Breast cancer is the most common cancer diagnosed in women. Each year, thousands die either because of disease progression or failure of treatment. Breast cancer is classified into different subtypes based on the molecular expression of estrogen receptor (ER), progesterone receptor, and/or human epidermal growth factor receptor 2 (HER2). These receptors represent important therapeutic targets either through monoclonal antibodies or through small-molecule inhibitors directed toward them. However, up to 40% of patients develop either a primary or a secondary resistance to the current treatments. Therefore, there is an urgent need for investigating new targets in order to overcome the resistance and/or enhance the current therapies. Cell cycle is altered in many human cancers, especially in breast cancer. Cyclin-dependent kinases (CDKs), especially CDK4 and CDK6, play a pivotal role in cell cycle progression that makes them potential targets for new promising therapies. CDK inhibition has shown strong antitumor activities, ranging from cytostatic antiproliferative effects to synergistic effects in combination with other antitumor drugs. In order to overcome the drawbacks of the first-generation CDK inhibitors, recently, new CDK inhibitors have emerged that are more selective to CDK4 and CDK6 such as palbociclib, which is the most advanced CDK4/6 inhibitor in trials. In preclinical studies, palbociclib has shown a very promising antitumor activity, especially against ERα+ breast cancer subtype. Palbociclib has gained world attention, and US the Food and Drug Administration has accelerated its approval for first-line treatment in combination with letrozole for the first-line systemic treatment of postmenopausal women with ERα+/HER2− locally advanced or metastatic breast cancer. In this review, we discuss the potential role of CDK inhibition in breast cancer treatment, and focus on palbociclib progress from preclinical studies to clinical trials with mentioning the most recent ongoing as well as planned Phase II and Phase III trials of palbociclib in advanced breast cancer.

Keywords: cyclin-dependent kinases, cell cycle, metastatic breast cancer, PD0332991

Introduction

A million and a half new cases of breast cancer are reported annually around the world.1 In the US, breast cancer is the most common cancer diagnosed in women, with an estimated number of 231,840 new cases in 2015.2 It accounts for 29% of the total cancers among women with 40,290 estimated deaths, ranking second in the cancer mortality list in women.2 Breast cancer is a heterogeneous disease with different clinical and biological behaviors. Although it affects the same anatomical organ, it has different clinical manifestations, etiology, prognosis, clinical outcomes, and responds differently to treatment.1 The therapeutic options vary from primary surgery to targeted
therapy, hormonal therapy, and/or chemotherapy; however, more studies and investigations need to be done for better and more effective treatment of breast cancer.4

Expression of hormonal receptors (HR), including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), is used to classify breast cancers and aid in selecting appropriate treatment therapies.3 Furthermore, breast cancers can be classified into luminal breast cancers expressing HR (such as ER and PR) and HER2 and basal-like cancers that lack expression of both HR and HER2.6 Based on the previous classification, breast cancers can also be subdivided into five subtypes: Luminal A (HR+/HER2−), luminal B (HR+/HER2+), HER2-enriched (HR−/HER2+), basal-like (80%–90% are triple negative), and normal breast-like/unclassified breast cancers.7,8 ERα+ breast cancer accounts for ~70% of breast cancers, and most of ERα+ subtypes show a good response to hormonal therapy, including selective ER modulators and aromatase inhibitors.9 Whereas the therapy of HER2+ cancers is based on targeting the overexpressed receptor with monoclonal antibodies.9 On the other hand, triple-negative breast cancer (TNBC) (with negative expression of ER, PR, and HER2) is mostly treated with cytotoxic chemotherapeutic drugs.10

Metastatic breast cancer
Advanced breast cancer, also known as stage IV breast cancer, is a type of breast cancer that is usually referred to the metastatic status of the tumor, which means that the tumor cells have spread from their local site to the surrounding and then to other distant sites. Breast cancer metastasis is the most common cause of cancer-related death owing to the incurable nature of these metastases.11,12 Metastatic disease develops in ~20% of patients with early-stage breast cancer.13 Approximately 75% of patients with metastatic breast cancers (MBCs) are HR+ with ERα+ and/or PR+.14 In general, HR+ breast cancer subtypes usually develop late bone metastasis, whereas early visceral metastasis is usually due to TNBC.15 Patients with MBC usually have median overall survival of 2–3 years from the time of their first diagnosis.13 Generally, metastasis accounts for >90% of all cancer mortalities.16 Tamoxifen, anastrazole, and letrozole are the first-line hormonal therapies approved for HR+ MBC due to their high efficacy and tolerability.9,17 Although hormonal therapy is effective in most patients with HR+ breast cancers, due to primary and secondary resistance, some patients will not respond to first-line hormonal treatment.18 Therefore, a complete resistance to hormonal therapy is usually developed in ~40% of initial responder patients, and eventually they will depend totally on chemotherapy.19,20 Furthermore, up to 30% of patients with breast cancer will relapse with metastasis.21

Hence, new targets have to be discovered, and new treatment therapies have to be studied in order to optimize the current therapies and improve patient outcomes. Studying the mechanisms of resistance to the current therapies has identified new possible targets to circumvent the resistance problem; such targets are cyclin-dependent kinase 4 and 6 (CDK4/6), phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway, and poly adenosine diphosphate ribose polymerase.22

Alterations of PI3K/mTOR genes occur in >80% of patients with breast cancer (28%–47% of ER+ breast cancers), and this pathway regulates many cellular processes that promote cell proliferation and metastasis.22 Cell proliferation by PI3K might be promoted through the activation of ER by phosphorylation.23 Interestingly, PI3K/mTOR pathway was reported to be upregulated in HR+ tumors that were resistant to endocrine therapy.22

Herein, we review the newly developed drug palbociclib and its impact on breast cancer, especially the metastatic disease.

CDK role in cell cycle
Cyclin D–CDKs–retinoblastoma (Rb) pathway drives cells through checkpoint in the cell cycle initiating the DNA replication and, hence, starting cell division.24 DNA synthesis (S), mitotic (M), and gaps (G1 and G2) phases are the four phases of cell cycle. During G1 phase, cells reach a checkpoint when they decide whether to transit to (S) phase or quit the current cell cycle.25 Alteration in cell cycle is one of the hallmarks of cancer.26 The activation of CDKs by cyclin D proteins plays an important role in G1/S cell cycle transition by phosphorylation of Rb protein. Rb protein acts as a tumor suppressor controlling G1/S transition of cell cycle.27 When Rb is phosphorylated, it loses its negative control on G1/S transition.28 Hence, activating E2F family of transcription factors that allows DNA replication to start.29 Cyclin D proteins provide a link between mitogenic signals and the machinery of cell cycle.30 Interestingly, the enforced overexpression of cyclin D in cultured cells can shorten the G1 interval.31 Therefore, increasing the replication capacity which might result in tumorigenesis.

The major role played by CDKs in cell cycle regulation was discovered for the first time in fission yeasts.32 CDKs are serine/threonine-based kinases comprising numerous subtypes, divided into two main groups according to their functions. Mainly CDK2, CDK4, and CDK6 are involved
in cell cycle G1/S transition, while CDKs 7–11 function as transcriptional regulators.

CDK4 and CDK6 have ~71% sequence homology, and both of them interact with the D-type cyclins (D1, D2, and D3). INK4 proteins, such as p16, are endogenous CDK4/6 inhibitors; they inhibit cyclin D–CDK4/6 function through binding to CDK4/6 and reduce the affinity to cyclin D proteins.

Recently, CDK6 was reported to promote the angiogenesis process. Moreover, CDK6 plays an important role in activating hemopoietic stem cells; thus, CDK6 inhibition may have an antiangiogenesis activity; however, myelosuppression is suspected to be a common side effect associated with selective CDK4/6 inhibitor therapy.

Around 90% of human solid cancers were reported to have alterations in cyclin D–CDK–Rb pathway. Alteration of such pathways can occur by different mechanisms, such as inactivation of p16 (happens in 50% of invasive breast cancers) and CDK4 mutations. Additionally, cyclin D1 was reported to be overexpressed in ~70% of breast cancer, and also overexpression of cyclin D1-encoding gene (CCND1) and CDK4 were characterized for breast cancer.

Loss of Rb expression has been reported in ~20%–30% of breast cancers especially in TNBC. In addition, loss of Rb facilitates epithelial-to-mesenchymal transition process, thus, increasing the metastatic and invasive potential of breast cancer cells.

CDK inhibitors
In the 1990s, first-generation CDK inhibitors were introduced in preclinical and clinical trials. Flavopiridol (administered as intravenous infusion), a nonselective first-generation CDK inhibitor, was the first to enter clinical trials, and it was found to have different strong antitumor effects such as enhancing cell cycle arrest, in addition to its antiangiogenic, proapoptotic, and synergetic potential with antitumor chemotherapeutic agents. However, due to their low therapeutic index, low sensitivity, and multitargets, first-generation CDK inhibitors have been discontinued. Therefore, there is an urgent need for developing more selective CDK inhibitors. Palbociclib (PD0332991), abemaciclib (LY2835219), and ribociclib (LEE011) were then introduced as a new generation of CDK inhibitors with high selective inhibition to CDK4 and CDK6.

Palbociclib
Palbociclib (brand name: Ibrance®) is an oral potent selective CDK4/6 inhibitor developed by Pfizer (NY, USA) (Figure 1). PD0332991 blocks ATP binding to the CDK4/6 enzymes with half-maximal inhibitory concentration (IC50) values of 0.011 µmol/L for CDK4/cyclin-D1, 0.009 µmol/L for CDK4/cyclin-D3, and 0.015 µmol/L for CDK6/cyclin-D2 complexes.

As we mentioned before, CDK4/6 inhibition can result in many pharmacological activities based on the different roles of these enzymes (Figure 2). It was expected that palbociclib would show strong antiproliferative and antiangiogenic activities. Currently, palbociclib is the most advanced selective CDK4/6 inhibitor in clinical development.

Other than breast cancer, preclinical studies of palbociclib on different types of cancers showed a promising antiproliferative activity. Palbociclib successfully inhibited tumor proliferation in different cancer cell lines and xenograft mouse models including neuroblastoma, glioblastoma, colorectal carcinoma, advanced Rb+ bladder cancer, gastric cancer, and sarcomas.

Preclinical trials
Among 47 human cell lines of different subtypes of breast cancer, ERα+ subtypes were found to be most sensitive to palbociclib growth inhibition. ERα+ subtypes’ sensitivity to CDK4/6 inhibitors may be due to the hyperactivation of cyclin D1 and CDK4/6 that was reported in those subtypes. While in Rb-deficient MDA-MB-468 (ERα−) human breast cancer cell lines, palbociclib showed no antiproliferative effect. Loss of Rb expression was reported to render the cancer cells resistant to CDK4/6 inhibition therapy. p16 overexpression in Rb-deficient breast cancer cells might account for the resistance to palbociclib, as CDK4/6 enzymes were already inhibited by the overexpressed p16. Interestingly, cyclin D1 overexpression and Rb phosphorylation in ERα+ cancers were reported to contribute to the resistance to the hormonal therapy.
Additionally, cyclin D1 is one of the ER transcriptional targets, thus, rationalizing the use of CDK4/6 inhibitors in ERα+ breast cancer.57

Besides antiproliferative activity, in MDA-MB-231 (ERα−) and T47D (ERα+) breast cancer cells, palbociclib has shown strong antimetastatic activity in a dose-dependent manner through reducing cyclooxygenase-II expression.58 Cyclooxygenase-II has been reported to be associated with the activation of epithelial-to-mesenchymal transition process, which helps the epithelial cells to lose their epithelial characteristics and gain mesenchymal characteristics, therefore, increasing their invasive and metastatic potentials.59,60 Moreover, CDK4/6 inhibition by palbociclib induced senescence in melanoma cell lines by promoting Forkhead Box M1 degradation.61

Furthermore, in two in vivo animal studies, palbociclib was found to be a substrate to efflux transporters P-glycated protein and breast cancer resistance protein. These transporters limit palbociclib delivery to the brain.62,63 When adding elacridal (dual P-glycated protein and breast cancer resistance protein inhibitor) to palbociclib, the brain levels of palbociclib were increased significantly, therefore enhancing its efficacy in treating brain metastasis.62 Breast cancer is highly metastatic to the brain, making it the second most common cause of brain metastasis; therefore, there is always a crucial need to enhance the crossing of antitumor drugs to the blood–brain barrier.62 On the other hand, abemaciclib (LY2835219) reached brain at low doses, suggesting that it may offer a better activity in treating breast cancer brain metastasis.64

Clinical trials of hormonal therapy combination with CDK4/6 inhibitors were triggered when hormonal therapy resistance was observed to be linked with genes that are regulated through cyclin D–CDK–Rb pathway.44 Moreover, apoptosis was observed to be increased, when cells were therapeutically arrested and then treated with hormonal therapy.41 Therefore, controlling cell cycle by controlling cyclin D–CDK–Rb pathway using CDK4/6 inhibitors may have a synergistic activity when combined with hormonal therapies, as well as, reduce the resistance acquired to that class of treatment..

**Clinical trials in breast cancer**

**Phase I trials**

Schwartz et al65 conducted the first Phase I study of palbociclib in humans to determine maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of the 2/1 schedule of palbociclib treatment (2 weeks once daily and 1 week off treatment). Patients with non-Hodgkin’s lymphoma and/or Rb+ advanced solid tumor were eligible for this study. Six patients, out of the 33 enrolled patients, experienced DLT. Myelosuppression was the common adverse effect including neutropenia (grade 3) that occurred in 24% of patients, whereas nonhematological toxicity was of mild-to-moderate
intensity including fatigue, diarrhea, and constipation. Moreover, the MTD was found to be 200 mg once daily.65

Another Phase I study by Flaherty et al66 identified the DLT and MTD for the 3/1 schedule of palbociclib treatment (3 weeks once daily and 1 week off treatment). The enrolled 41 patients had RB+ advanced solid tumors (five patients had breast cancer). The MTD was found to be 125 mg once daily. Only five patients had DLTs; neutropenia (grade 3, 12%) was the most common, while nonhematological adverse events were fatigue, diarrhea, and nausea. These results were consistent with the results of the Phase I study of Schwartz et al65, and both of the studies showed that palbociclib was well tolerated and neutropenia was the only significant DLT.66 Besides the MTD and DLTs, Schwartz et al65 and Flaherty et al66 determined the pharmacokinetic parameters of palbociclib for the 2/1 schedule and 3/1 schedule (Table 1).

### Phase II trials

DeMichele et al67 studied palbociclib in a Phase II trial as a single agent in advanced breast cancer. Eligible patients were confirmed to have RB-positive MBC, and of the 37 enrolled patients, 33 patients were HR+ (7% ERα+, 4% PR+, and 22% ERα+/PR+).67 Clinical benefit ratio was 21% for patients with HR+ and 29% for patients with HR+/HER2− who were exposed to least two prior lines of hormonal therapy. Progression-free survival (PFS) was significantly longer for patients with HR+ rather than HR− (P=0.03). On the other hand, patients exposed to chemotherapy with fewer than two prior therapies had greater clinical benefit ratio than those exposed to heavy treatment.67 Most adverse events were mostly cytopenias due to myelosuppression. Neutropenia (grade 3/4) was the most frequently occurring cytopenia with 51% of patients, and it was the reason for 46% of all dose modifications. Although neutropenia was common, neutropenic fever/infection was rare, suggesting that bone marrow progenitors were only suppressed during treatment but still functioning in infections.67 According to the presented results, palbociclib could be effective as a single agent, but more trials have to be conducted with larger sample size to confirm the applicability and efficacy of palbociclib as a single agent in MBC. Similarly, the other selective CDK4/6 inhibitors, abemaciclib and ribociclib, as well, showed a significant clinical activity in ER+ breast cancer in early clinical studies.68

Finn et al69 conducted the PALOMA-1/TRIO-18 trial; PALOMA-1 was a Phase I/II study. In Phase I, nine postmenopausal women with ERα+/HER2− breast cancer were enrolled to assess the safety, tolerability, and drug–drug interactions of combining palbociclib with letrozole. The combination was well tolerated and encouraged the Phase II of the study. Phase II was a randomized, open-label trial conducted on 165 eligible patients who were postmenopausal with advanced ERα+/HER2− breast cancer and never had any systematic treatment. This Phase II study assessed the efficacy of combination of palbociclib with letrozole versus letrozole alone.

The combination therapy showed a significant improvement in the PFS (primary end point) of 10 months longer in combination group (20.2 months) than letrozole alone group (10.2 months) (hazard ratio 0.488, 95% confidence interval [CI] 0.319–0.748; one-sided P=0.0004).1 Neutropenia (54% for grade 3/4), leukopenia (43% all grades), and fatigue (40% all grades) were the most common adverse events reported for the combination group (n=83). Febrile neutropenia had not occurred in any of the patients in the combination group.1 In the same study, amplification of cyclin D1 and loss of p16 did not show any benefit as biomarkers for CDK4/6 inhibition treatment patients’ selection.1

PALOMA-1 showed a significant improvement in the PFS when palbociclib was combined with letrozole. Thus, after the results were published, palbociclib received breakthrough therapy designation from US Food and Drug Administration (FDA) in April 2013.70 In February 2015, palbociclib received FDA accelerated approval for use in combination with letrozole for the first-line treatment of postmenopausal women with ERα+/HER2− locally advanced breast cancer or MBC.17,70 Apart from breast cancer, a Phase II trial conducted on liposarcoma showed an improved PFS when patients were treated with palbociclib.71

### Phase III trials

PALOMA-3, a randomized, double-blinded, Phase III study, involving 521 patients with advanced breast cancer, was conducted by Turner et al.72 The efficacy of palbociclib in combination with fulvestrant versus fulvestrant alone...
was assessed, and PFS was the primary end point. Eligible patients had advanced HR+/HER2− breast cancer and had relapsed or progressed disease during prior hormonal therapy. The PFS was improved in palbociclib/fulvestrant group (9.2 months) more than the median PFS of fulvestrant alone group (3.8 months) (hazard ratio for disease progression or death, 0.42; 95% CI, 0.32–0.56; *P*<0.001).72

The adverse events were consistent with the previous studies with neutropenia (occurred in 62% of patients) as the major adverse event, and only 0.6% of patients experienced febrile neutropenia. Finally, the ongoing and planned Phase II and Phase III clinical trials of palbociclib in MBC are presented in Table 2.

**Palbociclib in combination with chemotherapy**

Since TNBC has no target and its treatment depends on chemotherapy, the combination of palbociclib to cytotoxic chemotherapy has to be assessed as to whether it will have additive or antagonistic effects to the cancer chemotherapy.

In a preclinical study using Rb-proficient TNBC (MDA-MB-231 and Hs578T) cells, palbociclib when combined with anthracycline “doxorubicin” was found to antagonize doxorubicin cytotoxic effects. Additionally, in mice with Rb-proficient MDA-MB-231 xenografts, the cytotoxic effects of doxorubicin were inhibited upon co-administration of palbociclib. Moreover, the authors assessed the dependence of palbociclib on Rb expression status; they repeated the same in vivo experiment but used Rb-deficient MDA-MB-231 xenografts and found that palbociclib had no effect on cytotoxic effects of doxorubicin efficacy, suggesting that Rb expression is essential for palbociclib cytostatic activity.10

In another study, the impact of combining palbociclib with taxane and anthracycline chemotherapies was assessed using TNBC Rb-proficient MDA-MB-231 and Hs578T breast cancer cell models. The results of the combination were consistent with the previous study; palbociclib was found to antagonize their cytotoxic effects, suggesting that palbociclib altered DNA repair, blocked the chemotherapy-induced cell damage, and prevented cell death.73 In another in vivo study on genetically engineered murine models of Rb-proficient (MMTV-c-neu) and Rb-deficient (C3-TAg) mice, it was found that combining palbociclib with carboplatin resulted in decreased cytotoxic activity versus carboplatin alone in the Rb-proficient MMTV-c-neu mice. On the other hand, Rb-deficient (C3-TAg) mice were resistant to palbociclib and the combination therapy showed no antagonistic effect to carboplatin cytotoxicity.74

Interestingly and in contrast, paclitaxel cytotoxicity was found to be increased when cells were synchronized after short exposure to palbociclib (24 hours) prior to paclitaxel treatment. These observations suggest that the duration and the time of administration of palbociclib are important and should be considered carefully when we combine palbociclib with chemotherapies.73 Based on the last observation, a Phase I trial of palbociclib and paclitaxel combination was conducted, and the combination was found to be safe and well tolerated.75 Overall, we should wait for the results of the upcoming trials to determine the efficacy of these combinations in clinical practice.

**Conclusion and future directions**

Breast cancer is not a single disease; it is a set of different heterogeneous diseases that affect one anatomical organ. Major progress and discoveries have been made in breast cancer field; but unfortunately, breast cancer still has high incidence and limited therapeutic options. Current therapies are well tolerated and of high efficacy, but unfortunately, some patients develop resistance and relapse to more advanced and metastatic disease. Thus, the urge for developing new treatments is crucial. The extensive analysis of the resistance and its mechanisms are needed to discover new promising targets. CDKs are one of the most promising new therapeutic targets. First-generation CDK inhibitors showed good antitumor activities in preclinical studies; however, they showed a serious high toxicity due to their lack of specific targets. Therefore, new selective CDK4/6 inhibitors have emerged to overcome this drawback. Palbociclib is the most advanced member in this new generation of CDK4/6 inhibitors.

Preclinical data confirmed palbociclib antitumor activity in multiple tumors. In addition, Phase I studies showed its efficacy tolerability and safety, which encouraged going to the next step in clinical trials. Reversible neutropenia is the only significant adverse event for palbociclib, and fortunately, it can be managed easily by dose adjusting without affecting the efficacy. Palbociclib in combination with hormonal therapy (letrozole) gained FDA accelerated approval after PALOMA-1 results were published. This combination therapy showed a significant and remarkable improvement in PFS in postmenopausal women with ERα+/HER2− locally advanced breast cancer or MBC.

Until now, Rb protein is the only reliable indicator for palbociclib activity; in Rb-proficient cells, palbociclib showed antitumor activities, while in Rb-deficient/mutant cells, palbociclib lost its activity. We propose that Rb as an indicator is sufficient for now, in this early stage, for palbociclib applications, but in the future, we may have to find more
Table 2 Ongoing and future palbociclib trials

<table>
<thead>
<tr>
<th>Study intervention</th>
<th>Phase</th>
<th>Study design</th>
<th>Status</th>
<th>Estimated completion date</th>
<th>Estimated enrollments</th>
<th>Patients setting</th>
<th>Primary end point</th>
<th>ClinicalTrials.gov identifier</th>
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<td>Palbociclib/letrozole vs letrozole for first-line treatment (PALOMA-2)</td>
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<td>Postmenopausal women with ER+/HER2− ABC</td>
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<td>Not recruiting yet</td>
<td>September 2019</td>
<td>122</td>
<td>Premenopausal women with HR+ MBC</td>
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<td>NCT02592746</td>
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<tr>
<td>Palbociclib in combination with tamoxifen as first-line therapy</td>
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<td>Single arm open-labeled</td>
<td>Not recruiting yet</td>
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<td>HR+/HER2− MBC</td>
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<td>Palbociclib/letrozole vs letrozole for first-line treatment (PALOMA-4)</td>
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<td>MTD, RP2D, PFS</td>
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<td>Palbociclib/exemestane vs capecitabine (PEARL)</td>
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<td>HR+/HER2− MBC in patients resistant to NSAI</td>
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<td>Palbociclib and trastuzumab with or without letrozole (PATRICIA)</td>
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<td>Postmenopausal women with HER2+ MBC</td>
<td>PFS</td>
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<td>AR+ TNMBC</td>
<td>RP2D, PFS</td>
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<td>HR+ MBC previously exposed to PI3Ki</td>
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**Abbreviations:** ABC, advanced breast cancer; AR, androgen receptor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormonal receptor; MBC, metastatic breast cancer; MTD, maximum tolerated dose; NSAI, nonsteroidal aromatase inhibitors; PFS, progression-free survival; PI3Ki, PI3K inhibitors; RR, response rate; RP2D, recommended Phase II dose; TNMBC, triple negative metastatic breast cancer; TP, tumor progression.
indicators and biomarkers to assess palbociclib efficacy and monitor its activities. Additionally, more preclinical studies have to be conducted on combining palbociclib with cytotoxic chemotherapeutic agents and cautiously assess the safety and efficacy of these combinations. Overall, palbociclib seems to be a very promising drug and carries a hope for millions of patients with breast cancer, especially those who suffer from late-stage metastasis.

Author contributions
Conception and design, data acquisition and analysis, and writing the manuscript: Moataz Ehab and Mohamad Elbaz. Study supervision: Mohamad Elbaz.

Disclosure
The authors report no conflicts of interest in this work.

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