Review

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Advancements in breast cancer management: a comprehensive review of ribociclib combined with endocrine therapy

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Background: In this review, the complicated landscape of breast cancer management is explored with a focus on the promising synergies between ribociclib and endocrine therapy. Ribociclib mainly acts as a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, which disrupts cell cycle progression necessary for tumor growth. This, in combination with endocrine therapy, aims to produce hormone receptor-positive breast cancers, which is a very relevant subtype with challenging therapeutics.

Methods: A comprehensive review was conducted using multiple databases, PubMed, Embase, Scopus, Cochrane Library, and Web of Science, covering the period from January 1990 to May 2024.

Results: Pharmacokinetic studies underscore the efficacy and tolerability of ribociclib, thus providing vital information for dose adjustments, particularly among patients with renal and hepatic impairments. Ribociclib's value in extending progression-free survival and improving overall survival has been shown by clinical trials such as the MONALEESA series. Quality of life considerations and patient-reported outcomes from these trials indicate that ribociclib has a broader effect on the well-being of the patients. However, despite the success experienced by this drug in clinical practice, it still has some side effects, including hematologic toxicity, hepatotoxicity, and thromboembolism associated with it. Ribociclib resistance mechanisms are multifaceted mixtures comprising genetic variations or mutations, compensatory signaling pathways, and epigenomic changes. While overcoming resistance remains challenging, ongoing research seeks to reconcile.

Conclusion: Ribociclib combined with endocrine therapy represents a significant advancement in breast cancer treatment, albeit with challenges that necessitate ongoing research and holistic patient care approaches.

Keywords: breast cancer, CDK4/6 inhibitor, endocrine therapy, HER2-negative, personalized medicine, ribociclib

Introduction

Breast cancer remains a health concern globally, affecting millions of individuals worldwide. According to the WHO, breast cancer is the most diagnosed cancer among women, with an estimated 2.3 million new cases reported in 2020. Despite ongoing research and advancements in treatment strategies, breast cancer-related mortality accounted for ~685 000 deaths globally in 2020. The incidence and prevalence of breast cancer vary across different regions and populations, influenced by factors such as age, genetics, lifestyle, and environmental exposures. In developed countries, the incidence rates are generally

HIGHLIGHTS

- Ribociclib is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor that disrupts cell cycle progression necessary for tumor growth. When combined with endocrine therapy, it targets hormone receptor-positive breast cancers, enhancing treatment efficacy.
- Clinical trials, such as the MONALEESA series, have shown that ribociclib significantly extends progression-free survival and improves overall survival in breast cancer patients. Pharmacokinetic studies highlight its efficacy and tolerability, particularly in patients with renal and hepatic impairments.
- Patient-reported outcomes from clinical trials indicate that ribociclib not only improves clinical outcomes but also positively impacts patients' quality of life. The drug's broader effect on well-being is essential in its therapeutic use.
- Despite its success, ribociclib is associated with side effects such as hematologic toxicity, hepatotoxicity, and thromboembolism. Resistance mechanisms involve genetic variations, compensatory signaling pathways, and epigenomic changes.

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higher, while mortality rates have declined due to improved early detection and effective treatment strategies. However, in developing nations, the burden of breast cancer remains substantial, with limited access to screening and treatment resources contributing to higher mortality rates[1,2].

Traditionally, the management of breast cancer has relied heavily on surgical interventions, chemotherapy, and radiation therapy. However, targeted therapies and personalized medicine approaches have gained significant traction recently, offering patients more effective and tailored treatment options. One such advancement is the introduction of ribociclib, a selective cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, which has shown promising results when combined with endocrine therapy for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer[2–4]. This review aims to provide an in-depth analysis of the latest developments in breast cancer management, focusing on the role of ribociclib in combination with endocrine therapy.

Methodology

Literature search strategy

A comprehensive narrative review was conducted to gather and analyze relevant studies on the advancements in breast cancer management, specifically focusing on combining ribociclib with endocrine therapy. The literature search was performed across multiple databases, including PubMed, Embase, Scopus, Cochrane Library, and Web of Science, covering the period from January 1990 to May 2024. The search strategy employed a combination of keywords and Medical Subject Headings (MeSH) terms, including 'ribociclib', 'endocrine therapy', 'breast cancer', 'hormone receptor-positive', 'HER2-negative', 'clinical trials', 'efficacy', and 'safety'. Search filters were applied to limit results to articles published in English. Additionally, reference lists of relevant review articles and primary studies were hand-searched to identify additional sources.

Study selection criteria

Studies were included if they met the following criteria:

1. Focused on hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer.
2. Evaluated the combination of ribociclib with any form of endocrine therapy.
3. Published in peer-reviewed journals.
4. Provided data on clinical outcomes, including efficacy, safety, and quality of life.

Studies were excluded if they:

1. Articles not published in English.
2. Focused on preclinical or animal studies.
3. Lacked detailed methodology or results.

Data extraction and synthesis

The extracted data were synthesized narratively, focusing on key themes and patterns related to the efficacy, safety, and quality of life impacts of ribociclib combined with endocrine therapy. Quantitative data were presented in tables to facilitate comparison and interpretation.

Quality assessment

Due to this review's narrative nature, the quality of the included studies must be systematically assessed. However, studies were categorized based on their design (randomized controlled trials, observational studies, etc.) and the robustness of their methodologies to provide context for the reported findings.

Data presentation

The findings from the included studies were presented in a narrative format, emphasizing advancements in managing HR+ HER2- breast cancer with ribociclib and endocrine therapy. Key outcomes were highlighted and discussed, including progression-free survival, overall survival, safety profiles, and quality-of-life impacts. Tables were used to summarize quantitative data and facilitate comparison across studies.

Ethical considerations

This narrative review involved analyzing previously published data, so no ethical approval was required. The principles of ethical research conduct were adhered to throughout the study, including proper citation and acknowledgment of the original authors' work.

Results

Mechanism of action and pharmacology

The cell cycle is moderated by several regulatory proteins, with the tumor suppressor retinoblastoma protein (RB1) being an inhibitor of the G1 - S phase transition[5]. Phosphorylation of RB1 by cyclin-dependent kinases 4 and 6 works to deactivate RB1 and promote cell entry into the S phase[6–8]. The quiescent phase of the cell cycle encourages the expression of D-type cyclins that activate CDK4/6, which phosphorylate RB1 and release transcription factor E2F, allowing the transcription of genes essential for DNA synthesis and S phase initiation. Estrogen receptor (ER) positive breast cancer leads to an upregulation of cyclin D and CDK4/6, allowing uncontrolled proliferation[9,10]. Although breast cancer has several clinical subtypes, overexpression of cyclin D1 may be seen in up to half of all breast cancers, making it a valuable target for therapy[11].

Ribociclib is a weak base formulated as a succinate salt and classified as a low-solubility compound[12]. It is both a transport substrate and an inhibitor of P glycoprotein (Pgp). It has also been an inhibitor of OCT2, BCRP, multidrug and toxin extrusion protein one, and the bile salt export pump[13]. Pharmacokinetic studies have found it to have a 70% human protein binding with an estimated 1090 l volume of distribution[12]. CDK4/6 inhibitor is metabolized majorly by CYP3A4 and minorly by flavin-containing monooxygenase 1 and 3. Routes of excretion include feces and urine, accounting for 69.1% and 22.6%, respectively[12].

Dose adjustments are not required for mild and moderate renal-impaired patients. However, patients with end-stage renal disease having a GFR < 15 ml/min/1.73 m^2 are recommended a starting dose of 200 mg daily by the FDA[14]. Clinical studies involving hepatically impaired patients reported no required dose adjustments for mildly impaired. However, moderately impaired patients reported a C_{max} of 28%. They needed a reduction of the starting dose to 400 mg[14]. Pharmacological studies have found

no significant effect of preprandial or postprandial ribociclib use on absorption and bioavailability[15]. Further, changes in body weight from the reference value of 70 kg to 50 or 100 kg were also not found to have a statistically significant effect on ribociclib clearance, thereby not necessitating any dose adjustments[14].

Clinical trials ribociclib and endocrine therapy

MONALEESA series trials

Ribociclib has been trialed extensively with endocrine therapy for the treatment of hormone receptor (HR+) positive human epidermal growth factor receptor 2–negative advanced breast cancer. The largest of these is the MONALEESA trial series.

The first is MONALEESA-7, a phase 3 clinical trial of 672 premenopausal or perimenopausal women patients randomized to receive either ribociclib or placebo with endocrine therapy (goserelin and tamoxifen)[16]. Longer overall survival (OS) was reported in the ribociclib group. After 42 months of treatment, OS stood at 70.2% (95% CI: 63.5–76.0) in the ribociclib group and 46.0% (95% CI: 32.0–58.9) in the placebo group. The treatment group also reported longer disease progression times than the control[16]. The following published study, MONALEESA-3, included 484 mainly postmenopausal women treated with either ribociclib and fulvestrant or placebo with the same. Benefit in the treatment group was consistent with the previous trial, with MONALEESA-3 reporting a PFS of 33.6 months (95% CI: 27.1–41.3) in the treatment group compared to 19.2 months (95% CI: 14.9–23.6) for placebo[17]. Here, too, OS in the treatment arm was considerably better (57.8% (95% CI: 52.0–63.2) vs 45.9% (95% CI: 36.9–54.5))[17]. Updated results from MONALEESA-2 reported longer PFS for the treatment arm (25.3 months vs 16.0 months) than control. PIK3CA or TP53 mutation types did not affect ribociclib efficacy, and relative risk was measured at 42.5% for all patients treated with ribociclib plus letrozole versus 28.7% for patients on placebo plus letrozole[18].

Other concluded studies supported the results of the MONALEESA series. The RIBECCA phase 3b trial reaffirmed the increased PFS and OS found in previous trials, and the CompLEEment-1 study found a favorable safety profile for BC patients[19,20]. MAINTAIN demonstrated the benefit of CDK4/6 inhibitor therapy to BC patients with advanced disease who underwent disease progression[21]. The NATALEE trial of HR-positive HER2-negative early-stage BC patients reported invasive disease-free survival of 90.4% in patients treated with ribociclib and letrozole compared to 87.1% for letrozole alone (HR 0.75; 95% CI: 0.62–0.91; $P = 0.003$)[22]. The subsequent findings of these trials led to CDK4/6 inhibitors combined with endocrine therapy being a frontline treatment for HR-positive HER2-negative advanced BC.

Further, a stable quality of life (QoL) was reported in the MONALEESA experimental arms and a higher 8-week pain reduction compared to the control arm[23]. Looking at published comparative analyses and review studies of CDK4/6 inhibitors, we find an overall favorable report of ribociclib both in terms of efficacy and safety. Guo *et al.*'s[24] meta-analysis of 13 studies found ribociclib combined with fulvestrant to have the highest surface under the cumulative ranking curve (SUCRA) score of 85.0% for PFS out of 10 treatments. Ribociclib and fulvestrant also had the highest OS SUCRA score of 94.1% out of all surveyed treatments. They concluded the study as the best first-line option for HR-positive HER2-negative BC patients[24]. Network meta-analysis by Liu *et al.*[25] found A higher incidence of severe adverse events for ribociclib than for the other CDK4/6 inhibitors (Odds ratio 9.46, 95% CI = 2.07–43.14). Ranking CDK4/6 inhibitor regimens according to PFS, ribociclib was found inferior to abemaciclib and fulvestrant (SUCRA 28.7%); however, when OS for ribociclib was the most efficacious regimen (SUCRA = 34.11%)[25]. This result was repeated in another pooled analysis of 41 RCTs that reported on the superiority of abemaciclib combined with fulvestrant for PFS. In contrast, ribociclib given with fulvestrant was superior for OS[26].

As a second-line therapy, CDK4/6 inhibitors outperformed drugs of other classes. Ribociclib was found inferior to palbociclib in terms of PFS, but for OS, it outperformed all other CDK4/6 inhibitors (SUCRA 86.20%)[27]. Table 1 shows an overview of Clinical Trials Involving Ribociclib and Endocrine Therapy.

Safety profile and management of adverse effects

While generally well tolerated by BC patients, ribociclib has been associated with several adverse effects (AEs). The most reported AE in the MONALEESA trial series was hematologic, caused by neutropenia (57.1% in the ribociclib arm and 0.8% in the placebo arm in MONALEESA-3). Other reported grades 3 or 4 AEs included hepatobiliary toxicity, interstitial lung disease, and prolonged QTc interval[16,22]. Other less frequent but more severe side effects include cases of thromboembolism seen in patients undergoing therapy with the CDK4/6 inhibitor. MONALEESA-2 reported two thromboembolic events (0.6%) during a 13-month treatment[30]. Compared to this, MONALEESA 3 and 7 reported a higher rate of thromboembolism in the treatment arm. Twenty-seven patients (5.6%) developed pulmonary embolisms (PE) in MONALEESA-3, with MONALEESA-7 reporting 10 cases (3.3%). Further, MONALEESA-7 even reported several cases of arterial thrombosis and a single case of stroke in patients in the treatment arm[30]. With further data, thromboembolism may soon be a cause for clinical concern in patients undergoing ribociclib treatment. The RIBECCA study of 500 patients reported a 93.8% AE rate among ribociclib patients[19]. Of these, 52.2% necessitated dose interruptions, 2.8% required dose reductions, and 24.1% required discontinuation of further ribociclib therapy, most commonly due to elevated liver function tests[19]. Fasching *et al.* also reported two fatal AEs (pneumonia and febrile neutropenia), which they related to ribociclib treatment.

Evidence suggests geriatric patients are particularly vulnerable to AEs by ribociclib. In one case report by Muhiddin Er *et al.*, palbociclib-induced hepatotoxicity required switching to treatment with palbociclib 125 mg[31]. A Turkish prospective study of 160 geriatrics (> 65 years) undergoing either palbociclib or ribociclib therapy for metastatic breast cancer reported findings in line with previous trials[32]. Of 84 patients undergoing treatment with ribociclib, dose modification was required for 69% due to neutropenia, 10% due to raised LFTs, and 6% due to raised renal function tests[32]. Ribociclib withdrawal was also necessary in 6% of patients. Finally, a pooled analysis of the MONALEESA trial series reported heightened rates of neutropenia, nausea, leukopenia, vomiting, alopecia, anemia, rash, and pruritus for the treatment arm relative to placebo[28]. A review of the three trials found the first ribociclib dose reduction occurred 2–3 months after starting therapy, with neutropenia

Table 1

Overview of clinical trials involving ribociclib and endocrine therapy.

Trial	Phase	Population	Treatment arms	Primary endpoint	Key findings
MONALEESA-2[28]	Phase 3	Postmenopausal HR+/HER2- metastatic breast cancer, no prior therapy for advanced disease	Ribociclib + letrozole vs placebo + letrozole	Progression-free survival (PFS)	Improved PFS with ribociclib + letrozole vs placebo (median PFS: 25.3 vs 16.0 months; HR 0.57, 95% CI: 0.46–0.70)
MONALEESA-3[28]	Phase 3	Postmenopausal HR+/HER2- metastatic breast cancer, prior endocrine therapy	Ribociclib + fulvestrant vs placebo + fulvestrant	Progression-free survival (PFS)	Improved PFS with ribociclib + fulvestrant vs placebo (median PFS: 20.5 vs 12.8 months; HR 0.59, 95% CI: 0.48–0.73)
MONALEESA-7[28]	Phase 3	Premenopausal HR+/HER2- advanced breast cancer, no prior endocrine therapy	Ribociclib + goserelin + NSAI vs placebo + goserelin + NSAI	Progression-free survival (PFS)	Improved PFS with ribociclib + goserelin + NSAI vs placebo (median PFS: 27.5 vs 13.8 months; HR 0.57, 95% CI: 0.44–0.74)
Maintain[21]	Phase 2	HR+/HER2- metastatic breast cancer, progressed on prior CDK4/6 inhibitor + endocrine therapy	Switched endocrine therapy + ribociclib vs switched endocrine therapy + placebo	Progression-free survival (PFS)	Improved PFS with switched endocrine therapy + ribociclib vs placebo (median PFS: 5.29 vs 3.57 months; HR 0.55, 95% CI: 0.36–0.84)
REACH AUT[29]	Real-world study	HR+/HER2- metastatic breast cancer, first-line setting	Ribociclib + endocrine therapy	Safety, PFS	Favorable real-world PFS results with ribociclib + endocrine therapy

BC, breast cancer; HR, hormone receptor; NSAI, nonsteroidal aromatase inhibitor; PFS, progression-free survival.

being the most common reason. Of the 818 patients evaluated, 155 (14.6%) required discontinuations due to elevated LFTs[28]. A meta-analysis assessing toxicity profiles for the CDK4/6 inhibitors found increased tolerance in early-stage BC patients and a higher toxicity rate in metastatic patients of BC primarily due to an increased treatment duration[33]. Their analysis found neutropenia rates to be highest in patients treated with palbociclib and ribociclib; however, this was easily reversible with dose reductions[33]. Patients with lung or live comorbidities should be cautioned before starting ribociclib, mainly due to the higher observed rates of hepatotoxicity, respiratory injury, and QTc prolongation. Adverse Effects of Ribociclib and Management Strategies are shown in Table 2.

Resistance to CDK4/6 inhibitors

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, notably ribociclib, represent a breakthrough in the treatment of hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer. Despite the clinical progress of these inhibitors, resistance development has been identified as a significant challenge that undermines long-term therapeutic efficacy. The resistance to CDK4/6 inhibitors is multifactorial, with several underlying mechanisms contributing to the complexity of this issue[34]. One of the primary resistance mechanisms to CDK4/6 inhibitors involves genetic alterations, particularly mutations in the RB1 gene. These mutations play a pivotal role because RB1 is crucial in the cyclin D-CDK4/6-Retinoblastoma (RB) pathway, which is the main target of CDK4/6 inhibitors[35,36]. Research has indicated that loss of Rb function, driven by mutations in the RB1 gene, can lead to resistance against CDK4/6 inhibitors. This occurs because without the inhibitory influence of Rb, E2F transcription factors are not regulated, allowing for unchecked cellular progression to S-phase entry[37]. Clinical evidence of acquired RB1 mutations contributing to CDK4/6 inhibitor resistance was observed in patients with metastatic breast cancer, where somatic mutations were detected via ctDNA analyses at the point of disease progression and were not present before the initiation of CDK4/6 inhibition[38].

Furthermore, compensatory signaling pathways also significantly contribute to resistance to CDK4/6 inhibitors. The upregulation of cyclin E1 (encoded by the CCNE1 gene) and alterations in the PI3K/AKT/mTOR pathway can maintain cell cycle progression independent of CDK4/6 inhibition[39]. This bypass mechanism contributes to therapeutic resistance, with CCNE1 upregulation associated with resistance in models and patient samples. CCNE1 amplification and high levels have been associated with acquired resistance to palbociclib and have been shown to predict a lower antiproliferative response to treatment[34]. Epigenetic modifications represent another layer of complexity in the resistance mechanism against CDK4/6 inhibitors. The overexpression of histone deacetylase (HDAC) has been associated with reduced sensitivity to these inhibitors, suggesting that changes in the epigenetic landscape can significantly impact the effectiveness of these treatments. Specifically, a network meta-analysis by Ji *et al.* (2023)[34] compared the effects of CDK4/6 inhibitors, PI3K/mTOR inhibitors, and HDAC inhibitors as second-line treatments for hormone receptor-positive, HER2-negative advanced breast cancer, highlighting the evolving understanding of treatment strategies and resistance mechanisms.

Table 2

Adverse effects of ribociclib and management strategies.

Adverse effect	Frequency	Grade	Management strategy
Neutropenia	High	All grades common	Dose adjustments, G-CSF administration
QT Prolongation	Moderate	Uncommon	Correct electrolyte abnormalities, Avoid concomitant medications known to prolong QT interval, Regular ECG monitoring, dose modification
Hepatotoxicity	Low	Uncommon	Regular liver function tests, dose interruption/reduction
Fatigue	Moderate	All grades common	Dose modification, supportive care
Nausea	Moderate	Uncommon	Antiemetic medication, dose adjustment
Diarrhea	Low	Uncommon	Antidiarrheal medication, hydration
Febrile neutropenia	Low	Uncommon	dose interruption/reduction

Additionally, the tumor microenvironment, including interactions between cancer cells and immune cells, stromal components, and the secretion of growth factors and cytokines, can influence the response to CDK4/6 inhibitors. A study by Zhou *et al*. (2021) discussed how these factors within the tumor microenvironment might promote resistance, emphasizing the role of the extracellular matrix and cell-cell interactions in determining treatment outcomes. This study specifically identified HDAC5 loss as impairing RB repression of pro-oncogenic genes, conferring resistance to CDK4/6 inhibitors such as palbociclib in prostate and breast cancer cells. However, this effect was overcome by the BET-CBP/p300 dual inhibitor NEO2734, indicating potential therapeutic strategies to counteract resistance caused by epigenetic alterations[40]. Resistance to endocrine therapy, often used alongside CDK4/6 inhibitors for treating HR + and HER2- metastatic breast cancer, is a pivotal challenge. This resistance can indirectly foster resistance to CDK4/6 inhibitors themselves. Endocrine resistance mechanisms, such as mutations in the estrogen receptor (ER) and changes in co-regulator proteins, significantly diminish the efficacy of combination treatments. For instance, alterations in ER coactivators, cyclins (D and E), CDK proteins (CDK2 and CDK6), and signaling pathways like PI3K and RAS have been identified as contributors to resistance[41].

Quality of life considerations

In the management of breast cancer with ribociclib combined with endocrine therapy, understanding the impact of treatment on quality of life (QoL) is crucial. The QoL considerations include managing side effects, psychological well-being, and social support systems. Ribociclib has been associated with adverse effects such as neutropenia, nausea, and fatigue. These side effects, while manageable, necessitate careful monitoring and management strategies to ensure patients' well-being and adherence to treatment. Recent studies have emphasized the importance of considering QoL in treatment decisions and the effectiveness of ribociclib in improving or maintaining QoL in patients. The RIBBIT study highlighted the impact of ribociclib plus endocrine therapy on health-related quality of life, showing promising outcomes for patients with metastatic hormone receptor-positive and HER2-negative breast cancer[42].

Additionally, the NATALEE study provided insights into the QoL for patients receiving adjuvant ribociclib plus a nonsteroidal aromatase inhibitor, underscoring the significance of maintaining QoL in treatment protocols[43]. Moreover, pooled analyses from the MONALEESA trials have shown that ribociclib plus endocrine therapy is well tolerated across age groups, including elderly patients, and can delay the median time to first chemotherapy without compromising QoL. These findings are particularly relevant as they suggest that progression-free survival and overall survival benefits with ribociclib plus endocrine therapy in elderly patients are consistent with those observed in younger patients[44].

Incorporating comprehensive support services, such as mental health counseling and patient education on symptom management, into the treatment plan is essential to optimize patient outcomes. These measures can help mitigate the psychological burden of a cancer diagnosis and the side effects of ongoing treatment, ultimately enhancing the overall treatment experience for patients. Social support from family, friends, and cancer support groups is pivotal in improving a patient's psychological resilience, contributing positively to their quality of life during and after treatment. This support system has been identified as a crucial element in improving patient outcomes, underscoring the significance of emotional, informational, and tangible support in managing the stress, anxiety, and depression often associated with breast cancer diagnosis and treatment[45,46].

Moreover, integrating patient-reported outcomes (PROs) into clinical practice and research is essential for a comprehensive understanding of the quality-of-life impact from the patient's perspective. PROs provide insights into the tolerability of treatment regimens and their effects on daily life. They guide clinicians in adapting care to better meet patients' needs, highlighting the importance of personalized treatment plans to enhance the overall patient experience and outcome[47].

Future directions and ongoing research

The combination of ribociclib and endocrine therapy has changed the approach to treatment for HR+ HER2- breast cancer, providing new hope to those fighting this condition. This advancement uses the synergy between ribociclib and various agents, including immune checkpoint inhibitors, angiogenesis inhibitors, and PI3K inhibitors, aiming to boost cancer-fighting efficacy and address the resistance often encountered with single-agent therapies. The research by Ye *et al*. emphasizes the importance of understanding how different signaling pathways interact in breast cancer, such as PRLR and EGFR/HER2. By targeting these pathways, the therapeutic potential of ribociclib in combination treatments could be significantly enhanced[48,49]. The PALOMA-3 trial has demonstrated the benefits of pairing CDK4/6 inhibitors with fulvestrant in HR+ breast cancer patients who had previously progressed on endocrine therapy, showcasing the promising results of combination strategies[50].

Several strategies are being investigated to overcome resistance to CDK4/6 inhibitors, including developing next-generation CDK inhibitors, combination therapies targeting multiple pathways, biomarkers for predictive resistance, and adaptive dosing based on individual response patterns. Research has shown the clinical benefit of CDK4/6 inhibitors in overcoming estrogen resistance, particularly in patients with ESR1 mutations, which are linked to endocrine resistance. These mutations, prevalent in a significant percentage of HR+ metastatic breast cancer cases, do not seem to affect the response to CDK4/6 inhibitors, suggesting these inhibitors can surpass ESR1-dependent resistance[51]. Further, studies like PALOMA-3, MONALEESA-2, MONALEESA-3, and others have emphasized the efficacy of CDK4/6 inhibitors in enhancing progression-free survival (PFS) even after endocrine resistance has been established, showcasing their effectiveness irrespective of endocrine-resistant disease[45,52]. These insights underscore the complexity of resistance mechanisms and the necessity for a multifaceted treatment approach to combat resistance to CDK4/6 inhibitors effectively.

Ongoing investigations into CDK4/6 inhibitors, including ribociclib, for HER2-positive breast cancer reveal their ability to overcome resistance to targeted treatments. Clinical trials aim to assess their efficacy in treating HER2-positive brain metastasis, which is historically challenging due to the blood–brain barrier. The study shows that CDK4/6 inhibitors bring new hope, whether used alone or with other treatments[53]. Nonetheless, combating drug resistance remains a pivotal challenge in using ribociclib for breast cancer treatment. Researchers are digging into resistance mechanisms, such as changes in cell cycle regulation and tumor suppressor functions, to find methods for preventing or overcoming resistance. A deep understanding of these mechanisms is crucial for developing future therapies that maintain the long-term effectiveness of CDK4/6 inhibitors[54].

Moreover, resistance to HER2-targeted therapies, often linked to the hyperactivation of the PI3K/AKT/mTOR pathway, calls for novel treatment approaches. The integration of CDK4/6 inhibitors with HER2 inhibitors is under investigation as a strategy to resensitize tumors to HER2-directed treatments. Early studies indicate that combining these inhibitions could improve treatment outcomes and overcome resistance[55].

Parallel to these efforts, the field is shifting towards more personalized cancer treatment strategies. Significant research is dedicated to identifying and validating predictive biomarkers that can help pinpoint which patients are most likely to respond to ribociclib, thereby optimizing treatment outcomes and minimizing unnecessary exposure to potential side effects[56]. This personalized approach is further supported by ongoing studies investigating molecular pathways involved in resistance mechanisms, highlighting the role of precision medicine in customizing therapies based on individual genetic profiles[57]. The impact of treatment on the quality of life is a critical consideration, with ongoing studies aiming to assess and improve the holistic well-being of patients undergoing treatment with ribociclib. A study by Lee *et al*.[58] has highlighted the significance of patient-reported outcomes in evaluating the real-world impact of ribociclib on quality of life and advocated for a patient-centric approach in clinical trials and treatment planning, emphasizing the need to balance efficacy with quality-of-life considerations. Innovations in drug delivery systems, such as nanoparticle-based approaches, are being explored to enhance the targeting and effectiveness of ribociclib while reducing systemic toxicity. A study by Abdelmalak *et al*.[58] discussed nanotechnology's potential to improve cancer treatments' delivery and therapeutic index, suggesting that such advancements could lead to more effective and patient-friendly treatment modalities.

Clinical and practical implications

The therapeutic efficacy of ribociclib, underscored by its ability to prolong progression-free survival among patients significantly, comes with a spectrum of adverse effects that require meticulous management[59]. Neutropenia, a common side effect of ribociclib, necessitates a proactive approach. Clinical guidelines recommend regular monitoring of complete blood counts, particularly in the initial treatment phases, to mitigate risks. Strategies for managing severe neutropenia include dose adjustments or temporary treatment cessation, emphasizing personalized patient care to balance efficacy and safety[59]. Hepatotoxicity is also another noted concern with ribociclib therapy, stressing the importance of liver function tests both at baseline and periodically after that to detect any liver impairment early[58,59]. The MONALEESA-2 trial, a pivotal study in the evaluation of ribociclib's efficacy and safety, reported abnormal liver function tests as one of the standard grades 3/4 adverse events, underscoring the need for careful monitoring and management of liver health during treatment[11]. This proactive management emphasizes the importance of a vigilant clinical approach to mitigate risks and ensure patient safety.

The clinical use of ribociclib not only emphasizes the importance of managing physical side effects but also highlights the critical need for addressing the psychological and social dimensions of cancer care. The diagnosis and ongoing treatment for breast cancer can significantly impact a patient's mental health, making integrated psychological support, and counseling services essential components of comprehensive cancer care. Studies have shown that psychological interventions, such as structured short-term psychotherapy compared to nonspecific group discussions, can play a significant role in supporting breast cancer patients through rehabilitation, potentially improving outcomes like anxiety, depression, and overall quality of life[57]. Moreover, the broader psychosocial aspects of care, including emotional support and addressing the impact of cancer on a patient's life and relationships, are vital in enhancing the quality of life for those undergoing treatment for breast cancer[32]. Addressing these needs requires a multidisciplinary approach, incorporating psychological support alongside medical treatment to effectively support patients through the complexities of their treatment journey[55].

Financial considerations play a critical role in the practical implications of ribociclib treatment for breast cancer. The cost of ribociclib, combined with endocrine therapy, presents a significant financial burden to patients, reflecting its clinical value but also highlighting issues of financial toxicity in cancer care. Studies have evaluated the cost-effectiveness of ribociclib plus endocrine therapy, noting that while it offers better quality-adjusted life years (QALYs), it also comes with a higher total cost than placebo plus endocrine treatment[11,52,53]. This underscores the importance of exploring insurance coverage options, patient assistance programs, and policy initiatives to improve access to essential cancer medications. The evolving landscape of breast cancer treatment, with therapies like ribociclib, necessitates

Table 3

Current guidelines from ASCO, NCCN, ESMO, and CCO, including the use of ribociclib.

Guideline organization	Patient population	Recommended treatment regimen	Evidence level	Notes
ASCO[28,60]	HR+/HER2- advanced breast cancer	Ribociclib + Aromatase Inhibitor (AI) or Fulvestrant	High	Recommended for premenopausal and postmenopausal women. Regular monitoring of CBC and ECG
NCCN[28,60]	HR+/HER2- advanced or metastatic breast cancer	Ribociclib + Letrozole, Anastrozole, or Fulvestrant	Category 1	Preferred option for first-line treatment in combination with endocrine therapy
MASCC/ESMO[60]	HR+/HER2- advanced breast cancer	Ribociclib + AI (Letrozole or Anastrozole) or Fulvestrant	I, A	Strongly recommended based on Phase III trials. Emphasis on monitoring side effects
CCO[60]	HR+/HER2- advanced or metastatic breast cancer	Ribociclib + Aromatase Inhibitor (AI) or Fulvestrant	High	Supports the use based on high-level evidence from clinical trials, with emphasis on patient selection and monitoring

ASCO, American Society of Clinical Oncology; CCO, cancer care ontario; MASCC/ESMO, Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology; NCCN, national comprehensive cancer network.

ongoing clinical research and education to refine treatment protocols, enhance patient care, and address broader societal implications. The emphasis on financial toxicity highlights the need for comprehensive patient support, including managing short-term and long-term economic challenges associated with treatment[11]. As research advances, the integration of ribociclib into breast cancer management will likely evolve, aiming to balance efficacy, safety, and patient-centric care. Current guidelines from ASCO, NCCN, ESMO, and CCO, Including the Use of Ribociclib, are shown in Table 3.

Conclusion

The addition of ribociclib, a selective CDK4/6 inhibitor, to endocrine therapy has significantly improved outcomes for patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer. Clinical trials have demonstrated substantial improvements in progression-free survival and overall response rates when ribociclib is combined with various endocrine therapies, such as aromatase inhibitors or fulvestrant. Based on the compelling evidence, ribociclib, in combination with endocrine therapy, should be considered a standard of care for the treatment of HR+/HER2- advanced or metastatic breast cancer. While the results are promising, further research is needed to optimize the use of ribociclib and explore its potential in other breast cancer subtypes or earlier disease stages.

Ethical approval

The submitted article is a comprehensive review that does not require ethical approval.

Consent

As a secondary study not involving participants, written informed consent was not required.

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Author contribution

S.S.: conceptualization and writing – original draft preparation; Z.Q.: visualization, supervision, and draft preparation; F.A., A.S., M.K., and A.G.: writing – manuscript writing and editing; S.S.: writing – reviewing and editing. All the authors have read and approved the final manuscript.

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The authors declare no conflicts of interest.

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The paper was not invited.

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