CDK 4/6 inhibitors in the treatment of advanced breast cancer

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SUMMARY
Dysregulation of the cell cycle, especially in the cyclin D-cyclin dependent kinase (CDK) pathway, is a key component of carcinogenesis, also in breast cancer. Cyclin dependent kinase inhibition has emerged as an attractive targeted cancer therapy. Recently, three oral agents selectively targeting CDK 4/6 have been developed for the treatment of breast cancer: palbociclib (PD 0332991), ribociclib (LEE011), and abemaciclib (LY2835219). Clinical trials have shown an improvement in progression-free survival when palbociclib and ribociclib are used in combination with endocrine therapy. The next wave of studies will examine the efficacy of CDK 4/6 inhibitors in combination with other targeted therapies, in the (neo)-adjuvant situation, and in other breast cancer subtypes, such as HER2 positive breast cancer. Palbociclib and ribociclib recently received accelerated Food and Drug Administration approval for the treatment of hormone receptor positive advanced breast cancer in combination with endocrine therapy. This combination has become the new standard of care for the treatment of patients with hormone receptor positive breast cancer.

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INTRODUCTION
Breast cancer is the most common cancer diagnosis in women and annually affects millions of women worldwide. Unfortunately, despite scientific advances in treatment options, metastatic breast cancer remains incurable. New targeted therapies that block the cell division are emerging and have the potential to improve patient outcomes.

Dysregulated cell proliferation is one of the main mechanisms of cancer development. During cell division, the cell progresses through different stages controlled by multiple checkpoints. This process is known as the cell cycle. Cyclins and their associated cyclin-dependent kinases (CDKs) control the transition from one stage of the cycle to the next and are the key drivers of the cell cycle. CDK inhibitors are therefore potential cancer therapeutics. The first generation of CDK inhibitors was non-selective, had a high risk of toxicity and a lack of efficacy.

Three new selective CDK 4/6 inhibitors are currently in different stages of development: abemaciclib, palbociclib and ribociclib. This article reviews their mechanisms of action, preclinical studies on their efficacy, ongoing clinical trials in breast cancer, and their toxicity profiles.

CELL CYCLE
The cell cycle is a succession of steps that result in cell division. As depicted in Figure 1, during the cycle, the cell progresses from the G1 (first growth period) to the M (mitosis) phase, with the S (DNA replication) and G2 (second growth period) phases being intermediate steps. This process is regulated by several proteins, including cyclins that interact with their partners, known as CDKs. Cyclins D1, D2 and D3 bind to CDK 4/6. These activated complexes are the key drivers of the transition from the G1 to
the S phase. Indeed, this transition is controlled by the retinoblastoma-associated protein (RB1), which is phosphorylated by the cyclin D–CDK 4/6 complex. The phosphorylated RB1 reduces inhibitory controls resulting in DNA synthesis and cell division. Many oncogenic events in cancer stimulate CDK 4/6 activity either by inactivation of CDK inhibitors or by overexpression of cyclins. In breast cancer, it is well known that cyclin D1 is often overexpressed and strongly associated with the oestrogen receptor-positive (ER+) subtype. In these cases, cyclin D1 and CDK 4/6 are potential targets for cancer therapy.

**CYCLIN DEPENDENT KINASE (CDK) INHIBITORS**

Cyclin dependent kinases play an important role in cell proliferation and the inhibition of their activity may have therapeutic benefits. CDK inhibitors block the formation of the CDK-cyclin D complex by targeting the binding site of cyclin D. This inhibition induces a reduction of RB phosphorylation and can lead to G1 arrest in RB-positive (RB+) cells.

**FIRST-GENERATION OF CDK INHIBITORS**

The first developed CDK inhibitors were alvociclib and seliciclib, both orally bioavailable pan-CDK inhibitors. Alvociclib, also known as flavopiridol, inhibits CDK 1, 2, 4, 6, 7, and 9. Early phase trials showed activity in hematologic cell lines, but a lack of clinical efficacy in chronic lymphocytic leukaemia. Moreover, high risk of toxicity, such as fatigue, diarrhea and myelosuppression, was described in phase II trials. Seliciclib, which is active against CDKs 1, 2, 5, 7 and 9, failed to demonstrate objective tumour responses in two phase I studies. In addition, this drug causes a high rate of clinical toxicities, including fatigue, nausea, vomiting, hepatic dysfunction and hypokalaemia.

**SELECTIVE CDK 4/6 INHIBITORS**

More selective CDK inhibitors, targeting CDK 4 and CDK 6, have the potential to block the phosphorylation of RB1 and to induce the cell cycle arrest with improved effectiveness and fewer adverse effects than less selective inhibitors. Three oral agents selectively targeting CDK 4/6 have been developed in breast cancer: abemaciclib (LY2835219, Lilly), palbociclib (PD-0332991, Pfizer Inc., FDA-approved), and ribociclib (LEE011, Novartis). For two of them, palbociclib and ribociclib, phase III data are now available.

**PRECLINICAL MODELS**

A lot of preclinical studies have investigated the use of CDK 4/6 inhibitors in cancer, including breast cancer. All three CDK 4/6 inhibitors have globally the same molecular struc-
ture and bind the kinase at the ATP-binding pocket. They have a high degree of selectivity for CDK 4 and CDK 6 and they can inhibit these kinases at low nano-molar concentrations (with IC₅₀ values of <40 nM). They also have an inhibitory effect on other CDKs or tyrosine kinases, but more limited than on CDK 4/6.

Numerous preclinical models have studied palbociclib in many different cancer cell lines. The results of these studies have shown that the sensitivity to palbociclib is elevated in cells with overexpression of cyclin D1 or RB1 and in cells with reduced expression of p16 or E2F1.

In breast cancer models, palbociclib has been studied in different well characterised subgroups based on the ER and human epidermal growth factor receptor-2 (HER2) status, suggesting that CDK 4/6 inhibitors have a high activity in hormone receptor-positive breast cancer cell lines and probably also in HER2-amplified cell lines. Palbociclib has also been investigated in combination with tamoxifen and trastuzumab in breast cancer models. The conclusion of these studies was that there is a synergistic inhibitory effect of palbociclib with endocrine therapy in luminal breast cancer and between palbociclib and trastuzumab in HER2-amplified cells.

Ribociclib, another CDK 4/6 inhibitor, was also tested as a single agent in preclinical models. This agent has been shown to reduce the phosphorylation of RBI and inhibit the cell growth in liposarcoma and neuroblastoma cell lines and tumour xenografts. Similar findings have been noted with abemaciclib in colorectal cancer and melanoma xenografts. Furthermore, in addition to CDK 4 and CDK 6, abemaciclib has also been reported to inhibit the activity of CDK 9.

CLINICAL TRIALS
All three CDK 4/6 inhibitors - palbociclib, ribociclib and abemaciclib - have been studied in several clinical trials. In this section we will focus on those in breast cancer. The different phase II/III studies are summarised in Table I.

PALBOCICLIB
Among the CDK 4/6 inhibitors, palbociclib has been the most investigated in clinical trials and the first granted accelerated Food and Drug Administration (FDA) approval for use in combination with endocrine therapy for the treatment of advanced oestrogen receptor ER+, HER2-negative (HER2−) breast cancer in postmenopausal women. Three phase I studies demonstrated that palbociclib is well tolerated, with similar dose-limiting toxicities related mainly to neutropenia. They suggest that palbociclib should be given at doses of 125 mg daily for 21 days of a 28-day cycle, or 200 mg daily for 14 days of a 21-day cycle.

The efficacy of palbociclib as a single agent was further investigated in a phase II study of 37 patients with advanced breast cancer positive for the retinoblastoma protein. Only two patients had partial responses to treatment; stable disease was observed in five patients for at least six months.

PALOMA-1/TRIO-18, another phase II clinical trial, studied palbociclib in association with letrozole as first-line treatment in postmenopausal women with advanced ER+ and HER2− breast cancer. This study showed that PFS was significantly longer with the combination of palbociclib and letrozole than with endocrine therapy alone. Based on these results, the FDA approved palbociclib for postmenopausal, ER+ and HER2− breast cancer in February 2015.

In November 2016, the PALOMA-2/TRIO-22 phase III study confirmed the efficacy and safety of the combination of palbociclib plus letrozole in the initial treatment of advanced ER+ and HER2− breast cancer. In this double-blind study, 666 postmenopausal women were randomised in a 2:1 ratio to receive palbociclib plus letrozole or placebo plus letrozole. Patients treated with palbociclib plus letrozole had a significantly longer median progression-free survival of 24.8 months compared to the placebo-letrozole group which had a median PFS of 14.5 months (HR=0.58, 95% IC, 0.46 to 0.72, p<0.001). The most common grade 3 or 4 adverse events in the palbociclib-letrozole group were neutropenia (66.4% vs. 1.4% in the placebo-letrozole group), leukopenia (24.8% vs. 0%), anaemia (5.4% vs. 1.8%) and fatigue (1.8% vs. 1.5%). Palbociclib has also been investigated as second-line treatment for metastatic breast cancer that had relapsed or progressed after prior endocrine treatment.

The PALOMA-3 phase III study involved 521 women with ER+ and HER2− breast cancer. They were randomised in a 2:1 ratio to receive the combination of palbociclib plus fulvestrant or placebo plus fulvestrant. This study demonstrated a median PFS of 9.2 months in the palbociclib-fulvestrant group, statistically superior to the 3.8 months obtained with fulvestrant alone (HR=0.42, 95% IC, 0.32 to 0.56, p<0.001). Additional analyses have shown that patients treated with palbociclib have a better quality of life than patients treated with placebo-fulvestrant.

RIBOCICLIB
Ribociclib was studied as a single agent in a phase I trial in RB+ advanced-stage solid malignancies or lymphomas. A recent phase III trial, Monaleesa-2, confirmed the efficacy and safety of the combination of ribociclib and endocrine therapy as first-line treatment in postmenopausal patients with ER+ and HER2− advanced breast cancer. A cohort of 668 patients was randomised to receive letrozole and placebo or letrozole combined with ribociclib dosed at 600 mg daily for 21 out of 28 days. The median duration of progres-
### TABLE 1. Summary of the major phase II and III clinical trials with CDK 4/6 inhibitors in breast cancer.

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Phase</th>
<th>Primary Endpoint</th>
<th>Nbr of patients</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Palbociclib</strong></td>
<td></td>
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<tr>
<td><strong>Metastatic Setting</strong></td>
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<tr>
<td>A phase II trial of an oral CDK 4/6 inhibitor, PD0332991, in aBC.</td>
<td>II</td>
<td>Safety and efficacy</td>
<td>36</td>
<td>Published</td>
</tr>
<tr>
<td>The CDK 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of ER+, HER2- aBC (PALOMA-1/TRIO-18); a randomised phase 2 study.</td>
<td>II</td>
<td>PFS</td>
<td>165</td>
<td>Published</td>
</tr>
<tr>
<td>Palbociclib in combination with tamoxifen as first line therapy for metastatic HR+ BC.</td>
<td>II</td>
<td>RR</td>
<td>71</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Palbociclib in patients with metastatic HER2+ or triple negative BC with brain metastasis.</td>
<td>II</td>
<td>RR</td>
<td>33</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Palbociclib and Letrozole in aBC.</td>
<td>III</td>
<td>PFS</td>
<td>666</td>
<td>Published</td>
</tr>
<tr>
<td>Palbociclib (PD-0332991) combined with fulvestrant in HR+ HER2- metastatic BC after endocrine failure (PALOMA-3).</td>
<td>III</td>
<td>PFS</td>
<td>417</td>
<td>Published</td>
</tr>
<tr>
<td>Phase III study of palbociclib in combination with exemestane versus chemotherapy (capecitabine) in HR+/HER2- metastatic BC patients with resistance to nonsteroidal aromatase inhibitors (PEARL).</td>
<td>III</td>
<td>PFS</td>
<td>600</td>
<td>Recruiting</td>
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<tr>
<td><strong>Neoadjuvant Setting</strong></td>
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<tr>
<td>A phase II trial of neoadjuvant PD 0332991 in combination with anastrazole in stage 2 or 3 ER+ and HER2- BC.</td>
<td>II</td>
<td>Complete cell cycle arrest</td>
<td>55</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Efficacy of letrozole + palbociclib combination as neoadjuvant treatment of stage II-III A PAM 50 ROR-defined low or intermediate risk luminal BC, in postmenopausal women (NeoPAL).</td>
<td>II</td>
<td>Nbr of patients with a RCB 0-I index</td>
<td>132</td>
<td>Recruiting</td>
</tr>
<tr>
<td><strong>Adjuvant Setting</strong></td>
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<tr>
<td>A study of palbociclib in combination with adjuvant endocrine therapy for HR+, HER2- invasive BC.</td>
<td>II</td>
<td>Treatment discontinuation rate at 2 years</td>
<td>160</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>A study of palbociclib in addition to standard endocrine treatment in HR+ HER2-normal patients with residual disease after neoadjuvant chemotherapy and surgery (PENELOPE-B).</td>
<td>II</td>
<td>IDFS</td>
<td>1100</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Phase III trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+/HER2 early BC (PAL-LAS).</td>
<td>III</td>
<td>(IDFS)</td>
<td>4600</td>
<td>Recruiting</td>
</tr>
<tr>
<td><strong>Ribociclib</strong></td>
<td></td>
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<tr>
<td>Study of efficacy and safety of LEE011 in postmenopausal women with aBC (MONALEESA-2).</td>
<td>II</td>
<td>PFS</td>
<td>668</td>
<td>Published</td>
</tr>
<tr>
<td>Ribociclib or placebo in combination with either tamoxifen and goserelin or a nonsteroidal aromatase inhibitor and goserelin in premenopausal women with HR+ HER2- aBC (MONALEESA-7).</td>
<td>II</td>
<td>PFS</td>
<td>671</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>Ribociclib in combination with letrozole for the treatment of men and pre/postmenopausal women with HR+ HER2- aBC (COMPLEEMNT-1).</td>
<td>II</td>
<td>Safety and tolerability</td>
<td>3000</td>
<td>Recruiting</td>
</tr>
<tr>
<td><strong>Abemaciclib</strong></td>
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<tr>
<td>A phase 2 study of LY-2835219 for patients previously treated HR+, HER2- metastatic BC (MONARCH 1).</td>
<td>II</td>
<td>ORR</td>
<td>132</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>A study of abemaciclib combined with fulvestrant in women with HR+ HER2- BC (MONARCH 2).</td>
<td>II</td>
<td>PFS</td>
<td>630</td>
<td>Ongoing, not recruiting</td>
</tr>
<tr>
<td>A study of nonsteroidal aromatase inhibitors plus abemaciclib in postmenopausal women with BC (MONARCH 3).</td>
<td>II</td>
<td>PFS</td>
<td>450</td>
<td>Ongoing, not recruiting</td>
</tr>
</tbody>
</table>

Abbreviations: aBC, advanced breast cancer; BC, breast cancer; ER+, oestrogen receptor positive; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; IDFS, Invasive Disease Free Survival; Nbr, number; PFS, progression-free survival; RR, response rate; ORR, overall response rate.
Not reached' in patients treated with ribociclib (HR, 0.56, 95% CI, 0.43 to 0.72, p<0.001). In patients with measurable disease, the overall response rates were 52.7% in the ribociclib group and 37.1% in the placebo group (p<0.001). This study has a similar design to and similar results as the PALOMA2 study with palbociclib. Monaleesa-7 is another ongoing phase III study in which researchers are analysing the efficacy and safety of ribociclib and endocrine therapy in premenopausal women with hormone receptor positive and HER2-advanced breast cancer. Results of this trial should be available soon. Other combinations are currently investigated. A phase Ib/II trial is testing ribociclib in combination with alpelisib (BYL719), a selective oral PI3K inhibitor, in postmenopausal women with advanced or metastatic ER+/HER2-breast cancer. Patients are randomised into three groups; ribociclib plus letrozole, alpelisib plus letrozole or the triple combination of ribociclib plus alpelisib with letrozole. Only limited data from this study have been reported but we can expect a synergistic effect between CDK 4/6 and PI3K inhibitors, as suggested by preclinical data.

ABEMACICLIB
Like the other two CDK 4/6 inhibitors, abemaciclib has been studied in clinical breast cancer trials with promising results. However, this agent seems to have advantages compared to palbociclib and ribociclib; phase I trials suggest that it can be given continuously, without the need of one week-interruptions, and it might have a clinical activity in combination with fulvestrant as well as a single-agent activity for patients with advanced breast cancer. A phase II trial (MONARCH 1) has been performed with abemaciclib as a single agent in patients with progressive disease on or after endocrine therapy and chemotherapy. Preliminary results suggest that abemaciclib in monotherapy induces tumour responses in refractory ER+/HER2-breast cancer and is well tolerated. Two phase III randomised trials are ongoing in postmenopausal women with ER+/HER2-advanced breast cancer: MONARCH-2 investigates fulvestrant with either abemaciclib or placebo and MONARCH-3 studies nonsteroidal aromatase inhibitors (anastrozole or letrozole) with abemaciclib or placebo. Among hematologic toxicity, neutropenia is the most common; other cytopenias (anaemia and thrombocytopenia), are less frequent. In clinical trials, the incidence of neutropenia is highest with palbociclib compared with ribociclib and abemaciclib. However, even for palbociclib, neutropenia is mostly moderate (grade 1 or 2) and generally uncomplicated by febrile neutropenia. Dose adaptations are generally sufficient to manage this side effect. Gastrointestinal toxicities can occur with all three agents but are generally of low grade. They include nausea, vomiting and diarrhoea, which is the most frequent all-grade side effect for abemaciclib. Alopecia is another common side effect observed with CDK 4/6 inhibitors, but predominantly of grade 1 or 2. Furthermore, CDK 4/6 inhibitors can also lead to QTc interval prolongations, which are generally uncomplicated. In all clinical trials, the QTc interval is checked before treatment initiation in order to avoid exposure to patients at risk. Careful monitoring should be exercised when using concomitantly other drugs with potential QTc interval prolongation. Clinicians can check websites such as https://crediblemeds.org for an updated list of these drugs.

In total, the CDK 4/6 inhibitors seem to be safe for use and less toxic than chemotherapy.

FUTURE CHALLENGES

COMBINATION THERAPY
In breast cancer, CDK 4/6 inhibitors have been essentially investigated in combination with endocrine therapy in women with ER+ cancer. However, there are some pre-clinical data suggesting that these agents are also effective in combination with other classes of drugs, especially targeted therapies. In HER2-amplified cells, like in ER+ cells, amplification/overexpression of cyclin D1 was observed and suggested that this breast cancer subtype is sensitive to CDK 4/6 inhibition. The combination of palbociclib plus trastuzumab has been shown to be synergistic in HER2amplified breast cancer cells. Several early phase clinical trials are ongoing with this combination, including in a neoadjuvant setting. Furthermore, combinations of CDK 4/6 inhibitors with phosphatidylinositol 3-kinase (PI3K) inhibitors or mTOR inhibitors are also being investigated. These combinations of inhibitory drugs could prevent the emergence of resistance.

PREDICTIVE BIOMARKERS FOR CDK 4/6 INHIBITORS EFFICACY AND RESISTANCE
Although they are generally well tolerated, CDK 4/6 inhibitors are nonetheless more difficult to manage than endocrine therapy alone, because they require more frequent blood tests and hospital visits. Furthermore, with a market price of sev-
eral thousand euros per month, their financial burden on our already overstretched social security system is certainly not negligible. Unfortunately, the only predictive marker for the efficacy of CDK 4/6 inhibitors in patients with breast cancer is still ER-positivity. The medical community is in desperate need of more refined predictive biomarkers for CD4/6 inhibitor sensitivity, in order to guide patient selection beyond the use of ER positivity alone. While increased cyclin D1 (CCND1 gene amplification) and RB1 as well as decreased CDKN2A (loss of p16) were associated with sensitivity to CDK 4/6, the phase II PALOMA-1 study did not support this hypothesis for CCND1 and CDKN2A, and confirms that ER-positivity is until now the best predictive marker of CDK 4/6 inhibitors efficacy in breast cancer.19,36 As these data are still limited, further studies are necessary especially to examine the role of RB1 as a biomarker. Other strategies involve the use of modern imaging techniques in order to rapidly identify non-responders.45

In contrast with ER+ breast cancers, triple-negative breast cancers are resistant to CDK 4/6 inhibition in vitro.19 The mechanism of this primary resistance to CDK 4/6 inhibitors has been explained by the loss of RB1 activity and the increased expression of cyclin E1.46-48 Identification of mechanisms of acquired resistance to CDK 4/6 inhibitors could allow the development of further therapeutic strategies post-CDK 4/6 inhibitor.

DURATION OF CDK 4/6 INHIBITION
The duration of CDK 4/6 inhibition, and in particular the need to continue cell cycle blockade beyond progression, is another topic that should be addressed: at progression, should CDK 4/6 inhibitors be maintained as a backbone, with a mere change of endocrine therapy, as is already the case with HER2-targeting agents in HER2-positive (HER2+) metastatic breast cancer? It has been shown that trastuzumab continuation beyond disease progression in this population improves the PFS and the overall survival (OS) with few toxicities.49 About CDK 4/6 inhibitors, further studies are needed to know if there is a benefit of CDK 4/6 inhibition continuation beyond failure of first-line therapy containing this class of targeted therapy.

CONCLUSION
CDK 4/6 inhibitors are a new class of targeted agents that have proven efficacy in breast cancer, particularly in treating ER+ advanced breast cancer. This new class of drugs improves the response and the duration of response to endocrine therapies, although current data have not yet demonstrated an advantage in terms of OS. Palbociclib has been granted accelerated FDA approval for use in the treatment of metastatic breast cancer in combination with endocrine therapy. Its use was recently approved by the European Medicines Agency (EMA) for the treatment of hormone receptor-positive, HER2– locally advanced or metastatic breast cancer, either in combination with an aromatase inhibitor or in combination with fulvestrant in women who have received prior endocrine therapy. It is currently available in Belgium in a compassionate use program in first-line combination with letrozole.

KEY MESSAGES FOR CLINICAL PRACTICE

1. Cyclin dependent kinase (CDK) 4/6 inhibitors are new targeted therapies that block RB1 phosphorylation and induce cell cycle arrest in the G1 phase.

2. Three CDK 4/6 inhibitors have been developed: palbociclib (PD 0332991), ribociclib (LEE011), and abemaciclib (LY2835219). Palbociclib is approved by the FDA and EMA for use in combination with endocrine therapy in patients with ER+/HER2- advanced breast cancer.

3. The addition of CDK 4/6 inhibitors to endocrine therapy prolongs progression-free survival in ER+/HER2- advanced breast cancer. This combination therapy has become a new standard of care for these patients.

4. CDK 4/6 inhibitors are well-tolerated; side effects are generally moderate and consist essentially in myelosuppression, gastrointestinal toxicities and QTc interval prolongation.

5. Several studies are ongoing to investigate the role of CDK 4/6 inhibitors in the neoadjuvant/adjuvant setting and in combination with other targeted therapies, and to find predictive biomarkers of sensitivity and resistance.
Ribociclib has been granted FDA priority review and is currently under review by EMA. It is available in Belgium in a phase IIIb trial. Another phase III study is ongoing with abemaciclib vs. placebo in combination with an aromatase inhibitor. Further studies should confirm the synergetic effects between CDK 4/6 inhibitors and other therapeutic classes, such as PI3K inhibitors and mTOR inhibitors, and investigate their effects in the neoadjuvant and adjuvant settings. Priority should be given to the identification of predictive biomarkers of efficacy or resistance.

In conclusion, CDK 4/6 inhibitors are effective in breast cancer with only modest toxicity and have become a new standard of care for the treatment of ER+/HER2− metastatic breast cancer.

REFERENCES


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