2 A+F *vs.* F mPFS 16 *vs*. 9 months ORR 48% *vs*. 21% CBR 72% *vs.* 56%
Negative predictive factors	No	For first line — bone-only metastases[1]	For first line — bone-only metastases[1], TFI ≥ 36 months
Registration status	Registered by FDA and EMA in combination with HT in first as well as second and subsequent lines	Registered by FDA and EMA in combination with HT in first line	Registered by FDA in monotherapy and in combination with HT in second and subsequent lines

[1]Characteristics "bone-only metastases" has a dubious predictive value for first line treatment with CDK inhibitors 4 and 6 for the following reasons: contrary results have been obtained for particular drugs — in the PALOMA-2 study this feature was related to greater benefit from combination treatment — HR 0.36 (0.22–0.59); in MONALEESA-2 and MONARCH-3 studies HR values are threshold; in the individual studies there is no uniform definition of the concept "bone only disease/metastases" and assessment of bone metastases progression is not precise

FN — febrile neutropaenia; QTc — Corrected *QT* Interval; RB+ — immunohistochemically confirmed expression of RB protein; PR — partial response; SD — stable disease; ORR — overall response rate; CBR — clinical benefit rate; mPFS — median progression-free survival; mOS — median overall survival; P — palbociclib; L — letrozole; R — ribociclib; A — abemaciclib; F — fulvestrant; Ana — anastrozole; HT — hormone therapy; TFI — treatment-free interval; FDA — Food and Drug Administration; EMA — European Medicines Agency; NS — not significant; NR — not reached

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