Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 3 Issue 3 March 2019

Review Article

A Road-Map of Cyclin-Dependent Kinase 4/6 Inhibitors for Postmenopausal Women with Metastatic Breast Cancer

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Received: December 17, 2018; **Published:** February 23, 2019

Abstract

The cyclin-dependent kinase (CDK) 4/6 inhibitors have contributed to significant improvements in outcomes of patients with estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (BC), via blocking the tumor growth and proliferation. The three agents from the CDK 4/6 inhibitor class, palbociclib, ribociclib, abemaciclib, are generally well tolerated and convenient for patients, in whom a quality of life represents an important priority. This overview briefly presents profiles of these three CDK 4/6 inhibitors, including their efficacy, differences in dosing schedules, and adverse effects (AE), based on recent Randomized Controlled Trials (RCTs). Moreover, this short review focuses on comparison of the "real-world" practice and the RCT setting. Knowing the clinical research and "real-world" treatment patterns (e.g., combination therapy of CDK 4/6 inhibitors with endocrine-based therapy (ET)), as well as patient characteristics (e.g., menopausal status) is crucial for the treatment teams (e.g., physicians, pharmacists, and nurses) who are using these new class of medications in a daily clinical practice.

Keywords: Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors; Breast Cancer (BC); Estrogen Receptor (ER)-Positive BC; Postmenopausal Patients; Efficacy; Safety

Introduction

Cyclin-dependent kinase (CDK) 4/6 inhibitors represent a new class of selective medications, which induce cell cycle arrest and prevent progression of the neoplastic tumor [1-3]. The CDK 4/6 inhibitors block an activity of the cyclin D-CDK 4/6 holoenzyme, and in this manner, stop cell cycle progression from the G1 to the S phase [20]. In result, the application of CDK 4/6 targeted agents inhibits the tumor proliferation, in patients with estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (BC) [20]. Furthermore, it has been determined that the CDK 4/6 inhibitors may prolong the time interval until the development of endocrine resistance, among women with ER-positive/HER2-negative BC [20]. It should be highlighted that the CDK 4 activity is essential for progression through the G1 phase and into the mitotic cell cycle. As a consequence, inhibiting this kinase induces retinoblastoma (Rb)-positive cells to exit the cell cycle into either a quiescent or senescent state [21]. However, an inability to reduce MDM2 (Mouse Double Minute 2) homolog does not prevent CDK 4 inhibitor-induced withdrawal from the cell cycle. In such circumstances, the cells remain in a reversible quiescent state [21]. Furthermore, reducing MDM2 in these cells drives them into the more stable senescent state. In addition, CDK 4 inhibitor-induced senescence, associated with loss of MDM2, has been observed in some cases of BC (and other malignancies and cell lines). It should be pointed out that in some patients the changes in MDM2 expression may correlate with cancer outcomes. Moreover, MDM2 may represent a regulator of the controlling mechanism, known as geroconversion, by which quiescent cells become senescent [21]. In the future, geroconversion may be a new target for CDK 4 inhibitors [21]. For instance, it is conceivable that CDK 4 inhibitors alone can establish a G1 arrest in cancer cells, but the geroconversion is still inefficient. At this point, some other medications may change signalling pathways in the tumor or its microenvironment, in order to facilitate geroconversion [21]. To further elucidate this complex area, novel cellular model studies, in which geroconversion can be investigated as cells progress from quiescence to senescence, would be merited. At present, it is critical to understand the basic mechanisms, by which the CDK 4/6 inhibitors conduct their anti-cancer actions (e.g., via cytostatic growth inhibition and through interference with the cell senescence).

Recently, three CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, have been explored in clinical trials, and subsequently, have been approved for the therapy of patients with ER-positive/HER2-negative advanced or metastatic BC, in combination with an aromatase inhibitor (AI) or with an ER down-regulator – fulvestrant [1-9]. There are various subtypes of BC, based on the expression of hormone receptors (HR) for estrogen (ER) and progesterone (PR), and overexpression and/or gene amplification of HER2 [22]. In clinical practice, the expression of ER and overexpression of HER2 or lack of thereof (e.g., HER2-negative status) has been related to specific therapeutic implications and the BC prognosis (e.g., ER-positive/HER2-negative BC is more common among older patients and is usually characterized by a luminal A histological type and less aggressive behavior) [22]. The combination approach, including a CDK4/6 inhibitor with an AI was used as initial treatment in postmenopausal patients. Similarly, the combination of a CDK4/6 inhibitor with fulvestrant was applied in patients, who have received prior endocrine-based therapy (ET)) [6,9]. It should be emphasized that the key differences between the guideline recommendations and the "real-world" practice, can be relevant to the heterogenic nature of metastatic BC. In addition, some discrepan-

cies with regard to the definitions of response to therapy can generate slight variability in treatment patterns, depending on the physicians' choices [10].

This review briefly presents the efficacy, differences in dosing schedules, and adverse effect (AE) profiles of three CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib), according to the results of recent Randomized Controlled Trials (RCTs). Tables (1-5) provide an overview of the completed clinical trials, current recommendations for treatment of postmenopausal women with ER-positive, HER2-negative metastatic BC, and some safety issues of therapies with CDK 4/6 inhibitors. This article also discusses the RCT and "real-world" practice setting, in order to facilitate work of the treatment teams (e.g., physicians, pharmacists, and nurses) who are using these new of medications in their daily practice.

Key clinical trials leading to the approval of cyclin-dependent kinase (CDK) 4/6 inhibitors: palbociclib, ribociclib, and abemaciclib

Palbociclib was the first CDK 4/6 inhibitor, approved by the US Food and Drug Administration (FDA), in 2015, based on the beneficial results of the pioneering PALOMA-1/TRIO 18 study (which gathered the "real-world" records of patients with estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC) treated with palbociclib in combination with endocrine-based therapy (ET)) (Table 1) [1]. Similarly, the subsequent (phase 3) trials, including PALOMA, MONALEESA, and MONARCH (for palbociclib, ribociclib, and abemaciclib, respectively), have supported the use of these agents in combination with ET, for patients with advanced ER-positive/HER2-negative BC (Table 1) [2-9]. These three CDK 4/6 inhibitors have led to significant improvements in progression-free survival (PFS) in this population of patients. Moreover, these medications, as a class, are generally well tolerated, and have oral dosing schedules that are convenient for patients [12,15,23]. In general, phase 3 trials are essential in establishing standards of medical care. However, Randomized Controlled Trials (RCTs) may not always accurately represent the "real-world" population of women with BC. In particular, "real-world" evidence, which is predominantly gathered from medical documentation, patient registry data, or insurance claims, can be more appropriate for patients usually seen in clinical practice. For instance, the Ibrance Real World Insights (IRIS) study was focused on exploring the effectiveness and tolerability of palbociclib, in patients receiving this agent in combination with an aromatase inhibitor (AI), or fulvestrant, in postmenopausal patients with ER-positive/HER2-negative advanced or metastatic BC, in "real-world" setting [11]. Results of the IRIS trial have shown good effectiveness (e.g., longer progression-free and survival rates) among such patients. Certainly, further studies are merited to provide more long-term outcome data in this area [11].

RCT, author, year	CDK4/6 inhibitor	Progression-free survival (in RCT arms)	Therapeutic considerations in women with ER-positive, HER2-negative metastatic BC (postmenopausal)
Paloma 1 Finn 2015 [1]	Palbociclib	PFS = 20.2 ms for palbociclib + letrozole; PFS = 10.2 ms for placebo + letrozole	Palbociclib plus letrozole is beneficial
Paloma 3 Turner., *et al*. 2015 [2]	Palbociclib	PFS = 9.2 ms for palbociclib + fulvestrant; PFS = 3.8 ms for fulvestrant	Palbociclib plus fulvestrant is beneficial (after progress post ET)
PALOMA 2 Finn., *et al*. 2016 [3]	Palbociclib	PFS = 24.8 ms for palbociclib + an AI; PFS = 14.5 ms for an AI	Palbociclib plus an AI is beneficial
Paloma 2, Paloma 3 Finn., *et al*. 2016 [3] Turner., *et al*. 2015 [2]	Palbociclib	PFS was improved with palbociclib in combination with an AI or fulvestrant	Palbociclib plus an AI (as initial ET) or plus fulvestrant (after ET) is beneficial
Monaleesa 7 Hortobagyi., *et al.* 2018 [4]	Ribociclib	PFS was improved with ribocilclib	Ribociclib plus an AI (as initial ET) is beneficial
MONALEESA 7 Tripathy., *et al*. 2018 [5]	Ribociclib	PFS = 23.8 ms for ribociclib + an AI PFS = 13.0 ms for + an AI	Ribociclib plus an AI (as initial ET) is beneficial
Monaleesa 3 Slamon., *et al*. 2018 [6]	Ribociclib	PFS = 20.5 ms for ribociclib + fulvestrant PFS = 12.8 ms for fulvestrant + placebo	Ribociclib plus fulvestrant (as initial ET/after progress on ET) is beneficial
Monarch 1 Dickler., *et al.* 2017 [7]	Abemaciclib	PFS = 6.0 ms for abemaciclib	Abemaciclib as monotherapy (with BC progression after ET) is beneficial
Monarch 2 Sledge., *et al*. 2017 [8]	Abemaciclib	PFS= 16.4 ms for abemaciclib + fulvestrant PFS = 9.3 ms for fulvestrant	Abemaciclib plus fulvestrant (with BC progress after ET) is beneficial
Monarch 2, Monarch 3 Sledge., *et al*. 2017 [8] Goetz., *et al*. 2017 [9]	Abemaciclib	PFS was improved with abemaciclib	Abemaciclib plus an AI or fulvestrant (as initial ET or in patients who have received prior ET) is beneficial

Table 1: Progression-free survival in postmenopausal patients with ER-positive, HER2-negative metastatic breast cancer, treated with CDK 4/6 inhibitors combined with ET.

Abbreviations: CDK 4/6: Cyclin-Dependent Kinase 4/6; ER: Estrogen Receptor; HER2: Human Epidermal Growth Factor Receptor 2; AI: Aromatase Inhibitor; BC: Breast Cancer; CHT: chemotherapy; ET: Endocrine-Based Therapy; ms: Months; PFS: Progression-Free Survival; RCT: Randomized Controlled Trial.

A combination of endocrine-based therapy (ET) with CDK4/6 inhibitors in postmenopausal patients with metastatic BC

CDK4/6 inhibitors have shown promising results in many patients with metastatic BC. For instance, as initial ET in postmenopausal patients, palbociclib in combination with AIs (previously, it was approved for use in combination with letrozole as first-line or with fulvestrant as second-line therapy) and ribociclib in combination with an AI, have recently been indicated (Table 2) [3-5,12]. In addition, abemaciclib, as monotherapy, for patients who have received prior ET and chemotherapy (CHT) for metastatic BC, and as combination therapy with fulvestrant, in patients who have had BC progression after ET [7,8,12]. ET has been used in practice for a long time. Since ET affects bone mineral density, physicians have to take proactive approach with regard to osteopenia, osteoporosis, bone fractures, arthralgias and myalgias (Table 3) [12,15]. Moreover, some uncomfortable gynecologic side effects (e.g., hot flashes and vaginal dryness), as well as mood swings, hair thinning, alopecia, and dyslipidemia, should also be properly managed, since they affect the patient's quality of life [12,15].

Medication's name	Monotherapy or combination therapy
Anastrozole, Letrozole	Monotherapy with AI (nonsteroidal)
Exemestane	Monotherapy with AI (steroidal)
Fulvestrant	Monotherapy with ER down-regulator
Tamoxifen	Monotherapy with ER blocker
Exemestane + everolimus	Combination therapy: AI + mTOR kinase inhibitor
Palbociclib + letrozole	Combination therapy: CDK 4/6 inhibitor + AI
Palbociclib + fulvestrant	Combination therapy: CDK 4/6 inhibitor + ER down-regulator
Ribociclib + letrozole	Combination therapy: CDK 4/6 inhibitor + AI

Table 2: NCCN recommendations for treatment of postmenopausal women with ER-positive, HER2-negative metastatic BC [12].

Abbreviations: AI: Aromatase Inhibitor; BC: Breast Cancer; CDK 4/6: Cyclin-Dependent Kinase 4 and 6; ER: Estrogen Receptor; HER2: Human Epidermal Growth Factor Receptor 2; NCCN: National Comprehensive Cancer Care Network; +: Plus

Medication name and class	Dose, administration, estimated treatment time	Possible adverse effects
Tamoxifen ER blocker	20 mg PO daily 5 years	hot flushes, gynecologic symptoms; long-term: thrombosis, uterine cancer
Anastrozole nonsteroidal AI	1 mg PO daily 5 years alone or sequentially after 2-5 years of tamoxifen	arthralgias, hot flushes, gynecologic symptoms; long-term: osteoporosis
Letrozole nonsteroidal AI	2.5 mg PO daily 5 years alone or sequentially after 2-5 years of tamoxifen	arthralgias, hot flushes, gynecologic symptoms; long-term: osteoporosis
Exemestane steroidal AI	25 mg PO daily 5 years alone or sequentially after 2-5 years of tamoxifen	arthralgias, hot flushes, gynecologic symptoms; long-term: osteoporosis
Fulvestrant ERdown-regulator	500 mg IM into the gluteal area (1-2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and then once monthly, treatment time considered individually	arthralgias, hot flushes, fatigue and nausea

Table 3: Common endocrine therapy options for postmenopausal women with ER-positive breast cancer [12].

Abbreviations: AI: Aromatase Inhibitor; ER: Estrogen Receptor; PO: per os (orally); IM: Intramuscularly

A spotlight on adverse effects of CDK4/6 inhibitors

With the incorporation of targeted agents, such as CDK4/6 inhibitors, a new spectrum of adverse effects has emerged (Table 4) [13]. The most common side effects with this class are neutropenia (usually afebrile and noninfectious), anemia, thrombocytopenia, and fatigue. In some women with ER-positive metastatic BC, who already have had fatigue at baseline, this symptom may be aggravated. Since neutropenia is the most frequent AE associated with therapy with CDK 4/6 inhibitors (especially palbociclib and ribociclib), the patients should be monitored with a CBC prior to initiating the CDK 4/6 inhibitor, at the beginning of each therapy cycle, on day 14 of the first 2 cycles, and then, as clinically necessary (Table 4) [1-4,13]. In addition, with ribociclib, increased vigilance for the possible QT interval prolongation, cardiac arrhythmias, deep vein thrombosis, or the risk of pulmonary embolism, is necessary. ECG monitoring, as well as reviewing and adjusting doses of the other medications (e.g., some anti-emetic agents) is mandatory. Moreover, some patients, particularly older women with cardiac

comorbidities, who might have received anthracycline therapy for BC, also require ongoing ECG evaluation. Also, the potential liver toxicity (e.g., transaminitis) should be assessed by measuring Liver function tests (LFTs) [5,6,13]. Abemaciclib results in a greater incidence of diarrhea that can be successfully managed via dose reduction, and application of antidiarrheal agents. Also, thromboembolism may be a concern, so that the patients with cardiac risk factors need to be treated with caution [7-9,13]. In order to achieve therapeutic goals, it is necessary to be aware of what other medications or dietary supplements (e.g., botanical preparations) the patients are taking outside of the prescribed anti-cancer treatment [13]. For instance, it should be underscored that taking a proton-pump inhibitor (e.g., for relief of gastric symptoms), in a fasting state, can inhibit the absorption of the CDK4/6 inhibitor [13]. Furthermore, to minimize undesirable interactions, the patients have to be notified to avoid grapefruits, grapefruit juice, pomegranates and pomegranate juice (e.g., due to CYP3A4 inhibition by active substances, contained in these fruits) [13]. Since three CDK4/6 inhibitors have different adverse-effects, it is conceivable to rotate them (similarly to ETs), under careful monitoring of the patients symptoms, laboratory and ECG parameters. Possible interactions of CDK 4/6 inhibitors with other medications and foods, as well as safety recommendations for monitoring of necessary tests are presented in table 5 [12,13,15,23,24].

CDK 4/6 Inhibitor	Dose and schedule	Blood morphology (CBC and differential)	Serum electrolytes (K, Ca, Mg, P)	Liver function tests (AST, ALT, total bilirubin)	Adverse effects
Palbociclib (Ibrance)	125 mg daily, 3 wk on, 1 wk off	baseline, every 2 wk for 2 m, monthly for next 4 m, then every 3 m (if no more than grade 1 or 2 neutropenia in the first 6 m)	na	na	neutropenia rare febrile/infectious neutropenia
Ribociclib (Kisqali)	600 mg twice daily, 3 wk on, 1 wk off	baseline, every 2 wk for 2 m, monthly for 4 m	baseline, monthly for 6 m	baseline, every 2 wk for 2 m, monthly for 4 m	Neutropenia rare febrile/ infectious neutropenia QT interval prolongation (ECG - baseline, day 14 of cycle 1, day 1 of cycle 2; regular cardiac monitoring)
Abemaciclib (Verzenio)	150 mg twice daily – plus fulvestrant, or 200 mg twice daily in monotherapy	baseline, every 2 wk for 2 m, monthly for 2 m	na	baseline, every 2 wk for 2 m, monthly for 2 m	diarrhea

Table 4: Safety of CDK 4/6 inhibitors in patients with ER-positive BC [13].

Abbreviations: BC: Breast Cancer; ER: Estrogen Receptor; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CBC: Complete Blood Cell Count; CDK 4/6: Cyclin-Dependent Kinase 4 and 6; ECG: Electrocardiogram; na: Not Applicable; m: Month; wk: Week.

CDK 4/6 Inhibitor	Risk considerations for patients receiving CDK 4/6 inhibitors	Interactions with concomitant medications and recommended precautions		Instructions for patients – dietary precautions	Monitoring for AEs of CDK 4/6 inhibitors
Palbociclib (Ibrance) a weak inhibitor of CYP3A	Neutropenia with rare febrile neutropenia	Avoid concomitant use of strong CYP3A inhibitors; when coadministration cannot be avoided, reduce the palbociclib dose (e.g., to 75 mg/day) Avoid coadministration with moderate or strong CYP3A inducers	Palbociclib can increase sensitive CYP3A substrates, e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, midazolam, pimozide, quinidine, sirolimus, tacrolimus	Avoid food that inhibit CYP3A enzymes (they may increase the exposure to palbociclib) - e.g., pomegranates or pomegranate juice, grapefruit, grapefruit juice	Monitor CBC count prior to starting palbociclib, and at the beginning of each cycle (and also on day 14 of the first 2 cycles, and as medically indicated); dose interruption, reduction, or delay in starting another cycle - for patients who develop grade 3/4 neutropenia
Ribociclib (Kisqali) a CYP3A4 substrate/ CYP3A4 inhibitor	Possible QT interval prolongation in ECG; Use with caution, monitor and avoid meds that prolong QT interval: antiarrhythmics (e.g., amiodarone, disopyramide, procainamide, quinidine and sotalol), chloroquine, clarithromycin, haloperidol, methadone, moxifloxacin, pimozide, ondansetron	Meds that may increase ribociclib's plasma levels - avoid concomitant use of strong CYP3A inhibitors, e.g., clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, and voriconazole; If coadministration with a strong CYP3A inhibitor cannot be avoided, then reduce ribociclib dose to 400 mg/day)	Meds that may decrease ribociclib's plasma levels - avoid concomitant use of strong CYP3A inducers, e.g., phenytoin, rifampin, carbamazepine, anti-depressive herbal preparations (like St John's Wort); Use caution if ribociclib is coadministered with CYP3A4 substrates with a NTI, since ribociclib can increase their systemic actions (e.g., the dose of a sensitive CYP3A substrates with a NTI should be reduced); CYP3A substrates with a NTI include e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus	Avoid food that inhibit CYP3A enzymes (they may increase the exposure to ribociclib) – e.g., pomegranates or pomegranate juice, grapefruit, grapefruit juice	ECGs should be evaluated prior to starting treatment; Repeat ECGs at day 14 of the 1-st cycle and at the beginning of the 2-nd cycle, and as clinically indicated; In case of QT prolongation during treatment, often monitor ECG; Permanently discontinue ribociclib if QT interval prolongation is >500 ms or >60 ms change from baseline, and if it is associated with: torsades de pointes, polymorphic ventricular tachycardia, unexplained syncope, or signs/ symptoms of serious arrhythmia; Monitor serum electrolytes (e.g., K, Ca, Mg) before starting, at the beginning of the 1-st 6 cycles, and as indicated; correct abnormalities before starting ribociclib
Abemaciclib (Verzenio) metabolized by CYP3A4	Hematologic toxicities; Diarrhea; Hepatotoxicity; VTE (e.g., reported in patients treated with abemaciclib plus an AI and in patients treated with abemaciclib plus fulvestrant (e.g., deep vein thrombosis, PE, cerebral venous sinus thrombosis, pelvic venous thrombosis, subclavian and axillary vein thrombosis, inferior vena cava thrombosis)	Strong CYP3A4 inhibitors may cause toxicity; Avoid concomitant use of ketoconazole; with concurrent use of CYP3A inhibitors, in patients with starting doses of 150 mg or 200 mg BID, reduce dose to 100 mg BID	If a strong CYP3A inhibitor is discontinued, increase abemaciclib dose to the one that was used before starting this inhibitor	Avoid food that inhibit CYP3A enzymes (they may increase the exposure to abemaciclib) e.g., pomegranates or pomegranate juice, grapefruit, grapefruit juice	Monitor CBC before starting therapy, q 2 wk for the first 2 m, monthly for the next 2 m, and as clinically indicated; For diarrhea start treatment with antidiarrheal meds and increase hydration; Monitor ALT, AST, and serum bilirubin before starting therapy, q 2 ws for the first 2 m, monthly for the next 2 m, and as clinically indicated; Monitor for symptoms of venous thrombosis and PE, and treat/ prevent

Table 5: Interactions of CDK 4/6 inhibitors with other medications and foods [12,13,15,23,24].

Abbreviations: AI: Aromatase Inhibitor; AE: Adverse Effect; BC: Breast Cancer; CYP3A: Cytochrome P4503A; ER: Estrogen Receptor; ALT, Alanine Aminotransferase; AST: Aspartate Aminotransferase; BID: Twice Daily; CBC: Complete Blood Cell Count; CDK 4/6: Cyclin-Dependent Kinase 4 and 6; ECG: Electrocardiogram; K: potassium; Ca: Calcium; Mg: Magnesium; meds: Medications; m: Month; ms: Millisecond; wk: Week; NTI, Narrow Therapeutic Index; PE: Pulmonary Embolism; q: Every; VTE: Venous Thromboembolic Events

Useful criteria to select a CDK 4/6 inhibitor and treatment sequence

Due to the fact that the CDK 4/6 inhibitors display similar efficacy, and their safety profiles are slightly different, these differences can guide the selection of a particular medication for an individual patient. For instance, palbociclib or abemaciclib should be preferred over ribociclib, among patients with an abnormal ECG (e.g., prolonged QT interval). Similarly, the patients using a pharmacotherapy that can interfere with the QT interval should not choose ribociclib. In addition, it should be highlighted that patients with poor prognosis (e.g., liver metastasis, or high-grade breast tumors) can benefit from adding the abemaciclib to ET [14]. It still remains unclear whether any one of the three CDK 4/6 inhibitors is significantly more effective than any other [24]. Also, it is not known whether changing the CDK 4/6 inhibitor after BC progression will bring any significant advantages [24]. It is important to keep in mind that when patients stop responding to a certain kind of ET, it is crucial to consider whether to proceed with another type of ET or to switch to CHT. In patients, who experienced disease progression after 2 lines of ET, before making therapeutic decisions, the prior treatment response, tumor burden, and personal preferences should be considered [15]. According to the current guidelines, CHT should be used only for visceral crisis or BC progression (e.g., post ET) [15]. In addition, exploring the details of sensitivity and resistance to CDK 4/6 inhibitors will allow to more precisely guide further treatment of patients with advanced or metastatic BC. It has been estimated that about 20% of such patients will fail to respond to CDK 4/6 inhibitors at the beginning of this therapy, and all patients may finally become resistant [13].

CDK 4/6 inhibitors as a possible solution for endocrine resistance dilemmas in patients with metastatic BC – practical lessons learned from clinical trials

Postmenopausal patients with ER-positive/HER2-negative breast tumors represent the majority of women with advanced or metastatic BC [16]. According to current guidelines, ET should be offered as first-line therapy in patients, who do not have visceral crises [17]. However, after receiving first-line ET, many patients experience BC progression, secondary to endocrine resistance. In these circumstances, such patients are often offered CHT as second-line therapy [17,18]. It should be highlighted that the combination of palbociclib plus letrozole and palbociclib plus fulvestrant have demonstrated trends in efficacy, comparing to CHT regimens, for the first- and second-line treatments of such postmenopausal patients [2,3,12]. In particular, these combination therapies with palbociclib have shown significant advantages in outcomes (e.g., PFS) [1-3,12]. The above described beneficial effects of CDK 4/6 inhibitors are related to the fact that the ER-positive BC is particularly dependent on CDK 4 for the cell proliferation [3]. In particular, the ER signalling pathway is closely connected to the cyclin D1 - CDK 4 axis. This link may explain why some BC cells are particularly sensitive to the anti-proliferative effects of CDK 4/6 inhibitors (especially, if they are administered in combination with ET) [3]. For instance, in the recent TREnd trial, women with ER-positive, HER2-negative advanced BC, who received one or two prior lines of ET, were randomly assigned to palbociclib or palbociclib plus the ET (which they have recently received). Both groups demonstrated clinical advantages. However, PFS was higher in those, who received ET plus palbociclib (10.8 months), compared to those, who received palbociclib alone (6.5 months) [19]. Likewise, some trials investigating ET and CDK 4/6 inhibitors were based on the line of therapy that the patients were receiving. In general, in the first-line therapy, endocrine-sensitive patients used an AI with or without a CDK 4/6 inhibitor. In the second-line therapy, endocrine-resistant patients used fulvestrant with or without a CDK 4/6 inhibitor (Table 2) [12]. For instance, in the MONALEESA-3 study, fulvestrant was used in either first- or second-line setting (Table 1) [6]. In fact, this was the first trial to assess a CDK 4/6 inhibitor-based combination with fulvestrant, among women with the ER-positive/HER2-negative advanced BC (e.g., women with a new diagnosis of BC, and those who had a relapse more than one year after completion of neoadjuvant ET with no other therapy for advanced BC) [6]. The results of the MONALEESA-3 study have clearly demonstrated that the use of CDK 4/6 inhibitors, combined with ET (e.g., fulvestrant), is an effective first-line treatment for patients with ER-positive/HER2-negative advanced BC (Table 1) [6].

Conclusion

Women with HR-positive metastatic BC are now living longer and less symptomatic lives thanks to the recent, more convenient, usually well tolerated treatments, such as CDK 4/6 inhibitors. Three CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, have recently been approved for the treatment of ER-positive, HER2-negative advanced or metastatic BC. The National Comprehensive Cancer Care Network (NCCN) guidelines for postmenopausal women with ER-positive metastatic BC include palbociclib with letrozole, palbociclib with fulvestrant, and ribociclib with letrozole. A typical adverse event related to palbociclib and ribociclib includes neutropenia (usually reversible upon interruption of the medication), while febrile neutropenia is rather infrequent. Conversely, ribociclib is associated with QT interval prolongation, and thus, cardiac monitoring, review of other medications (focused on their possible cardiotoxicity), and dose adjustment may be necessary. Abemaciclib is characterized by gastrointestinal toxicity (e.g., diarrhea) that should be managed with dose reduction and antidiarrheal agents. Differences in safety profiles of the CDK 4/6 inhibitors can guide the most appropriate selection of a particular agent for a given patient. Since the CDK4/6 inhibitors have their advantages and dis-

advantages, the ultimate choice of the target medication should be individualized, depending on the patient's clinical status. Moreover, close collaboration between physicians and pharmacists, focused on individual patient's medical context, is necessary to assess any possible interactions or AEs (which in consequence may reduce the efficacy of CDK4/6 inhibitors). A key question that needs to be answered in up-coming trials, conducted in neoadjuvant and adjuvant setting relates to a possible selection of women with early BC, for whom a combination of CDK 4/6 inhibitor therapy and ET may be the most effective initial approach. In addition to the treatment with CDK 4/6 inhibitors and ET, open communication between patients and treatment teams is necessary for the improvement of outcomes, despite the advanced stage of BC. Understanding how CDK 4/6 inhibitors are used in "real-world" practice and how their dosing schedules and safety monitoring should be performed will allow the most optimal and individualized application of these promising medications.

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