THERAPEUTIC ADVANCES in
Medical Oncology

Review

CDK4/6 inhibitors: basics, pros, and major cons in breast cancer treatment with specific regard to cardiotoxicity – a narrative review

Ther Adv Med Oncol

2023, Vol. 15: 1–19

DOI: 10.1177/17588359231205848

Dragica Pavlovic*, Danijela Niciforovic*, Dragana Papic*, Katarina Milojevic and Marina Markovic

***Abstract*:** Breast cancer is characterized by the uncontrolled proliferation of breast cells, with a high incidence reported in 2020 to have affected over 2 million women. In recent years, the conventional methods of treating breast cancer have involved radiotherapy and chemotherapy. However, the emergence of CDK4/6 inhibitors has shown potential as a promising cancer therapy. Cyclin-dependent kinases (CDK) inhibitors are a class of molecules that impede the formation of an active kinase complex, thereby hindering its activity and consequently halting the progression of the cell cycle. It was discovered that they have a significant impact on impeding the progression of the cancer. This is evident with the Food and Drug Administration's approval of drugs such as palbociclib, ribociclib, and abemaciclib for hormone receptor-positive metastatic breast cancer in combination with specific endocrine therapies. In spite of enormous success in breast cancer treatment, certain obstacles have emerged, such as therapy resistance, side effects, and most of all, cardiotoxicity. Some of these drawbacks have been successfully overcome by dosage reduction, different combinations of the drugs, and the assessment of each patient's condition and suitability prior to treatment. Yet other drawbacks still require tenacious research, especially certain cases of cardiotoxicities. This article delves into the biological mechanisms of CDK4/6 in the cell cycle and cancer, as well as the clinical advantages and most common adverse events (AEs) associated with CDK4/6 inhibitors. The primary objective of this review is to provide a comprehensive analysis of cardiotoxic AEs and elucidate the underlying pathophysiological mechanisms responsible for the cardiotoxicity of CDK4/6 inhibitors.

Keywords: adverse events, breast cancer, cardiotoxicity, CDK4/6 inhibitors, therapy

Received: 4 June 2023; revised manuscript accepted: 18 September 2023.

Correspondence to:
Dragica Pavlovic
Department of Genetics, Faculty of Medical Sciences, University of Kragujevac, 69 Svetozar Markovic Street, Kragujevac 34000, Serbia
dragica.miloradovic8@gmail.com

Danijela Niciforovic
Katarina Milojevic
Center for Internal Oncology, University Clinical Center Kragujevac, Kragujevac, Serbia

Dragana Papic
Department of Genetics, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

Marina Markovic
Center for Internal Oncology, University Clinical Center Kragujevac, Kragujevac, Serbia

Department of Internal Medicine, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

*These authors contributed equally and share first authorship.

Introduction

Breast cancer is a significant health issue affecting women, primarily due to its elevated rates of mortality and morbidity. According to a study, the survival rate for patients with metastatic breast cancer is below 30%, despite the administration of adjuvant chemotherapy.[1] According to the International Agency for Research on Cancer, the latest GLOBOCAN 2018 statistics from 185 countries indicate that there were 2.3 million new cases of breast cancer, accounting for 11.7% of all cancer cases, and a mortality rate of 6.9%.[2] The course of therapy of breast cancer is determined by the unique expression of certain markers in the tumor, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER) 2, the proliferation marker Ki-67, and the extent of the disease. The integration of surgical procedures, chemotherapy, and radiation therapy alongside targeted therapy has resulted in a significant improvement in patient outcomes over the last 20 years. Presently, the mean 5-year survival rate stands at roughly 87%.[3] Given that the most prevalent subtype of both early and advanced breast cancer is hormone receptor positive (HR+) disease, novel targeted

therapies such as CDK4/6 inhibitors (CDKIs) (monotherapy in conjunction with endocrine therapy) have been the first-line treatment option for patients with HR-positive/HER2-negative metastatic morphologies, since the U.S. Food and Drug Administration (FDA) approval of palbociclib in 2015.[4] The canonical mechanism underlying the activity of CDK4/6 inhibitors is the inhibition of phosphorylation of the retinoblastoma tumor suppressor protein, which prevents the proliferation of cancer cells. CDK4/6 inhibitors commonly used to treat breast cancer include palbociclib, ribociclib, and abemaciclib, which have been utilized with great success in the treatment of hormone receptor-positive breast cancers, and are undergoing testing for many other forms of tumors. However, the application of molecular targeting drugs for breast cancer, and the new therapeutic cardiac toxicity has progressively attracted a rising level of concern regarding breast cancer prognosis.[5] This is crucial to reconsider, since cardiotoxicity caused by breast cancer treatment can have a significant impact on survivors' quality of life and contribute to premature morbidity and mortality, especially in a subset of patients.[6] This article will discuss the mechanism of action, clinical benefits, and most common adverse events (AEs) with an emphasis on the cardiotoxicity of CDK4/6 inhibitors in patients with breast cancer.

Methods

We performed a review of the literature based on the narrative literature review guidelines outlined by Green *et al.*[7] The PubMed (Medline) database was queried from its date of inception until 28 May 2023, for MeSH terms as well as different keywords including CDK4/6 inhibitors, breast cancer, cardiotoxicity, and AEs. Peer-reviewed clinical trials and large retrospective studies published in the English language that reported on CDK4/6 inhibitors and cardiotoxicity in breast cancer patients were included.

To critically appraise the literature and assess any bias of studies is performed by SANRA – a scale for the quality assessment of narrative review articles,[8] which include:

The six items which form the revised scale are rated from 0 (low standard) to 2 (high standard) and cover the following topics: explanation of (1) the importance (which is explicitly justified) and (2) the aims of the review (one or more concrete aims or questions are formulated), (3) literature search (the literature search is described briefly) and (4) referencing (key statements are supported by references) and presentation of (5) evidence level (appropriate evidence is generally presented), and (6) relevant endpoint data (relevant outcome data are generally presented appropriately).

(1) *The importance*

Research on CDK4/6 inhibitors and their potential cardiotoxicity is important for several reasons:

1. Cancer treatment: CDK4/6 inhibitors are a class of drugs used in cancer treatment, particularly for breast cancer. Understanding their cardiotoxic effects is crucial because cancer patients are already at risk of heart-related issues, and any additional risk from the treatment needs to be carefully assessed.
2. Patient safety: Assessing cardiotoxicity helps ensure the safety of cancer patients undergoing CDK4/6 inhibitor therapy. If significant cardiotoxic effects are identified, doctors can monitor patients more closely and take preventive measures.
3. Treatment optimization: Research in this area can lead to the development of strategies to minimize or mitigate cardiotoxicity while still reaping the benefits of CDK4/6 inhibitors for cancer treatment. This can improve the overall effectiveness of these drugs.
4. Long-term health: Understanding the long-term cardiac effects is essential since cancer survivors may live for many years after treatment. It's important to ensure that cancer therapies do not compromise their long-term heart health.
5. Scientific understanding: Studying CDK4/6 inhibitors and their effects on the heart can also contribute to our broader understanding of how these drugs interact with various body systems and may uncover new insights into cancer biology and cardiovascular health.

In summary, research on CDK4/6 cardiotoxicity is essential to strike a balance between the benefits of cancer treatment and the potential risks to a patient's heart health. It ultimately aims to improve patient outcomes and quality of life.

(2) *The aims of the review*

Research on CDK4/6 cardiotoxicity aims to achieve several important goals:

1. Safety assessment: Evaluate the potential cardiotoxic effects of CDK4/6 inhibitors, which are commonly used in cancer treatment, to ensure patient safety.
2. Mechanism understanding: Investigate the mechanisms by which CDK4/6 inhibitors may cause cardiotoxicity. Understanding these mechanisms can help in developing strategies to mitigate these effects.
3. Risk prediction: Identify patient populations at higher risk of cardiotoxicity when using CDK4/6 inhibitors. This can involve genetic, demographic, or other factors that predispose individuals to these side effects.
4. Biomarker discovery: Discover biomarkers that can serve as early indicators of cardiotoxicity. These markers can be used for monitoring patients during treatment.
5. Prevention and intervention: Develop strategies and interventions to prevent or minimize cardiotoxicity in patients receiving CDK4/6 inhibitors. This might involve dose adjustments, co-administration of protective agents, or other approaches.
6. Treatment optimization: Optimize the use of CDK4/6 inhibitors in cancer treatment to balance their efficacy against the risk of cardiotoxicity.
7. Regulatory guidance: Provide data and insights to regulatory agencies to guide the approval and monitoring of CDK4/6 inhibitors.

Overall, the aim is to ensure that cancer patients can benefit from CDK4/6 inhibitors while minimizing the potential harm to their cardiovascular health.

(3) *literature search*-already explained above in the methods section.
(4) *referencing* **(**key statements are supported by references throughout the manuscript for each section separately) and presentation of (5) *evidence level* (appropriate evidence is generally presented**)** and (6) *relevant endpoint data* (relevant outcome data are generally presented appropriately**).**

Objectives

This study evaluated the biological mechanisms of CDK4/6 in the cell cycle and cancer, the clinical advantages and most common AEs associated with CDK4/6 inhibitors, and cardiotoxic AEs and pathophysiological mechanisms responsible for the cardiotoxicity of CDK4/6 inhibitors. Cardiotoxicity of CDK4/6 inhibitors is primarily focused on results of studies that examined the cardiotoxic effects of CDK4/6 inhibitors with trastuzumab or everolimus along with standard hormonal treatment or with fulvestrant in breast cancer patients, with each cardiotoxic side effect being noted, such as Arrhythmias, new hypertension, atrial fibrillation (AF), myocardial infarction (MI), cardiac failure, and pericardial effusion, vascular inflammation, hypertensive response, and left ventricle remodeling, type 2 atrioventricular (AV) block and prolongation of QT interval (the duration of ventricular electrical systole) as the most common cardiotoxic AEs.

Mechanism of action of CDK4/6 inhibitors in cell cycle and cancer

The capacity to reproduce is a crucial characteristic of living organisms and is facilitated by a series of intricate reactions and mechanisms collectively referred to as the cell cycle (Figure 1). The process of cell division is governed by the cell cycle, which oversees the duplication of deoxyribonucleic acid (DNA) and the distribution of the replicated DNA into a newly formed daughter cell.[9] The predominant state of cells within the human body is quiescence, characterized by a lack of differentiation and proliferation unless prompted by a specific stimulus. The decision to progress from the G1 phase to the S phase and subsequently to the G2 phase, where protein synthesis occurs and the cell prepares for mitosis, is governed by distinct restriction points. This process involves DNA replication.[10] The activation of DNA repair mechanisms and reevaluation of DNA replication completeness may occur during the S phase and G2 phase, where checkpoints may also be present.[11] The uncontrolled proliferation observed in cancer is initiated by the dysregulation of restriction points.[12] The advancement of each stage of the cellular life cycle is subject to rigorous regulation by a number of cellular cycle constituents, including cyclins, Cyclin-dependent kinases (CDKs), and CDK inhibitors, which operate through phosphorylation and dephosphorylation reactions.[13] Remarkably,

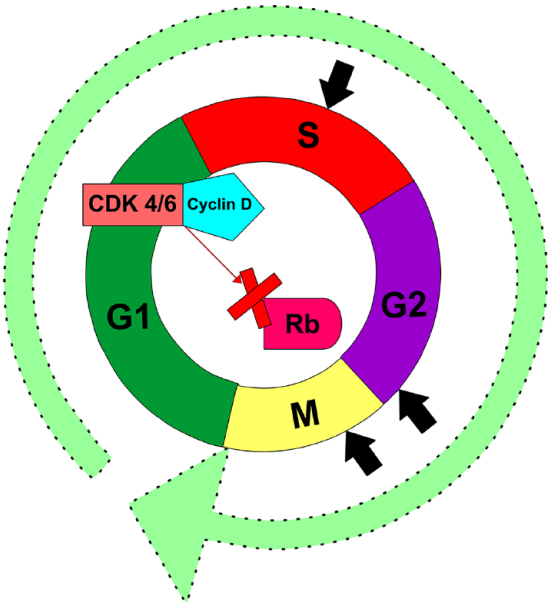

Figure 1. Mechanism of action of CDK4/6 inhibitors in cell cycle and cancer. This diagram illustrates the cell cycle, a process that leads to cell division. As depicted by the circular dotted arrow in this diagram, normal cell replication progresses from the G1 (first growth period) to the S (DNA replication), G2 (second growth period), and M (mitosis period) phases. A number of proteins, including CDKs, regulate this process. CDK 4/6 forms a complex with cyclin D, which phosphorylates the tumor suppressor protein retinoblastoma protein (Rb) and results in its inactivation (thin arrow in figure). Ultimately, this permits the progression from G1 to S in the cell cycle. CDK 4/6 inhibitors block the formation of the CDK 4/6-cyclin D1 complex and the phosphorylation of Rb to arrest the cell cycle. The uncontrolled proliferation observed in cancer is initiated by the dysregulation of restriction points (depicted with thick black arrows in figure).
CDKs, cyclin-dependent kinases; DNA, deoxyribonucleic acid; Rb, retinoblastoma protein.

this checkpoint is frequently overexpressed in HR+ breast cancer cells, making it an excellent aim for targeted drug therapy.[14] The significance and role of individual CDKs in regulating the cell cycle have been extensively examined in several publications.[15–18] So, over the past 30 years, many drugs that target CDK activity have been made and tested in clinical trials. These tests show that certain features of all cancers interfere with the regular control of the cell cycle.[19] CDK 4/6 and cyclin D form a complex within the cell cycle. This complex phosphorylates the retinoblastoma protein (Rb), which deactivates this tumor suppressor protein, resulting in gene transcription and the progression of the cell cycle from the G1 to S phase, ultimately leading to cell division.[20,21] Cell replication is inhibited by intrinsic CDK inhibitors and tumor suppressor proteins such as p16 and Rb.[20] In cancer cells, the process of cell division becomes unrestrained, leading to rapid expansion and the formation of a tumor. The deregulation of the cell cycle in cancerous cells is attributed to various mechanisms, such as the amplification and hyperactivity of CDK 4/6, or their genomic instability. These factors may lead to the oncogenic activation of CDK 4/6, thereby driving cell replication.[22] By circumventing these mechanisms, neoplastic cells can sustain their proliferation by inducing the transition from G1 to S phase.[23] The observed phenomenon seems to be enabled by a reduction in the duration of the G1 phase. CDK 4/6 in a cancerous cell acts as an antagonist to intrinsic tumor suppression mechanisms such as cell senescence and apoptosis, thereby amplifying the tumor's growth.[22] In addition to the aforementioned, cancerous cells exhibit an increase in the expression of various cyclins and CDKs, while concurrently reducing the activity of intrinsic CDK inhibitors and tumor suppressor proteins.[21,24] The dysregulation of the cell cycle results in the proliferation of malignant cells and ultimately leads to the onset of cancer.[21] The development of inhibitors that are potent and selective in targeting cyclin D1 to obstruct the formation of the CDK 4/6-cyclin D1 complex by impeding the binding site of cyclin D1 and destabilizing the complex has generated significant attention in the field of cancer therapy.[23] The CDK 4/6 inhibitors, which are recently developed, have the ability to hinder the phosphorylation of Rb, leading to the arrest of the cell cycle (Figure 1).[20,25–27] The emergence of orally active inhibitors with high selectivity toward CDK4 and CDK6 has significantly altered the therapeutic approach to CDK inhibition. The compounds' selectivity is attributed to their direct interaction with the ATP-binding cleft of CDK4 and CDK6, which exhibit a difference of only one amino acid in the active site (GLU144 in CDK6, GLN149 in CDK4).[28] The gene *CCND1* is responsible for encoding cyclin D1 and is observed to be commonly amplified in cases of breast cancer in humans.[29] The findings of the study, which involved the analysis of 3617 samples and the integration of the METABRIC and TCGA (Firehose Legacy data), revealed that the amplification of CDK4 is infrequent, occurring in only 1.3% of cases, and is often accompanied by cyclin D1 amplification. Overexpression, gene amplification, transcriptional induction, or post-transcriptional induction can lead to an increase in the abundance

of cyclin D1 protein in more than 50% of breast cancers.[29] The overexpression of cyclin D1 is predominantly observed in luminal breast cancer subtypes, namely luminal A and luminal B, which are commonly associated with ERα+ breast cancer. In accordance with the theoretical framework positing the role of cyclin D1 in the induction of chromosomal instability, there exists a positive correlation between heightened levels of cyclin D1 and the manifestation of chromosomal instability signature. CDKIs have been observed to decrease retinoblastoma (RB) protein phosphorylation in tissue culture, which in turn leads to the inhibition of E2F release from binding to Rb and subsequent G1 cell cycle arrest.[30–32] Furthermore, CDKIs exhibit supplementary anticancer properties in breast cancer, such as amplifying the immunogenicity of cancer cells and stimulating cellular senescence.[33]

Historical and contemporary challenges and recent advances associated with CDKIs

There are three different types of CDKIs right now. Even though preclinical tests of the first and later generations showed promising results, they could not be used because they were not selective enough, which led to toxicity. Also, the exact mechanism of the first generations of CDK inhibitors has not been completely deciphered. In the same manner, the suppression of vital CDKs that are crucial for proliferation, survival, checkpoint activation, DNA repair, and replication led to increased cytotoxicity in normal cells. In contrast, the third generation of CDKIs, specifically CDK4/6 inhibitors, have demonstrated promising outcomes, advanced to clinical trials, and obtained FDA approval without encountering the aforementioned issues. Notwithstanding clinical success, intrinsic and acquired resistance limits their usage. Clinically, it has been noted that only a portion of treated patients respond to the advanced generation of CDKIs, whereas some patients demonstrate inherent resistance and fail to receive any benefit from these drugs, often moving to chemotherapy.[33] Mechanisms of CDKIs resistance have been thoroughly elaborated in recent reports. [33–36] Despite the abundance of published preclinical studies, a clinically validated context for CDKI resistance mechanisms has yet to be investigated. Therefore, more research is required to pinpoint the precise mechanism of resistance and identify the ideal patients and therapeutic approaches for the treatment of breast cancer with CDKIs. In both adjuvant and metastatic settings, endocrine therapy is very efficacious for breast cancer. However, some adjuvant patients will relapse with terminal metastatic disease due to endocrine therapy resistance.[37] HR+ metastatic breast cancer patients eventually become endocrine-resistant, requiring lifelong treatment.[37] Thus, enhancing the efficacy of endocrine therapy in adjuvant and metastatic contexts will greatly benefit many breast cancer patients. Novel medicines targeting cellular growth and regulatory mechanisms are being developed to improve HR+ breast cancer endocrine treatment. Several CDKIs targeting distinct CDKs have been devised over the last couple of decades to inhibit cancer cell proliferation.[38] The outcomes obtained from preclinical and clinical studies on CDKIs as a treatment for breast cancer have revolutionized the management of breast cancer. Several notable studies have described the preclinical and early clinical results of CDKIs in breast cancer therapy.[39–41]

Clinical explanation for CDK4/6 inhibitors selection

The comparative efficacy of the three CDK4/6 inhibitors has not been established through randomized clinical studies. Anyway, the selection of a specific inhibitor for use with endocrine therapy is primarily based on considerations such as safety profiles, dosing schedules, and patient comorbidities.[42] In a phase II study with a single-arm design, 37 patients diagnosed with Rb-positive metastatic breast cancer were enrolled. The study revealed that among the subset of patients with ER-positive/HER2-negative breast cancer, comprising 84% of the cohort, two patients achieved partial remission, whereas five patients maintained stable disease for a period exceeding 6 months.[43] The combination of palbociclib with trastuzumab or tamoxifen in breast cancer models resulted in a synergistic inhibitory effect on HER gene amplification and ER-positive cell proliferation. Similarly, the combination of palbociclib with endocrine therapy demonstrated a similar synergistic effect.[44] As per the findings of the MONALEESA-2 clinical study, the use of ribociclib in combination with letrozole resulted in a significant increase in overall survival among patients who were sensitive to endocrine therapy. The risk of mortality was observed to decrease by 24%, and the median survival time was recorded as 63.9 months.[45] The OS advantage was verified through statistical analysis in the endocrine-sensitive group of the MONALEESA 3 trial, which

administered ribociclib in combination with fulvestrant as the initial treatment.[46] The MONALEESA 7 clinical trial observed that pre- and perimenopausal patients who received ribociclib in conjunction with endocrine therapy (aromatase inhibitor or tamoxifen) and goserelin exhibited a comparable reduction in the risk of mortality.[47] Additionally, in a separate meta-analysis, it was observed that ribociclib and abemaciclib exhibited a noteworthy reduction in mortality risk, while only palbociclib did not exhibit a statistically significant hazard ratio with respect to overall survival.[48] According to the findings of the MONARCH 3 clinical trial, which involved postmenopausal women with endocrine-sensitive illness, the combination of abemaciclib and AI resulted in an overall response rate of 61% and a mean response duration of 32.7 months.[49] The phase II single-arm MONARCH-1 study investigated the efficacy of Abemaciclib monotherapy. The study findings revealed an objective remission rate of 19.7%, median progression-free survival (PFS) of 6 months, and median overall survival of 17.7 months.[47] Furthermore, empirical research has demonstrated that it can be utilized as a monotherapy or in conjunction with gemcitabine.[50] Here are mentioned only the most prominent clinical trials that validate and analyze the clinical benefits of CDK4/6 inhibitors, while thorough analysis of the latest advancements of these medications has been revised recently. [51]

Most common AEs of CDK4/6 inhibitors

CDK4/6 inhibitors are generally well-tolerated agents from a safety perspective, with comparable safety profiles. However, there are variations in the occurrence and frequency of toxicities among them, which may impact the selection of a specific medication.[52] Abemaciclib exhibits a unique structural composition compared to the other CDK4/6 inhibitors and demonstrates a higher level of specificity toward CDK4 in comparison to CDK6.[50] Its potency against CDK4 is 14 times greater than its potency against CDK6. CDK4 is more important for breast tumorigenesis, while CDK6 is associated with hematopoietic stem cell differentiation.[15] CDK4/6 inhibitors may cause nausea, vomiting, and diarrhea, fatigue, alopecia, and infections [50] whereas ribociclib and palbociclib reduce such adverse effects. All three CDK4/6 inhibitors have the potential to cause diarrhea, but abemaciclib – the most potent of the three – is more likely to do so due to its higher potency against CDK4 than CDK6, which may also account for its lower hematological toxicity.[53] Therefore, ribociclib and palbociclib are associated with a toxicity profile characterized by hematological AEs, with neutropenia being the most commonly reported AE.[42,54] Most recently in a meta-analysis, the addition of CDK4/6 inhibitors to endocrine therapy substantially increased the risk of infections of all grades, infections of grade 3 or higher, and urinary tract infections.[55] Additionally, it has been observed that ribociclib exhibits a greater frequency of QT interval prolongation and elevated liver enzymes.[42] Each of the three CDK4/6 inhibitors – palbociclib, abemaciclib, and ribociclib – are authorized by the FDA and based on major trials: PALOMA-1,2,3,[56,57] MONARCH-1,2,3[50,52]; and MONALEESA-2,7.[45,54]

Transaminitis

In the PALOMA-3 study, 4% of palbociclib patients had a grade 1/2 alanine transaminase ALT increase and 3% had a grade 3.[46] In the MONARCH-3 experiment, 5.8% and 0.6% of patients had grade 3 and 4 ALT increases, whereas 3.8% had grade 3 aspartate aminotransferase AST increases. Patients treated with abemaciclib and nonsteroidal AIs exhibited no ALT elevation of grade four.[45] In the MONALEESA-2 study, 9.3% and 5.7% of patients had grade 3/4 ALT and AST increases after ribociclib and letrozole.[42]

Gastrointestinal toxicities

In the MONARCH-1 trial, 90% of abemaciclib monotherapy patients had diarrhea during 7 days of therapy, which led to dose reductions of 21%. It typically lasted 7.5 days for second grade and 4.5 days for third grade.[47] In total, 73% of abemaciclib patients in MONARCH-2 had grade 1 or 2 diarrhea, whereas 13.4% had grade 3 diarrhea. Antidiarrheal drugs and dose changes helped manage it in the first treatment cycle.[48] In the MONARCH-3 trial, 27.2% of the patients had grade 2 diarrhea, and only 9.5% of patients had grade 3 diarrhea.[45] One study investigated a possible link between abemaciclib's early toxicities and patients' PFS. Individuals given abemaciclib with diarrhea within the first 7 days or who did not have diarrhea within the first 7 days demonstrated an improvement in PFS when compared to the placebo group. The correlation between dosage levels (150, 100, and 50 mg) and PFS was investigated using a time-dependent analysis. There was no evident difference in the PFS of patients reduced from 150 to 100 mg or

50 mg compared to the PFS of patients treated at 150 mg.[49]

Neutropenia

Neutropenia is the most frequently observed adverse effect of grade 3/4 across all clinical trials. CDK4/6 inhibitors induce cell cycle arrest without DNA damage or apoptosis of proliferating neutrophil precursor cells, resulting in faster neutrophil count recovery than chemotherapy.[58] As mentioned above, Abemaciclib has greater CDK4 selectivity than palbociclib and ribociclib,[49] resulting in a 50% lower neutropenia rate across all grades. In the MONARCH-3 trial, 41.3% of abemaciclib patients exhibited neutropenia, 16.2% grade 2, 19.6% grade 3, and 1.5% grade 4. By cycle two, all grades of neutropenia were typically present, whereas grade 3 and grade 4 neutropenia were sporadic in subsequent cycles.[59] Neutropenia occurred in 63.8% of ribociclib-treated patients in the MONALEESA-2 trial.[60] In the PALOMA trial, 70% of patients receiving palbociclib–fulvestrant experienced neutropenia of grade 3 or 4, with febrile neutropenia still being rare, occurring in only 1% of patients.[54]

Cardiotoxicity of oncologic therapies

Besides most common AEs, it is crucial to pinpoint cardiotoxicity of these therapies. Thus, Ewer and Ewer presented a comprehensive summary of cardio-oncology.[61] The scope of cardio-oncology has expanded to encompass various cardiovascular diseases, such as vascular toxicity and arrhythmias, in addition to cardiotoxicity. The shift toward targeted agents and immunotherapies in cancer treatment can be attributed to advancements in cancer therapeutics over the past century. The lack of a universal definition for the term 'cardiotoxicity' has led to its broad application to various disease entities. This applies to cardiomyopathies related to cancer therapy. Numerous anticancer drugs used for advanced/metastatic breast cancer treatment have been linked to cardiac side effects such as left ventricular (LV) dysfunction, heart failure, arrhythmias, myocardial ischemia, valvular disease, thromboembolic disease, pulmonary hypertension, arterial hypertension, and pericarditis.[62–66] Cardiac function may deteriorate due to direct cardiomyocyte damage, changes in perfusion, innervation, hormonal milieu, or inflammatory cell infiltration in the myocardium. These are categorized as cancer therapy-related cardiomyopathies, with four known forms of cardiotoxicities caused by oncologic drugs[67–69]:

1. Acute cardiotoxicity is a rare side effect that happens right after the first time a drug is taken and is not dependent on the dosage. The clinical presentation encompasses hypotony, arrhythmias, and myocardial ischemia. The condition typically exhibits reversibility upon cessation of drug infusion.
2. Subchronic cardiotoxicity shows up within weeks of therapy, often causing myocarditis or pericarditis.
3. Early-onset chronic cardiotoxicity appears as progressive heart failure within a few weeks after therapy cessation.
4. Late-onset chronic cardiotoxicity is a condition that manifests several years following the cessation of treatment and results in heart failure.

In the same manner, it is worth mentioning that especially protein kinase inhibitors (KIs) can cause various cardiovascular toxicities such as hypertension, arrhythmias, cardiomyopathy, fluid retention, thromboembolic events, and myocardial ischemia or infarction.[70–82] On the other hand, the complete understanding of the mechanism underlying KIs-induced cardiotoxicity remains elusive, as evidenced by existing literature.[81–85] In broad terms, cardiac toxicity mechanisms can be classified into on-target and off-target mechanisms.[85] On-target mechanisms refer to the phenomenon where the use of KIs results in the inhibition of a molecule, leading to an anticancer effect in malignant cells. However, this effect may also result in toxicity in normal cells. Conversely, off-target mechanisms manifest when KIs impede the activity of a kinase in cancerous cells, resulting in an anti-tumor response, as well as other kinases in healthy cells, culminating in cardiac toxicity. For instance, anthracyclines, considered to be among the favored treatment options for HER2-negative metastatic breast cancer where chemotherapy is deemed appropriate,[86,87] are shown to have a greater impact on the cardiac system compared to other chemotherapeutic agents. The use of an anthracycline-based regimen resulted in a fivefold increase in the risk of clinical cardiac events and cardiac death when compared to a non-anthracycline regimen. Cardiac events related to anthracycline usually manifest within the initial year of treatment.[88,89] But it has been said that they can show up as soon as one dose of anthracyclines or as

long as a few years after the end of treatment.[88,90,91] The acute occurrences primarily comprise of arrhythmias and ECG anomalies, while the untreated delayed cardiomyopathy can lead to gradual deterioration of LV function and consequent heart failure.[88,90,91] In the same manner, due to their lower binding specificity, tyrosine kinase inhibitors (TKIs) are considered multi-target agents, which may result in significant cardiotoxic effects.[92,93] Lapatinib, a TKI, is employed in the management of HER2-positive metastatic breast cancer.[94] The current approval for Lapatinib involves its use in combination with capecitabine for patients with advanced or metastatic breast cancer who have not responded to treatments involving anthracycline, paclitaxel, and trastuzumab.[95] Trastuzumab was associated with cardiac dysfunction in up to 27% of subjects treated with trastuzumab alone and symptomatic heart failure in 64% of subjects treated concurrently with trastuzumab and anthracycline in the first clinical trial in patients with metastatic breast cancer.[96] In subsequent adjuvant HER21 breast cancer trials, the incidence of symptomatic heart failure has decreased significantly due to modifications in administration, avoidance of anthracyclines, and routine cardiac function monitoring. Current regulatory and clinical practice guidelines recommend routine assessment of LV function prior to and during treatment with trastuzumab, as well as withholding or discontinuing treatment in patients with LV dysfunction and/or heart failure.[96] Cardiomyopathy induced by trastuzumab negatively impacts cardiac and oncology outcomes. In cardio-oncology, strategies for risk stratification, early diagnosis, and prevention of trastuzumab-induced cardiomyopathy have emerged as an important topic of collaborative trials. QTc prolongation is exclusively linked to Lapatinib, which acts as the sole inhibitor of ErbB2. One study was conducted on patients with advanced cancer, wherein an uncontrolled, open-label approach was employed. The study revealed a correlation between the concentration of the drug and the prolongation of the QTc interval.[94] Besides QTc prolongation, latest studies emphasize LV dysfunction in patients taking Lapatinib.[97,98] Finally, the molecular mechanisms of KI-induced cardiotoxicity and qTc prolongation are intricate and not entirely comprehended. [74,99]

CDK4/6 inhibitors-induced cardiotoxicity

CDK4/6 inhibitors have simplified therapy for patients with no significant organ impairments due to metastases, thereby eliminating the need for chemotherapy. Furthermore, the disease-related outcomes of these inhibitors are comparable.[100,101] The combination of CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) and endocrine therapy has been approved for treating advanced breast cancer in patients with HR+ and HER2-negative (HER2-) subtypes.[102–104] Anyway, even though CDK-4/6 inhibitors are generally considered safe, there are some studies that have displayed various cardiotoxic effects of these drugs (Table 1). One study utilized the OneFlorida Data Trust to analyze a cohort of 1035 adult patients, who had not previously been diagnosed with cardiovascular disease and had received at least one CDK 4/6 inhibitor within the timeframe of 1 January 2012 to 31 December 2018.[105] Cardiotoxicity was observed in 16.8% of the patients, with a mortality rate of 17.2% among those affected. A total of 61 instances of arrhythmias were observed, with a mortality rate of 24.6%. Additionally, 97 cases of new hypertension were recorded, with a mortality rate of 15.5%. The present study revealed that the use of CDK 4/6 inhibitors is frequently associated with cardiotoxicity, which in turn is linked to elevated mortality rates and occurrences of arrhythmias. Notably, hypertension appears to be a significant contributor to this observed phenomenon. One group examined the cardiac toxicity of CDK 4/6 inhibitor therapies offered by FDERS in 2018 and 2019.[106] Namely, a total of 27,079 AEs from CDK4/6 inhibitors ribociclib, palbociclib, and abemaciclib were reported. Atrial fibrillation,[107] myocardial infarction (190), cardiac failure (85), and pericardial effusion (70) were the most prevalent cardiac AEs reported. The reported incidence of cardiac AEs was 2.2%, 5.4%, 7.9%, and 7.2% for palbociclib, abemaciclib, ribociclib, and trastuzumab, respectively. Specifically, 2.9% of reported adverse reactions to CDK4/6 inhibitors were cardiovascular toxicities, with ribociclib being associated with a higher incidence of cardiac complications than palbociclib and abemaciclib. A cohort of 22 female patients diagnosed with metastatic breast cancer, who were administered CDK4/6 inhibitors or everolimus along with standard hormonal treatment, were studied by a research team to examine the cardiovascular burden and vascular inflammation over a period of 6 months.[108] The present investigation revealed that the administration of CDK 4/6 inhibitors and hormonal therapy induces vascular inflammation, hypertensive response, and left ventricle remodeling. Unlike these studies, one study

Table 1. CDK4/6 inhibitors-induced cardiotoxicity.

Drug	Year	Cardiotoxicity	Reference
CDK4/6 inhibitors	2012–2018	Arrhythmias, new hypertension	Fradley *et al.*[105]
CDK4/6 inhibitors and trastuzumab	2018–2019	AF, MI, cardiac failure, and pericardial effusion	Master[106]
CDK4/6 inhibitors or everolimus along with standard hormonal treatment	2021	vascular inflammation, hypertensive response, and left ventricle remodeling	Papageorgiou *et al.*[108]
Palbociclib and fulvestrant	2021	No cardiotoxicity	Vazdar *et al.*[109]
Reboxinib or abemaciclib	2022	type 2 AV block	Cicini *et al.*[110]
CDK4/6 inhibitors	2016, 2012, 2015, 2018	prolongation of QT interval	VERZENIO (abemaciclib),[104] Infante *et al.*,[113] Flaherty *et al.*,[114] Kondo *et al.*[115]
CDK4/6 inhibitors	2019, 2021	ribociclib-induced prolongation of QT interval	Braal *et al.*,[53] Petrelli *et al.*[121]
Ribociclib, tamoxifen, letrozole	2016–2018	higher incidence of QTcF values	Cristofanilli *et al.*,[46] Hortobagyi *et al.*,[116] Tripathy *et al.*,[117] Lyon *et al.*,[119] Durairaj *et al.*,[120] Iwata *et al.*[122]

AF, Atrial fibrillation; AV, atrioventricular; CDK, cyclin-dependent kinases; MI, myocardial infarction; QTcF, Fridericia's corrected QT interval.

observed no cardiac adverse effects of palbociclib. Accordingly, a recent study conducted a retrospective analysis of data collected from four patients with advanced breast cancer, with a median age of 64 years, who had a history of cardiovascular diseases and significant risk factors for heart disease (including dilated cardiomyopathy NYHA II/III, atrial fibrillation, hypertension, and pacemaker implantation).[109] These patients were treated with a combination of palbociclib and fulvestrant as a first-line treatment for metastatic hormone-sensitive HER2-negative breast cancer. Over the course of the treatment period spanning 3–15 months, there were no observable changes in the electrocardiogram (ECG) record, specifically with regard to the emergence of repolarization disorders and changes in the Fridericia's corrected QT interval (QTcF) interval. Additionally, there was no clinically significant deterioration in cardiac function, and all patients benefited from therapy in terms of disease control, with left ventricular ejection fraction (LVEF) remaining stable. The administration of palbociclib and fulvestrant in combination did not present any safety issues in patients with notable cardiac comorbidities and heightened cardiac risk. Of note are two new cases of type 2 atrioventricular block necessitating permanent cardiac pacing, that have been reported in patients with metastatic breast cancer treated with reboxinib or abemaciclib.[110] Remarkably, a mouse model investigation has revealed that palbociclib has the potential to safeguard cardiac tissue against necrosis, localized fibrosis, and hypertrophy of cardiomyocytes in diabetic cardiomyopathy.[111] However, in the initial stages of development, preclinical investigations into CDK4/6 inhibitors indicated a likelihood of QT prolongation.[112,113] Subsequently, phase I clinical trials conducted on patients with advanced cancer reported potential QT prolongation effects.[113–115] One patient discontinued treatment in the phase II MONARCH1 study of abemaciclib monotherapy for earlier metastatic breast cancer due to QT prolongation.[104] Phase III trials of palbociclib and ribociclib have reported occurrences of QT prolongation events. Among these trials, the phase III trials of ribociclib have implemented the most frequent monitoring schedule for the detection of such events.[46,116–120] In an extensive meta-analysis of six clinical trials involving a total of 3743 patients, palbociclib demonstrated a significantly reduced likelihood of QTc prolongation compared to ribociclib,[121] whereas ribociclib-induced prolongation

during the initial treatment cycle.[53] The administration of tamoxifen is associated with a low likelihood of QT prolongation, even when used concomitantly with QT-prolonging agents. However, the MONALEESA-7 study revealed a higher occurrence of significant QTcF values in patients who received placebo plus tamoxifen and ribociclib plus tamoxifen, in comparison to those who were administered a nonsteroidal aromatase inhibitor. This outcome was unexpected and has been documented in several studies.[46,116–119,122] It is primarily observed with ribociclib that prolongation of the QTc interval may result in torsades de pointes (TdP).[123] However, the incidence of QT prolongation-related discontinuation or dose reduction of ribociclib or palbociclib was low, and no instances of TdP or clinical manifestations of QT prolongation were documented in several studies.[46,116–118] Recently, the first European Society of Cardiology guideline on cardio-oncology has elaborated on recent studies in the field to provide an up-to-date perspective on cardiotoxicity associated with oncologic therapies.[119] The ribociclib phase III trials included routine ECG monitoring.[119] ECGs should be repeated on day 14 of the first cycle, prior to the second cycle, if the dose is increased, and as clinically indicated. A multidisciplinary team (MDT) should discuss the risks and benefits of ribociclib in patients who have or are at high risk of developing QT prolongation. Importantly, the combination of ribociclib with pharmaceuticals known to prolong the QT interval and/or potent CYP3A inhibitors should be avoided.[119] Due to the increased risk of QTc prolongation, ribociclib is not recommended in combination with tamoxifen.[119] In 2017, the FDA authorized the combined use of reboxinib and aromatase inhibitors as the primary endocrine therapy for postmenopausal women who have HR-positive and HER2-negative advanced or metastatic breast cancer.[74] The primary manifestation of reboxinib-induced cardiovascular toxicity is QT interval prolongation. Although no instances of TdP were documented, a single occurrence of sudden cardiac death (0.3%) was observed in a patient with concurrent hypokalemia.[74] In spite of all the clinical outcomes elucidated above, the exact mechanism by which CDK-4/6 inhibitors impact cardiac function remains unknown. Accordingly, a thorough analysis of the present literature proposing potential mechanisms of CDK4/6 QT interval prolongation may offer potential answers.

Potential causes and mechanisms supporting CDK4/6 inhibitors-induced prolongation of the QT interval

There are multiple factors that can induce QT prolongation among cancer patients [107,124]: anticancer drugs, the presence of multiple coexisting risk factors (hypothyroidism congenital long QT syndrome, LV dysfunction, myocardial ischemia), the concomitant treatments (antidepressants, antiemetics, antibiotics, antipsychotics, antifungal syndrome medications, antihistamines, and methadone), various side effects (nausea and vomiting, dehydration, which may subsequently result in electrolyte imbalances such as hypokalemia, hypomagnesemia, and hypocalcemia) and finally kidney failure, liver dysfunction, and poorly controlled diabetes. So, it's important to improve patient care by acquiring knowledge about the different types of anticancer drugs and the other medical issues that patients have that are linked with QTc prolongation. Also important are the careful collection of data using the 'tangent' method to measure the QT interval and the 'Balzettand Fredericia' formulas to correct the heart rate, the identification of risk factors, the correction of electrolyte imbalances, especially with potassium and magnesium, and a thorough evaluation of any cardiac or non-cardiac drug therapy that prolongs the QT interval.[107,124,125] A QTc interval exceeding 500 ms is linked to a 2–3 times higher likelihood of developing TdP. TdP can result in syncope, ventricular fibrillation, or sudden cardiac death in clinical settings.[126] Many KIs impact the hERG subunit, which is responsible for the rapid component of the delayed rectifier potassium current channel, leading to a variable effect on the duration of the QTc interval and a low incidence of TdP. KIs affect QT interval duration; however, the causes are still unknown. These medicines inhibit one or more kinases, which may modify ion channel protein function and potassium, sodium, or calcium current.[126] The mechanisms of QT interval prolongation may involve aberrant gene expression of long QT syndrome-related genes such as *KCNH2*, *SCN5A*, and *SNTA1*. Anyway, reboxinib-induced long QT intervals may be caused by the modulation of one or more associated genes. One study found that treatment with reboxinib resulted in differential expression of three LQT-syndrome-related genes, namely *KCNH2*, *SCN5A*, and *SNTA1*, in human leukemia cell lines. Specifically, *KCNH2* expression decreased,

whereas *SCN5A* and *SNTA1* expression increased.[127] Other proposed mechanism includes changes in potassium and sodium channels and could decipher the QT interval prolongation in patients taking these medications.[128] Accordingly, recent reports noted that drug-induced QT interval prolongation results from the blocking of potassium channels encoded by the human ether-go-go-related gene (hERG),[129] whereas, one recent study revealed that hERG inhibition was induced by reboxinib when compared to the safety of palbociclib.[128] Finally, drug–drug interactions (DDIs) can potentially extend QT intervals, whereas drug co-administration may enhance arrhythmia risk.[130] Ribociclib has the potential to cause pharmacokinetic DDIs by inhibiting the activities of four CYP (cytochrome p 450) isoforms (CYP1A2, CYP3A4, CYP3A5, and CYP2C9)[131]. Consequently, CYP isoform inhibitors can considerably affect drug exposure and increase the risk of QT interval prolongation, which may cause TdP.[132,133] In the aftermath, there remains a question longing for an answer: what could be potential solutions for avoiding and/or diminishing the negative impact of CDK4/6 inhibitors on cardiac function? Since the potential predictive value of certain genotypes in relation to QTc prolongation induced by ribociclib has not been studied thus far,[134] genetic variations linked to drug-induced QTc-prolongation may aid in identifying individuals at higher risk, as demonstrated in cases of antipsychotic and thiazide-induced QTc-prolongation.[135,136] Possible candidate genes include those that encode cytochrome P450 enzymes involved in drug metabolism, drug transporters, genes linked to QT interval duration, and those associated with congenital long QT syndromes.[132] The hepatic metabolism of ribociclib and palbociclib is dependent on the cytochrome P450 enzyme CYP3A. The presence of polymorphisms in the CYP3A gene may have a direct impact on the risk of toxicity and QTc prolongation.[137,138] Researchers hope that their future work will help them learn more about this issue and help them figure out which patients are more likely or less likely to have QTc prolongation caused by ribociclib, as well as the risk of developing severe ventricular arrhythmias. Finally, the randomized trials of ribociclib revealed that some patients experienced QTc interval prolongation, which was reversible and effectively managed through dose interruption and reduction, without any discernible clinical repercussions.[139] Therefore, the administration of ribociclib is advised solely for individuals whose QTc interval is less than 450 ms. It is imperative to avoid administering ribociclib to patients who are at a heightened risk of developing QTc prolongation and uncontrolled cardiac diseases. Furthermore, it is strongly advised to avoid the concurrent administration of ribociclib with drugs that are recognized to prolong the QTc interval.[140]

Management strategies

Managing the cardiotoxic effects of CDK4/6 inhibitors is essential for the well-being of patients receiving these cancer treatments. Individual patient factors, including age, pre-existing cardiac conditions, and the type of cancer being treated, will influence the choice and application of these strategies. Close collaboration among healthcare providers is essential to effectively manage cardiotoxicity while optimizing cancer treatment outcomes.[95,141]

Here are some management strategies:

1. Cardiac monitoring: Regularly monitor the patient's cardiac function through echocardiograms, electrocardiograms (ECGs), and other cardiac tests. Establish a baseline before starting treatment.
2. Patient selection: Carefully select patients with a lower risk of pre-existing cardiac issues for CDK4/6 inhibitor therapy. Evaluate their cardiovascular history and consider alternative treatments if necessary.
3. Dose modification: Adjust the dosage of CDK4/6 inhibitors based on cardiac function and patient tolerance. Lower doses may help mitigate cardiotoxicity while maintaining therapeutic efficacy.
4. Cardiologist consultation: Collaborate with a cardiologist or cardiac oncologist to assess and manage cardiac risks. They can provide specialized expertise in dealing with cardiotoxicity.
5. Lifestyle modifications: Encourage patients to adopt heart-healthy lifestyle changes such as a balanced diet, regular exercise, smoking cessation, and stress reduction.
6. Blood pressure control: Monitor and manage blood pressure, as hypertension is a common side effect of CDK4/6 inhibitors. Antihypertensive medications may be needed.
7. Risk assessment: Use risk assessment tools to identify patients at higher risk

for cardiotoxicity. These tools can guide decision-making regarding treatment options and monitoring frequency.
8. Early detection: Educate patients about the signs and symptoms of heart problems, such as chest pain, shortness of breath, and palpitations, and advise them to seek immediate medical attention if they occur.
9. Regular follow-ups: Schedule regular follow-up appointments to assess cardiac function and overall health. Adjust treatment as needed based on monitoring results.
10. Multidisciplinary team: Form a multidisciplinary team including oncologists, cardiologists, and nurses to collaborate on patient care and decision-making.
11. Alternative therapies: Explore alternative treatment options or combinations with lower cardiotoxicity profiles, depending on the specific cancer type and stage.
12. Clinical trials: Consider enrolling eligible patients in clinical trials investigating new CDK4/6 inhibitors with potentially reduced cardiotoxic effects.
13. Patient education: Provide thorough education to patients about the potential cardiotoxicity of CDK4/6 inhibitors, the importance of adherence to treatment, and the need for close monitoring.

Future directions

Research on CDK4/6 inhibitors and their potential cardiotoxicity is an important area of study, as these drugs have shown promise in cancer treatment but may have cardiotoxic effects.[105,106,108–122] Some future research directions could include:

1. Mechanisms of cardiotoxicity: Investigating the underlying mechanisms of how CDK4/6 inhibitors affect the heart at a cellular and molecular level. Understanding the pathways involved can help in developing targeted interventions.
2. Biomarker discovery: Identifying specific biomarkers that can predict or detect early signs of cardiotoxicity in patients undergoing CDK4/6 inhibitor treatment. This could enable more proactive monitoring and management.
3. Risk stratification: Developing risk stratification models to determine which patients are more susceptible to cardiotoxicity from CDK4/6 inhibitors. This could help in personalized treatment decisions.
4. Cardioprotective strategies: Exploring strategies to mitigate or prevent cardiotoxicity while still maintaining the efficacy of CDK4/6 inhibitors in cancer treatment. This might involve co-administration of other drugs or lifestyle interventions.
5. Long-term effects: Studying the long-term cardiovascular effects of CDK4/6 inhibitor treatment, as some side effects may manifest years after treatment has ended.
6. Clinical trials: Conducting well-designed clinical trials with larger patient populations to gather more data on the incidence and severity of cardiotoxicity associated with these drugs.
7. Animal models: Developing and using animal models to simulate and study cardiotoxicity, allowing for controlled experiments and investigations into potential interventions.
8. Patient outcomes: Analyzing real-world patient outcomes and experiences with CDK4/6 inhibitors, including their cardiovascular health and quality of life.
9. Combination therapies: Investigating the safety and efficacy of combining CDK4/6 inhibitors with other cancer treatments, as certain combinations might have different cardiotoxic profiles.
10. Regulatory guidance: Collaborating with regulatory agencies to establish guidelines and recommendations for monitoring and managing cardiotoxicity associated with CDK4/6 inhibitors.

Interdisciplinary collaboration between oncologists, cardiologists, pharmacologists, and researchers in various related fields will be crucial for advancing our understanding of CDK4/6 inhibitor cardiotoxicity and improving patient outcomes.

Conclusion

The utilization of CDK4/6 inhibitors has significantly impacted breast cancer therapy over recent decades. The advancement of novel CDK4/6 inhibitors has facilitated the closure of several gaps, particularly with respect to the issue of therapy resistance. However, previous and recent reports on the occurrence of AEs, particularly those related to cardiac toxicity, have prompted

apprehension regarding their widespread utilization. Thus, it is imperative to thoroughly evaluate all facets of the patient's medical status and possible advantages and drawbacks before administering any form of therapy. Several cardio-oncologists have emphasized the significant advantages of CDK4/6 inhibitors therapy in breast cancer patients. However, others have also observed fatal or potentially fatal cardiac events in some cases. Hence, it is imperative to conduct further and comprehensive preclinical and clinical investigations, along with the implementation of the latest clinical protocols for administering CDK4/6 inhibitors in the management of breast cancer patients, to ensure efficacious treatment outcomes.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Dragica Pavlovic: Conceptualization; Visualization; Writing – original draft; Writing – review & editing.

Danijela Niciforovic: Conceptualization; Visualization; Writing – original draft; Writing – review & editing.

Dragana Papic: Conceptualization; Visualization; Writing – original draft; Writing – review & editing.

Katarina Milojevic: Visualization; Writing – original draft.

Marina Markovic: Conceptualization; Supervision; Writing – review & editing.

Acknowledgements
None.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Agreement No. 451-03-47/2023-01/200111).

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

ORCID iDs
Dragica Pavlovic https://orcid.org/0000-0002-7474-7495

Danijela Niciforovic https://orcid.org/0009-0001-6123-456X

Katarina Milojevic https://orcid.org/0009-0000-3056-1608

References
1. Riggio AI, Varley KE and Welm AL. The lingering mysteries of metastatic recurrence in breast cancer. *Br J Cancer* 2021; 124: 13–26.
2. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
3. Broberg AM, Geisler J, Tuohinen S, *et al.* Prevention, detection, and management of heart failure in patients treated for breast cancer. *Curr Heart Fail Rep* 2020; 17: 397–408.
4. Shimoi T, Sagara Y, Hara F, *et al.* First-line endocrine therapy for postmenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer: a systematic review and meta-analysis. *Breast Cancer* 2020; 27: 340–346.
5. Lanza O, Ferrera A, Reale S, *et al.* New insights on the toxicity on heart and vessels of breast cancer therapies. *Med Sci* 2022; 10: 27.
6. Xie Y, Collins WJ, Audeh MW, *et al.* Breast Cancer Survivorship and cardiovascular disease: emerging approaches in cardio-oncology. *Curr Treat Options Cardiovasc Med* 2015; 17: 60.
7. Green BN, Johnson CD and Adams A. Writing narrative literature reviews for peer-reviewed journals: secrets of the trade. *J Chiropr Med* 2006; 5: 101–117.
8. Baethge C, Goldbeck-Wood S and Mertens S. SANRA-a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev* 2019; 4: 5.
9. Coffman JA. Cell cycle development. *Dev Cell* 2004; 6: 321–327.

10. Kar S. Unraveling cell-cycle dynamics in cancer. *Cell Syst* 2016; 2: 8–10.

11. Harper JV and Brooks G. The mammalian cell cycle: an overview. *Methods Mol Biol* 2005; 296: 113–153.

12. Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144: 646–674.

13. Alberts B, Johnson A, Lewis J, *et al*. *Molecular biology of the cell*. 4th ed. New York: Garland Science, 2002.

14. Cersosimo RJ. Cyclin-dependent kinase 4/6 inhibitors for the management of advanced or metastatic breast cancer in women. *Am J Health Syst Pharm* 2019; 76: 1183–1202.

15. Malumbres M and Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm. *Nat Rev Cancer* 2009; 9: 153–166.

16. Satyanarayana A and Kaldis P. Mammalian cell-cycle regulation: several CDKs, numerous cyclins and diverse compensatory mechanisms. *Oncogene* 2009; 28: 2925–2939.

17. Gopinathan L, Ratnacaram CK and Kaldis P. Established and novel CDK/cyclin complexes regulating the cell cycle and development. *Results Probl Cell Differ* 2011; 53: 365–389.

18. Matthews HK, Bertoli C and de Bruin RAM. Cell cycle control in cancer. *Nat Rev Mol Cell Biol* 2022; 23: 74–88.

19. Zhang M, Zhang L, Hei R, *et al*. CDK inhibitors in cancer therapy, an overview of recent development. *Am J Cancer res* 2021; 11: 1913–1935.

20. Dickson MA. Molecular pathways: CDK4 inhibitors for cancer therapy. *Clin Cancer Res* 2014; 20: 3379–3383.

21. Fry DW, Harvey PJ, Keller PR, *et al*. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther* 2004; 3: 1427–1438.

22. Choi YJ and Anders L. Signaling through cyclin D-dependent kinases. *Oncogene* 2014; 33: 1890–1903.

23. Ferrer JL, Dupuy J, Borel F, *et al*. Structural basis for the modulation of CDK-dependent/independent activity of cyclin D1. *Cell Cycle* 2006; 5: 2760–2768.

24. Węsierska-Gądek J and Kramer MP. The impact of multi-targeted cyclin-dependent kinase inhibition in breast cancer cells: clinical implications. *Expert Opin Investig Drugs* 2011; 20: 1611–1628.

25. Fry DW, Bedford DC, Harvey PH, *et al*. Cell cycle and biochemical effects of PD 0183812. A potent inhibitor of the cyclin D-dependent kinases CDK4 and CDK6. *J Biol Chem* 2001; 276: 16617–16623.

26. Li C, Qi L, Bellail AC, *et al*. PD-0332991 induces G1 arrest of colorectal carcinoma cells through inhibition of the cyclin-dependent kinase-6 and retinoblastoma protein axis. *Oncol Lett* 2014; 7: 1673–1678.

27. Finn RS, Dering J, Conklin D, *et al*. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res* 2009; 11: R77.

28. Kalra S, Joshi G, Munshi A, *et al*. Structural insights of cyclin dependent kinases: implications in design of selective inhibitors. *Eur J Med Chem* 2017; 142: 424–458.

29. Di Sante G, Pagé J, Jiao X, *et al*. Recent advances with cyclin-dependent kinase inhibitors: therapeutic agents for breast cancer and their role in immuno-oncology. *Expert Rev Anticancer Ther* 2019; 19: 569–587.

30. Casimiro MC, Di Sante G, Crosariol M, *et al*. Kinase-independent role of cyclin D1 in chromosomal instability and mammary tumorigenesis. *Oncotarget* 2015; 6: 8525–8538.

31. Piezzo M, Cocco S, Caputo R, *et al*. Targeting cell cycle in breast cancer: CDK4/6 inhibitors. *Int J Mol Sci* 2020; 21: 6479.

32. Johnson J, Thijssen B, McDermott U, *et al*. Targeting the RB-E2F pathway in breast cancer. *Oncogene* 2016; 35: 4829–4835.

33. Schoninger SF and Blain SW. The ongoing search for biomarkers of CDK4/6 inhibitor responsiveness in breast cancer. *Mol Cancer Ther* 2020; 19: 3–12.

34. Huang W and Wang H. Potential biomarkers of resistance to CDK4/6 inhibitors: a narrative review of preclinical and clinical studies. *Transl Breast Cancer Res* 2021; 2: 1–12.

35. Papadimitriou MC, Pazaiti A, Iliakopoulos K, *et al*. Resistance to CDK4/6 inhibition: mechanisms and strategies to overcome a therapeutic problem in the treatment of hormone receptor-positive metastatic breast cancer. *Biochim Biophys Acta Mol Cell Res* 2022; 1869: 119346.

36. Xu XQ, Pan XH, Wang TT, *et al.* Intrinsic and acquired resistance to CDK4/6 inhibitors and potential overcoming strategies. *Acta Pharmacol Sin* 2021; 42: 171–178.
37. Salvo EM, Ramirez AO, Cueto J, *et al.* Risk of recurrence among patients with HR-positive, HER2-negative, early breast cancer receiving adjuvant endocrine therapy: a systematic review and meta-analysis. *Breast* 2021; 57: 5–17.
38. Figel S and Fenstermaker RA. Cell-cycle regulation. In: Newton HB (ed.) *Handbook of brain tumor chemotherapy, molecular therapeutics, and immunotherapy*. London: Elsevier Academic Press, 2018, pp.257–269.
39. Mayer EL. Targeting breast cancer with CDK inhibitors. *Curr Oncol Rep* 2015; 17: 443.
40. Vidula N and Rugo HS. Cyclin-dependent kinase 4/6 inhibitors for the treatment of breast cancer: a review of preclinical and clinical data. *Clin Breast Cancer* 2016; 16: 8–17.
41. Senderowicz AM and Sausville EA. Preclinical and clinical development of cyclin-dependent kinase modulators. *J Natl Cancer Inst* 2000; 92: 376–387.
42. Hortobagyi GN, Stemmer SM, Burris HA, *et al.* Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol* 2018; 29: 1541–1547.
43. DeMichele A, Clark AS, Tan KS, *et al.* CDK 4/6 inhibitor palbociclib (PD0332991) in Rb+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. *Clin Cancer Res* 2015; 21: 995–1001.
44. Robert M, Frenel JS, Bourbouloux E, *et al.* An update on the clinical use of CDK4/6 inhibitors in breast cancer. *Drugs* 2018; 78: 1353–1362.
45. Goetz MP, Hamilton EP, Campone M, *et al.* Acquired genomic alterations in circulating tumor DNA from patients receiving abemaciclib alone or in combination with endocrine therapy. *J Clin Oncol* 2020; 38: 3519–3519.
46. Cristofanilli M, Turner NC, Bondarenko I, *et al.* Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol* 2016; 17: 425–439.
47. Dickler MN, Tolaney SM, Rugo HS, *et al.* MONARCH 1, A phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory hr+/her2- metastatic breast cancer. *Clin Cancer Res* 2017; 23: 5218–5224.
48. Sledge GW Jr, Toi M, Neven P, *et al.* MONARCH 2: abemaciclib in combination with fulvestrant in women with hr+/her2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol* 2017; 35: 2875–2884.
49. Johnston S, Martin M, Di Leo A, *et al.* MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer* 2019; 5: 5.
50. Gelbert LM, Cai S, Lin X, *et al.* Preclinical characterization of the CDK4/6 inhibitor LY2835219: in-vivo cell cycle-dependent/independent anti-tumor activities alone/in combination with gemcitabine. *Investig New Drugs* 2014; 32: 825–837.
51. Mughal MJ, Bhadresha K and Kwok HF. CDK inhibitors from past to present: a new wave of cancer therapy. *Semin Cancer Biol* 2023; 88: 106–122.
52. Raschi E, Fusaroli M, Ardizzoni A, *et al.* Cyclin-dependent kinase 4/6 inhibitors and interstitial lung disease in the FDA adverse event reporting system: a pharmacovigilance assessment. *Breast Cancer Res Treat* 2021; 186: 219–227.
53. Braal CL, Jongbloed EM, Wilting SM, *et al.* Inhibiting CDK4/6 in breast cancer with palbociclib, ribociclib, and abemaciclib: similarities and differences. *Drugs* 2021; 81: 317–331.
54. Turner NC, Slamon DJ, Ro J, *et al.* Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med* 2018; 379: 1926–1936.
55. Bas O, Erul E, Guven DC, *et al.* Infectious complications of cyclin-dependent kinases 4 and 6 inhibitors in patients with hormone-receptor-positive metastatic breast cancer: a systematic review and meta-analysis. *Support Care Cancer* 2022; 30: 9071–9078.
56. Stravodimou A and Voutsadakis IA. The future of ER+/her2- metastatic breast cancer therapy: beyond PI3K inhibitors. *Anticancer Res* 2020; 40: 4829–4841.
57. Pernas S, Tolaney SM, Winer EP, *et al.* CDK4/6 inhibition in breast cancer: current practice and future directions. *Ther Adv Med Oncol* 2018; 10: 1758835918786451.
58. Hu W, Sung T, Jessen BA, *et al.* Mechanistic investigation of bone marrow suppression associated with palbociclib and its differentiation

from Cytotoxic chemotherapies. *Clin Cancer Res* 2016; 22: 2000–2008.

59. Goetz MP, Toi M, Campone M, *et al.* MONARCH 3: abemaciclib as initial therapy for Advanced Breast Cancer. *J Clin Oncol* 2017; 35: 3638–3646.

60. Im SA, Lu YS, Bardia A, *et al.* Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med* 2019; 381: 307–316.

61. Ewer MS and Ewer SM. Cardiotoxicity of anticancer treatments. *Nat Rev Cardiol* 2015; 12: 547–558.

62. Schmitz KH, Prosnitz RG, Schwartz AL, *et al.* Prospective surveillance and management of cardiac toxicity and health in breast cancer survivors. *Cancer* 2012; 118: 2270–2276.

63. Zamorano JL, Lancellotti P and Rodriguez Muñoz D. The task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37: 2768–2801.

64. Guglin M, Aljayeh M, Saiyad S, *et al.* Introducing a new entity: chemotherapy-induced arrhythmia. *Europace* 2009; 11: 1579–1586.

65. Suter TM and Ewer MS. Cancer drugs and the heart: importance and management. *Eur Heart J* 2013; 34: 1102–1111.

66. Hahn VS, Lenihan DJ and Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. *J Am Heart Assoc* 2014; 3: e000665.

67. Gonciar D, Mocan L, Zlibut A, *et al.* Cardiotoxicity in HER2-positive breast cancer patients. *Heart Fail Rev* 2021; 26: 919–935.

68. Bhagat A and Kleinerman ES. Anthracycline-induced cardiotoxicity: causes, mechanisms, and prevention. *Adv Exp Med Biol* 2020; 1257: 181–192.

69. Shaikh AY and Shih JA. Chemotherapy-induced cardiotoxicity. *Curr Heart Fail Rep* 2012; 9: 117–127.

70. Perez IE, Taveras Alam S, Hernandez GA, *et al.* Cancer therapy-related cardiac dysfunction: an overview for the clinician. *Clin Med Insights Cardiol* 2019; 13: 1179546819866445.

71. Mincu RI, Mahabadi AA, Michel L, *et al.* Cardiovascular adverse events associated with BRAF and MEK inhibitors: a systematic review and meta-analysis. *JAMA Netw Open* 2019; 2: e198890.

72. Arangalage D, Degrauwe N, Michielin O, *et al.* Pathophysiology, diagnosis and management of cardiac toxicity induced by immune checkpoint inhibitors and BRAF and MEK inhibitors. *Cancer Treat Rev* 2021; 100: 102282.

73. Banks M, Crowell K, Proctor A, *et al.* Cardiovascular effects of the MEK inhibitor, Trametinib: a case report, literature review, and consideration of mechanism. *Cardiovasc Toxicol* 2017; 17: 487–493.

74. Shah A, Bloomquist E, Tang S, *et al.* FDA approval: ribociclib for the treatment of postmenopausal women with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer. *Clin Cancer Res* 2018; 24: 2999–3004.

75. Zhu X, Stergiopoulos K and Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. *Acta Oncol* 2009; 48: 9–17.

76. Rini BI, Quinn DI, Baum M, *et al.* Hypertension among patients with renal cell carcinoma receiving axitinib or sorafenib: analysis from the randomized phase III AXIS trial. *Target Oncol* 2015; 10: 45–53.

77. Chu TF, Rupnick MA, Kerkela R, *et al.* Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007; 370: 2011–2019.

78. Schmidinger M, Zielinski CC, Vogl UM, *et al.* Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2008; 26: 5204–5212.

79. Kim KW, Shinagare AB, Krajewski KM, *et al.* Fluid retention associated with imatinib treatment in patients with gastrointestinal stromal tumor: quantitative radiologic assessment and implications for management. *Korean J Radiol* 2015; 16: 304–313.

80. de Jesus-Gonzalez N, Robinson E, Moslehi J, *et al.* Management of antiangiogenic therapy-induced hypertension. *Hypertension* 2012; 60: 607–615.

81. Allouchery M, Tomowiak C, Lombard T, *et al.* Safety profile of ibrutinib: an analysis of the WHO pharmacovigilance database. *Front Pharmacol* 2021; 12: 769315.

82. Singh AP, Glennon MS, Umbarkar P, *et al.* Ponatinib-induced cardiotoxicity: delineating the signalling mechanisms and potential rescue strategies. *Cardiovasc Res* 2019; 115: 966–977.

83. Lamore SD, Kohnken RA, Peters MF, *et al.* Cardiovascular toxicity induced by kinase inhibitors: mechanisms and preclinical approaches. *Chem Res Toxicol* 2020; 33: 125–136.

84. Giudice V, Vecchione C and Selleri C. Cardiotoxicity of novel targeted hematological therapies. *Life* 2020; 10: 344.

85. Cheng M, Yang F, Liu J, *et al*. Tyrosine kinase inhibitors-induced arrhythmias: from molecular mechanisms, pharmacokinetics to therapeutic strategies. *Front Cardiovasc Med* 2021; 8: 758010.

86. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Breast Cancer, version 3.2018, https://www.nccn.Org/professionals/physician_gls/pdf/breast.pdf (2018, accessed 16 January 2019).

87. Cardoso F, Senkus E and Costa A. 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4). *Ann Oncol* 2018; 29: 1634–1657.

88. Cardinale D, Colombo A, Bacchiani G, *et al*. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation* 2015; 131: 1981–1988.

89. Cardinale D, Colombo A, Lamantia G, *et al*. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol* 2010; 55: 213–220.

90. ADRIAMYCIN (doxorubicin). Prescribing information. Bedford, OH: Bedford Laboratories™, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/062921s022lbl.pdf (2012, accessed 9 October 2018).

91. ELLENCE (epirubicin). Highlights of prescribing information. New York, NY: Pfizer, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050778s021lbl.pdf (2014, accessed 9 October 2018).

92. Hasinoff BB. The cardiotoxicity and myocyte damage caused by small molecule anticancer tyrosine kinase inhibitors is correlated with lack of target specificity. *Toxicol Appl Pharmacol* 2010; 244: 190–195.

93. Shah RR, Morganroth J and Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). *Drug Saf* 2013; 36: 295–316.

94. Lee HA, Kim EJ, Hyun SA, *et al*. Electrophysiological effects of the anti-cancer drug lapatinib on cardiac repolarization. *Basic Clin Pharmacol Toxicol* 2010; 107: 614–618.

95. Liu Y, Zheng L, Cai X, *et al*. Cardiotoxicity from neoadjuvant targeted treatment for breast cancer prior to surgery. *Front Cardiovasc Med* 2023; 10: 1078135.

96. Barish R, Gates E and Barac A. Trastuzumab-induced cardiomyopathy. *Cardiol Clin* 2019; 37: 407–418.

97. Jerusalem G, Lancellotti P and Kim SB. HER2+ breast cancer treatment and cardiotoxicity: monitoring and management. *Breast Cancer Res Treat* 2019; 177: 237–250.

98. Blackwell KL, Burstein HJ, Storniolo AM, *et al*. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol* 2010; 28: 1124–1130.

99. Lenz G, Hawkes E, Verhoef G, *et al*. Single-agent activity of phosphatidylinositol 3-kinase inhibition with copanlisib in patients with molecularly defined relapsed or refractory diffuse large B-cell lymphoma. *Leukemia* 2020; 34: 2184–2197.

100. Gennari A, André F, Barrios CH, *et al*.; ESMO Guidelines Committee. ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 2021; 32: 1475–1495.

101. Martin M, Zielinski C, Ruiz-Borrego M, *et al*. Palbociclib in combination with endocrine therapy versus capecitabine in hormonal receptor-positive, human epidermal growth factor 2-negative, aromatase inhibitor-resistant metastatic breast cancer: a phase III randomised controlled trial—PEARL. *Ann Oncol* 2021; 32: 488–499.

102. KISQALI (ribociclib). Highlights of prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation, https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kisqali.pdf (2018, accessed 9 October 2018).

103. IBRANCE (palbociclib). Highlights of prescribing information. New York, NY: Pfizer, September 2018, http://labeling.pfizer.com/ShowLabeling.aspx?id=2191 (2018, accessed 9 October 2018).

104. VERZENIO (abemaciclib). Highlights of prescribing information. Indianapolis, IN: Eli Lilly and Company, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208855s000lbl.pdf (2018, accessed October 9, 2018).

105. Fradley GM, Nguyen N and Chen Y. Cardiovascular toxicities of cyclin dependent kinase (cdk) 4/6 inhibitors in metastatic breast cancer patients. *Circulation* 2020; 142: A16720.

106. Master SR. Cardiac complications of CDK4/6 inhibitors for breast cancer. *J Clin Oncol* 2020; 38: e13038–e13038.

107. Li EC, Esterly JS, Pohl S, *et al.* Drug-induced QT-interval prolongation: considerations for clinicians. *Pharmacotherapy* 2010; 30: 684–701.

108. Papageorgiou C, Zagouri F, Tampakis K, *et al.* Vascular inflammation and cardiovascular burden in metastatic breast cancer female patients receiving hormonal treatment and CDK 4/6 inhibitors or everolimus. *Front Cardiovasc Med* 2021; 8: 638895.

109. Vazdar LJ, Pavlović M, Tečić V, *et al.* Cardiac safety of palbociclib in breast cancer patients with cardiac risk. In: *Libri Oncologici: 3th Regional Congress of Medical Oncology*, Zagreb, 7–9 May 2021, pp. 45–45.

110. Cicini MP, Ferretti G, Morace N, *et al.* Second-degree type 2 atrioventricular block requiring permanent cardiac pacing in patients on CDK4/6 inhibitors: report of two cases. *Breast Care* 2022; 17: 330–335.

111. Wang Z, Li J, Wang Y, *et al.* Palbociclib improves cardiac dysfunction in diabetic cardiomyopathy by regulating Rb phosphorylation. *Am J Transl Res* 2019; 11: 3481–3489.

112. Turner NC, Ro J, André F, *et al.* Palbociclib in hormone-receptor–positive advanced breast cancer. *N Engl J Med* 2015; 373: 209–219.

113. Infante JR, Cassier PA, Gerecitano JF, *et al.* A phase I study of the cyclin-dependent kinase 4/6 inhibitor ribociclib (LEE011) in patients with advanced solid tumors and lymphomas. *Clin Cancer Res* 2016; 22: 5696–5705.

114. Flaherty KT, Lorusso PM, Demichele A, *et al.* Phase I, dose-escalation trial of the oral cyclin-dependent kinase 4/6 inhibitor PD 0332991, administered using a 21-day schedule in patients with advanced cancer. *Clin Cancer Res* 2012; 18: 568–576.

115. Kondo S, Yamamoto N and Tamura K. *314: Phase I study of abemaciclib, a CDK 4 and 6 inhibitor, as a single agent for Japanese patients with advanced cancer*. In: Vienna, Austria, Poster presented at: European Cancer Congress; 25–29 September 2015.

116. Hortobagyi GN, Stemmer SM, Burris HA, *et al.* Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med* 2022; 386: 942–950.

117. Tripathy D, Im SA, Colleoni M, *et al.* Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol* 2018; 19: 904–915.

118. Finn RS, Martin M, Rugo HS, *et al.* Palbociclib and letrozole in advanced breast cancer. *New Engl J Med* 2016; 375: 1925–1936.

119. Lyon AR, Lopez-Fernandez T, Couch LS, *et al.* ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). *Eur Heart J* 2022; 43: 4229–4361.

120. Durairaj C, Ruiz-Garcia A, Gauthier ER, *et al.* Palbociclib has no clinically relevant effect on the QTc interval in patients with advanced breast cancer. *Anticancer Drugs* 2018; 29: 271–280.

121. Petrelli F, Ghidini A, Pedersini R, *et al.* Comparative efficacy of palbociclib, ribociclib and abemaciclib for ER+ metastatic breast cancer: an adjusted indirect analysis of randomized controlled trials. *Breast Cancer Res Treat* 2019; 174: 597–604.

122. Iwata H, Im SA, Masuda N, *et al.* PALOMA-3: Phase III trial of fulvestrant with or without palbociclib in premenopausal and postmenopausal women with hormone Receptor-Positive, human epidermal growth factor receptor 2-negative metastatic breast cancer that progressed on prior endocrine therapy-safety and efficacy in Asian patients. *J Glob Oncol* 2017; 3: 289–303.

123. Chandrasekhar S and Fradley MG. QT interval prolongation associated with Cytotoxic and targeted cancer therapeutics. *Curr Treat Options Oncol* 2019; 20: 55.

124. Yeh ET. Onco-cardiology: the time has come. *Tex Heart Inst J* 2011; 38: 246–247.

125. Maurea N, Spallarossa P, Cadeddu C, *et al.* A recommended practical approach to the management of target therapy and angiogenesis inhibitors cardiotoxicity: an opinion paper of the working group on drug cardiotoxicity and cardioprotection, Italian Society of Cardiology. *J Cardiovasc Med* 2016; 17: e93–e104.

126. Alexandre J, Moslehi JJ, Bersell KR, *et al.* Anticancer drug-induced cardiac rhythm disorders: current knowledge and basic underlying mechanisms. *Pharmacol Ther* 2018; 189: 89–103.

127. Tao YF, Wang NN, Xu LX, *et al.* Molecular mechanism of G_1 arrest and cellular senescence induced by LEE011, a novel CDK4/CDK6 inhibitor, in leukemia cells. *Cancer Cell Int* 2017; 17: 35.

128. Santoni M, Occhipinti G, Romagnoli E, *et al.* Different cardiotoxicity of palbociclib and ribociclib in breast cancer: gene expression and pharmacological data analyses, biological basis, and therapeutic implications. *BioDrugs* 2019; 33: 613–620.

129. Gintant GA, Su Z, Martin RL, *et al*. Utility of hERG assays as surrogate markers of delayed cardiac repolarization and QT safety. *Toxicol Pathol* 2006; 34: 81–90.

130. Wiśniowska B, Tylutki Z, Wyszogrodzka G, *et al*. Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect – comprehensive overview of clinical trials. *BMC Pharmacol Toxicol* 2016; 17: 12.

131. Sorf A, Hofman J, Kučera R, *et al*. Ribociclib shows potential for pharmacokinetic drug-drug interactions being a substrate of ABCB1 and potent inhibitor of ABCB1, ABCG2 and CYP450 isoforms in vitro. *Biochem Pharmacol* 2018; 154: 10–17.

132. Niemeijer MN, van den Berg ME, Eijgelsheim M, *et al*. Pharmacogenetics of drug-induced QT interval prolongation: an update. *Drug Saf* 2015; 38: 855–867.

133. Aerssens J and Paulussen AD. Pharmacogenomics and acquired long QT syndrome. *Pharmacogenomics* 2005; 6: 259–270.

134. Altena R, Bajalica-Lagercrantz S and Papakonstantinou A. Pharmacogenomics for prediction of cardiovascular toxicity: landscape of emerging data in breast cancer therapies. *Cancers* 2022; 14: 4665.

135. Aberg K, Adkins DE, Liu Y, *et al*. Genome-wide association study of antipsychotic-induced QTc interval prolongation. *Pharmacogenomics* 2012; 12: 165–172.

136. Seyerle AA, Sitlani CM, Noordam R, *et al*. Pharmacogenomics study of thiazide diuretics and QT interval in multi-ethnic populations: the cohorts for heart and aging research in genomic epidemiology. *Pharmacogenomics* 2018; 18: 215–226.

137. Cazzaniga ME, Danesi R, Girmenia C, *et al.*; NetworkER+. Management of toxicities associated with targeted therapies for HR-positive metastatic breast cancer: a multidisciplinary approach is the key to success. *Breast Cancer Res Treat* 2019; 176: 483–494.

138. De Mattia E, Cecchin E, Guardascione M, *et al*. Pharmacogenetics of the systemic treatment in advanced hepatocellular carcinoma. *World J Gastroenterol* 2019; 25: 3870–3896.

139. Abdel-Razeq H and Sharaf B. Expanding the clinical use of CDK4/6 inhibitors in the treatment of hormone receptor-positive, HER2-Negative breast cancer from metastatic setting to adjuvant setting. *Drug Des Devel Ther* 2022; 16: 727–735.

140. Coppola C, Rienzo A, Piscopo G, *et al*. Management of QT prolongation induced by anti-cancer drugs: target therapy and old agents. Different algorithms for different drugs. *Cancer Treat Rev* 2018; 63: 135–143.

141. Grela-Wojewoda A, Pacholczak-Madej R, Adamczyk A, *et al*. Cardiotoxicity induced by protein kinase inhibitors in patients with cancer. *Int J Mol Sci* 2022; 23: 2815.