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Ribociclib (LEE011): mechanism of action and clinical impact of this selective cyclin-dependent kinase 4/6 inhibitor in various solid tumors

Debu Tripathy1*, Aditya Bardia2, William R. Sellers3

1Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 2Department of Hematology/Oncology, Massachusetts General Hospital Cancer Center/Harvard Medical School, Boston, MA, USA; 3Novartis Institutes for BioMedical Research, Cambridge, MA

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*Corresponding author

Professor Debu Tripathy
Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center
1515 Holcombe, Unit 1354, Houston, Texas 77030

Phone: (713) 792-2817

Fax: (713) 563-0903

Email: dtripathy@mdanderson.org

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Abstract

The cyclin D–cyclin-dependent kinase (CDK) 4/6–p16–retinoblastoma (Rb) pathway is commonly disrupted in cancer, leading to abnormal cell proliferation. Therapeutics targeting this pathway have demonstrated antitumor effects in preclinical and clinical studies. Ribociclib is a selective, orally bioavailable inhibitor of CDK4 and CDK6, which was granted priority review by the US Food and Drug Administration in November 2016, and is set to enter the treatment landscape alongside other CDK4/6 inhibitors, including palbociclib and abemaciclib. Here we describe the mechanism of action of ribociclib, and review preclinical and clinical data from Phase I, II, and III trials of ribociclib across different tumor types, within the context of other selective CDK4/6 inhibitors. The pharmacokinetics, pharmacodynamics, safety, tolerability, and clinical responses with ribociclib as a single agent or in combination with other therapies are discussed, and an overview of the broad portfolio of ongoing clinical trials with ribociclib across a wide range of indications is presented. Based on the available data, ribociclib has a manageable tolerability profile and therapeutic potential for a variety of cancer types. Its high selectivity makes it an important partner drug for other targeted therapies and it has been shown to enhance the clinical activity of existing anticancer therapies and delay the development of treatment resistance, without markedly increasing toxicity. Ongoing trials of doublet and triplet targeted therapies containing ribociclib seek to identify optimal CDK4/6-based targeted combination regimens for various tumor types and advance the field of precision therapeutics in oncology.
Introduction

Cancer development is often characterized by abnormal cellular proliferation and dysregulation of cell cycle control (1). The cell cycle is regulated at different stages by various cyclin–cyclin-dependent kinase (CDK) complexes (Figure 1). The G1 (pre-DNA synthesis) to S (DNA synthesis) cell cycle checkpoint is regulated by the cyclin D–CDK4/6–p16–retinoblastoma (Rb) pathway, which ensures conditions are appropriate for cell growth and division before the cell is irreversibly committed to division (2-4). In this pathway, cyclin D is the key entry point at which various mitogenic and growth arrest signaling pathways converge to regulate the cell cycle (3). In response to mitogenic signaling, levels of D-type cyclins rise and associate with CDK4 or CDK6. The resulting active cyclin D–CDK4/6 complexes phosphorylate Rb, relieving its repression of E2 transcription factors (E2F). The released E2F consequently activates the transcription of genes required for the G1–S transition and cell cycle progression (5, 6). The tumor suppressor and negative regulator of the cyclin D–CDK4/6 complex, p16, is a critical mediator of cellular senescence, limiting the replicative life span of cells (7).

In cancer, the cyclin D–CDK4/6–p16–Rb pathway is commonly disrupted in favor of cell cycle progression and continued growth, rendering this pathway a key target for cancer therapeutics (5, 8). In hormone receptor-positive (HR+) breast cancer, CDK4/6 pathway activation has also been associated with resistance to endocrine therapy (9, 10). p16 is frequently inactivated by gene deletion, point mutation, or transcriptional silencing by methylation (5). Amplification of CDK4 and CCND1 (encoding cyclin D1) and overexpression of cyclin D protein (e.g. through chromosome 11 translocations or inversions) are also frequent in human cancers (5, 11). The abnormalities of the cyclin D–CDK4/6–p16–Rb pathway vary across cancer types (Supplementary Table 1). The pathway can also be upregulated as a result of upstream oncogenic mutations (3, 12, 13). This provides a therapeutic potential for targeting CDK4 and CDK6 in the treatment of cancer.

Advent of CDK4/6 inhibitors

Preclinical evidence showing a role for the cyclin D–CDK4/6–p16–Rb pathway in cancer led to the development of a first generation of broad-acting pan-CDK inhibitors (14). The first such inhibitor to enter clinical trials was flavopiridol; however, clinical studies demonstrated poor efficacy, complex pharmacokinetics (PK), and dose-limiting toxicities due to off-target effects (14, 15). The late 1990s/early 2000s saw the development of second-generation CDK inhibitors. These inhibitors showed preferential inhibition of CDK1 and CDK2 and/or increasing overall potency. Of these, dinaciclib, an inhibitor of CDK1, CDK2, CDK5, and CDK9, was most extensively studied in the clinic; however, Phase II trials showed limited efficacy (14, 16, 17).

More recently, inhibitors specific for CDK4 and CDK6 have entered clinical trials. Such selective inhibitors spare CDK2 activity, avoiding inhibition of general S-phase activity. Three selective CDK4/6 inhibitors are in late-stage clinical development: ribociclib (LEE011, Novartis), palbociclib (Ibrance®; PD-0332991; Pfizer), and abemaciclib (LY-2835219; Eli Lilly). Palbociclib combined with letrozole or fulvestrant has demonstrated efficacy in patients with HR+ advanced breast cancer (ABC; Table 1) (18, 19), and is approved in the USA and Europe for use in these combinations (20, 21). Abemaciclib has shown efficacy as a single agent and in combination with endocrine therapies in patients with HR+ ABC, and has entered Phase III development, with an US Food and Drug Administration (FDA)
Breakthrough Therapy Designation granted in 2015 for patients with refractory HR+ ABC (Table 1) (22-24).

Ribociclib is a selective CDK4/6 inhibitor, which received FDA Breakthrough Therapy designation in August 2016 and Priority Review in November 2016 in combination with letrozole for the first-line treatment of HR+, human epidermal growth factor receptor 2-negative (HER2−) ABC (25). This review will outline the development of ribociclib, and provide an overview of the preclinical and clinical data for ribociclib across various tumor types.

Characteristics of ribociclib

Ribociclib, palbociclib, and abemaciclib are all orally bioavailable, small molecule inhibitors, that bind to the ATP cleft of CDK4 and CDK6. However, abemaciclib appears to bind more readily to the ATP cleft and forms a hydrogen bond with a catalytic residue (Lys43) that is conserved among kinases, suggesting it binds with less selectivity than ribociclib and palbociclib (26). In contrast, ribociclib and palbociclib appear to have greater lipophilicity (Table 2) and larger binding site side chains than abemaciclib, which might reduce the number of off-target kinase ATP-binding pockets they interact with (26). Indeed, ribociclib, palbociclib, and abemaciclib exhibit varying half maximal inhibitory concentration (IC_{50}) values against different CDK− and non-CDK−cyclin complexes in biochemical assays (Table 2) (26-29). Interestingly, in a chemoproteomics study of CDK4/6 inhibitor activity in lung carcinoma cell lines and primary tumor samples, ribociclib was found to be significantly more selective towards CDK4 and CDK6 than palbociclib, which interacted with more than twice as many kinases than ribociclib (30).

Early clinical experience with ribociclib

The first Phase I clinical studies evaluated single-agent ribociclib across a range of Rb-positive advanced solid tumors and lymphomas in US/European (N=132) and Japanese patients (N=17) (31, 32). The recommended Phase II dose (RP2D) of single-agent ribociclib was declared as 600 mg/day on a 3-weeks-on/1-week-off schedule (31, 32). Pharmacokinetic analyses determined that ribociclib is rapidly absorbed, with a time to maximum concentration (T_{max}) of 1–5 hours, and a half-life (t_{1/2}) of 33–42 hours (Table 2) (31, 32). In Japanese patients, ribociclib exposure appeared higher on average than in non-Japanese patients, although considerable inter-patient variability was observed (31, 32). In a separate, healthy volunteer study, overall exposure of a single oral dose of 600 mg ribociclib was unaffected in fed versus fasted states, indicating that ribociclib may be taken with or without food (33).

Safety analyses from the Phase I studies indicated that single-agent ribociclib is associated with a manageable safety profile. The most common treatment-related adverse events (AEs) were hematologic, particularly neutropenia, consistent with on-target CDK4/6 inhibitor toxicity (31, 32). Non-hematologic AEs included nausea and fatigue (31, 32). Grade 1/2 QTc prolongation was reported in patients receiving the RP2D and subsequent trials included additional cardiac monitoring (31). AEs were generally mild-to-moderate in severity, and were reversible upon ribociclib interruption (31, 32).
Preliminary antitumor activity was observed in the Phase I studies (31, 32). Among US/European patients, the large majority of whom were heavily pretreated, three had partial responses (PRs) and 41 had stable disease (SD); eight patients had SD for >6 months (31). The PRs occurred in a patient with head and neck acinar carcinoma and CDKN2A loss, another with PIK3CA-mutant, CCND1-amplified, estrogen receptor-positive (ER+) breast cancer, and another with BRAF/NRAS-wild-type, CCND1-amplified melanoma (31). In the Japanese population, who were also heavily pretreated, SD was observed in four patients treated at the RP2D: two with peritoneal cancer, one with esophageal cancer, and one with breast cancer (32). These data suggest that ribociclib, through its specific mechanism of action, has activity in humans.

Preclinical and clinical experience with ribociclib in individual indications

Ribociclib has demonstrated antitumor activity in preclinical and clinical studies of a wide variety of tumor types, including breast cancer, melanoma, and neuroblastoma. While single-agent activity has been demonstrated for ribociclib, it has also been shown to enhance the activity of combination partners and delay the development of treatment resistance in preclinical and clinical studies.

Breast cancer

Preclinical

Breast tumors frequently harbor aberrations of the cyclin D–CDK4/6–p16–Rb pathway (34-36) (Supplementary Table 1), and this pathway is also implicated in resistance to endocrine therapy (3). Therefore, targeting both the cyclin D–CDK4/6–p16–Rb and ER pathways may delay the development of resistance. In a preclinical study of 50 breast cancer cell lines, ribociclib demonstrated inhibitory activity predominantly against ER+ cell lines (37), suggesting that ER+ breast cancer cells might be particularly susceptible to CDK4/6 inhibition. In vivo, ribociclib showed significant tumor growth inhibition in xenograft mouse models of ER+ breast cancer (37). A preclinical study in CDK4/6 inhibitor-resistant breast cancer cell lines suggests that mechanisms of resistance differ between ribociclib and palbociclib. Ribociclib resistant clones demonstrated increased E2F1, compared with increased cycle E protein levels in palbociclib resistant clones (38). Combinations of ribociclib with endocrine therapies was also associated with potent antitumor effects in ER+ breast cancer models compared with the respective single agents (38, 39).

The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway has also been widely implicated in breast cancer tumorigenesis and treatment resistance (8). As cyclin D1 is frequently regulated in a PI3K/AKT/mTOR-dependent manner, combinations of upstream and downstream inhibitors might act cooperatively. Indeed, combination of ribociclib with the PI3K inhibitor alpelisib (BYL719) resulted in enhanced tumor regression (–57%) versus single-agent treatments with ribociclib (–9%) and alpelisib (–15%) (39). More recently, large-scale, patient-derived breast cancer xenografts (PDX) were used to evaluate such combinations in mouse preclinical trials. Treatment of 38 PDX mouse models with ribociclib plus alpelisib demonstrated increased response rates and progression-free survival (PFS) with this combination compared with the single agents (40). Interestingly, the ribociclib plus alpelisib combination appeared more active in PDX models than in cell lines, suggesting a possible disconnect between in vitro cell-based assays and in vivo PDX-based results (40). Furthermore, the addition of PI3K inhibitors to ribociclib and
either letrozole or fulvestrant demonstrated increased antitumor activity, including some complete regressions, without significant toxicity in mouse models of ER+ breast cancer (37). These regressions were sustained for ~4 weeks post treatment and occurred in both PI3K/PTEN-wild-type and -altered backgrounds. Taken together, the synergistic activity of ribociclib in combination with various anticancer therapies suggest that ribociclib may complement existing breast cancer treatments in the clinic.

**Clinical**

The combination of ribociclib and endocrine therapies in HR+, HER2– breast cancer is being investigated in Phase Ib–III studies (Table 3 and Supplementary Table 2). These studies have demonstrated that ribociclib exposure is unaffected by combinations with exemestane, letrozole, or fulvestrant in patients with HR+ ABC (41, 42). Similarly, letrozole exposure when combined with ribociclib was within the range of values observed from single-agent letrozole (41, 43). The addition of ribociclib to exemestane, letrozole, or fulvestrant was also associated with manageable tolerability profiles in all studies (Table 3). The most common AEs were hematologic, and Grade 3/4 neutropenia was frequent but uncomplicated (42, 44-46). QT prolongation has been observed following ribociclib treatment in combination with endocrine therapy; cases were predominantly Grade 1–2 in severity with prolongation limited by proactive dose modifications (31, 46). AEs were manageable and reversible upon treatment interruption (46, 47). In the Phase III MONALEESA-2 study of ribociclib plus letrozole in the first-line treatment of postmenopausal women with HR+, HER2– ABC, ribociclib dose intensity was 88% despite dose interruptions, and only 7.5% of patients discontinued ribociclib plus letrozole treatment due to AEs (46).

Clinical activity of ribociclib was observed in studies of HR+ ABC (Table 3) (42, 44-46). In MONALEESA-2, where 668 patients with HR+ ABC were randomized to receive ribociclib plus letrozole or placebo plus letrozole, ribociclib plus letrozole significantly increased PFS relative to placebo plus letrozole in the first-line setting (median PFS: not reached vs 14.7 months; hazard ratio=0.56; \( P=3.29\times10^{-6} \)) (46). The PFS rate at 12 months was 72.8% versus 60.9% in the ribociclib and placebo groups, respectively (46). A significant hazard ratio benefit for ribociclib plus letrozole was also observed across all pre-specified patient subgroups, including older patients (≥65 years) and those with visceral metastases, bone-only disease, or de novo ABC (46, 48, 49). In the ribociclib plus letrozole arm, decreased tumor size at the initial evaluation (~Week 8) was observed in 76% of evaluable patients with measurable disease (50). In newly diagnosed Grade II/III HR+, HER2– invasive breast cancer, a randomized pre-surgical study demonstrated an enhanced reduction in expression of the Ki67 marker for cell proliferation upon combination of ribociclib and letrozole (>92%) versus letrozole alone (69%), further supporting a role for ribociclib in enhancing the antitumor effects of its combination partner (43). An ongoing trial (NCT02712723) is investigating ribociclib plus letrozole in the neoadjuvant setting (Supplementary Table 2). Preliminary clinical activity has also been established with ribociclib plus fulvestrant in pretreated HR+, HER2– ABC, and PRs were observed in patients who received prior fulvestrant (42). When evaluating potential biomarkers of response, preliminary clinical activity with ribociclib plus letrozole or fulvestrant was reported in patients with ER+ breast cancer tumors carrying alterations in PI3K/AKT/mTOR or cyclin D–CDK4/6–p16–Rb pathways, suggesting a possible benefit in patients whose tumors carry these alterations (42, 45).
Encouraging preliminary clinical activity has also been demonstrated with triplet therapy of ribociclib, exemestane, and everolimus (mTOR inhibitor), as well as ribociclib, letrozole, and alpelisib (PI3Kα selective inhibitor) in pretreated patients with HR+ ABC (Table 3 and Supplementary Table 2) (47, 51, 52). While ribociclib exposure remained unaltered by combination with everolimus, exposure to everolimus, which is metabolized by cytochrome P450 3A4 (CYP3A4), increased 1.5–3-fold when combined with ribociclib (41). However, use of lower doses of everolimus (e.g. 2.5 mg/day) resulted in exposures within the ranges achieved with single-agent everolimus dosing (e.g. 5–10 mg/day), with potentially lower toxicity (41, 52). Triplet therapy with ribociclib, everolimus, and exemestane in pretreated patients with ER+ ABC was associated with manageable safety (Table 3) (52). During triplet therapy with ribociclib, alpelisib, and letrozole, PK indices for ribociclib and alpelisib were generally consistent with historic single-agent data (51). The combination of ribociclib, alpelisib, and letrozole also demonstrated an acceptable safety profile (Table 3) (51). Both triplet regimens have demonstrated antitumor activity in patients whose ER+ breast cancer tumors harbor PI3K/AKT/mTOR and/or cyclin D–CDK4/6–p16–Rb pathway modifications (51, 52). Further evaluation and validation of biomarkers of response is ongoing.

Melanoma

Preclinical

The now-refined genetic landscape of melanoma has highlighted the centrality of RAS signaling in this disease. Indeed, activating mutations occur in critical components of this pathway, including \(BRAF^{V600}\) (35–50%), \(NRAS\) (10–25%), and \(NF1\) (~15%) (53, 54). The cyclin D–CDK4/6–p16–Rb pathway is also commonly dysregulated in melanomas. Mutations, deletions, or hypermethylation of \(CDKN2A\) are key driver alterations in melanomas, and \(CCND1\) (cyclin D1) and \(CDK4\) are frequently amplified (Supplementary Table 1) (53-57). Germline mutations in \(CDKN2A\) and \(CDK4\) are also linked to familial melanoma (58). High \(CCND1\) and low \(CDKN2A\) copy numbers have been associated with reduced PFS with BRAF inhibitors (59).

Approved treatments for \(BRAF\)-mutant melanoma include targeted therapy with BRAF and/or MEK inhibitors (60). Binimetinib (MEK162), a MEK inhibitor, and encorafenib (LGX818), a selective BRAF inhibitor, have demonstrated antitumor activity as single agents in \(NRAS\)- and \(BRAF\)-mutant melanomas, respectively, and in combination in \(BRAF\)-mutant melanomas (61-63). The combination of ribociclib and binimetinib demonstrated enhanced tumor regression (34% tumor/control [T/C] ratio) in xenograft models of \(NRAS^{Q61K}\)-mutant melanoma relative to single-agent binimetinib (12% T/C) or ribociclib (32% T/C) (27, 62). In \(BRAF^{V600E}\)-mutant melanoma models, low-dose ribociclib exhibited synergistic activity with encorafenib (27, 61). The addition of ribociclib to encorafenib also appeared to prevent resistance to encorafenib (27, 61), suggesting that simultaneous inhibition of BRAF and cyclin D–CDK4/6–p16–Rb pathways may provide a therapeutic benefit in the clinical setting. The enhanced antitumor activity of ribociclib plus encorafenib relative to single agents was confirmed in a large-scale in vivo screen of PDX melanoma models, where the combination was associated with a 100% response rate, including 87% PR and CR (exceeding the 72% PR and CR for binimetinib plus encorafenib) (40). The combination also resulted in a significant improvement in PFS and delayed the development of resistance in the tumor models (\(P=1.8\times10^{-3}\)), with no drug–drug interactions (40).
Clinical

The combinations of ribociclib plus binimetinib or encorafenib have been evaluated in two dose-escalation expansion Phase Ib/II studies of advanced NRAS- and BRAF-mutant melanoma, respectively (Table 3) (61, 62). In patients with advanced NRAS-mutant melanoma, combination of ribociclib and binimetinib did not affect the PK exposures of either drug (41, 62). Common AEs experienced with ribociclib plus binimetinib included creatine phosphokinase (CPK) elevation, acneiform dermatitis, nausea, rash, edema, leukopenia, and creatinine elevation, whereas Grade 3/4 AEs included CPK elevation, neutropenia, acneiform dermatitis, and rash (Table 3) (62). This combination was also associated with preliminary antitumor activity, including cases of PR (33%) and SD (52%) (Table 3) (62). In patients with advanced BRAFV600-mutant melanomas, the combination of ribociclib and encorafenib resulted in reduced ribociclib exposure and increased encorafenib exposure, most likely due to encorafenib-mediated CYP3A4 induction and to ribociclib-mediated CYP3A4 inhibition, respectively (41). The combination of ribociclib and encorafenib demonstrated clinical activity and an acceptable tolerability profile, with AEs consisting of hand–foot syndrome, nausea, pruritus, rash, and myalgia (Table 3) (61). Cases of PR and SD were observed in patients receiving ribociclib plus encorafenib whose tumors exhibited p16 loss or CDK4 mutation (61). There was little evidence of response in patients resistant to BRAF inhibition (61). The use of ribociclib and binimetinib and/or encorafenib combinations in melanoma is being investigated further in ongoing trials (Supplementary Table 2).

Neuroblastoma

Preclinical

Neuroblastoma is frequently driven by oncogenic activation of anaplastic lymphoma kinase (ALK), often resulting in cyclin D1 upregulation and cell proliferation (64). Consistent with this, extensive overexpression of cyclin D–CDK4/6 components have been observed in neuroblastomas (65). Array-based data showed that cyclin D1 expression is 3–8 times higher in neuroblastoma tumors than in libraries of 18 other common malignancies, including breast cancer (65). High expression of CDK4 and CDK6 and deletions of CDKN2A have also been associated with these tumors (Supplementary Table 1) (65-67).

Ribociclib activity has been profiled against >500 cell lines in the Cancer Cell Line Encyclopedia study, whereby neuroblastoma cell lines were identified as particularly sensitive to ribociclib (27). Here, ribociclib induced cytostasis at nanomolar concentrations in 12/17 human neuroblastoma-derived cell lines (67). In sensitive neuroblastoma cell line-derived xenograft mouse models, treatment with ribociclib was accompanied by a reduction in phosphorylated Rb, Ki67, and cell proliferation, leading to significant tumor growth delay throughout the treatment period (P<0.0001) (67). CDK4/6 is therefore an attractive target for neuroblastoma treatment.

Clinical

The efficacy and safety of single-agent ribociclib in patients with neuroblastoma was evaluated as part of the Phase I study investigating ribociclib in 31 pediatric patients (median age [range]: 5 [1–20] years) with malignant rhabdoid tumors (MRT), neuroblastoma, or CDK4/6 pathway-activated tumors (68). Consistent with single-agent data in adults, the maximum tolerated dose (MTD) and
RP2D were 470 mg/m²/day (adult equivalent dose ≈800 mg/day) and 350 mg/m²/day (adult equivalent dose ≈600 mg/day), respectively, on a 3-weeks-on/1-week-off dosing schedule (68). Ribociclib was rapidly absorbed with a median $T_{\text{max}}$ of 2–5 hours, regardless of age (69). As in adults, ribociclib exposure in pediatric patients appeared to accumulate 2–3-fold in plasma, reaching steady state within 8 days (69). Clearance was 2–3 times slower in pediatric patients compared with adults, presumably due to their lower body weight (69). Ribociclib was well tolerated with mild-to-moderate reversible AEs, the majority of which were hematologic (68). Three patients, two with neuroblastoma and one with MRT, received ribociclib for ≥4 cycles; SD was the best overall response (68). Ribociclib remains the only CDK4/6 inhibitor investigated in a clinical trial of neuroblastoma.

**Ongoing trials with ribociclib**

Multiple trials of ribociclib are ongoing across different tumor types, including $BRAF^{V600E}$- and $NRAS$-mutant melanoma, non-small cell lung cancer, teratoma, liposarcoma, myelofibrosis, and gynecologic cancers; these are summarized in Supplementary Table 2. The most advanced trials are investigating ribociclib combinations in HR+ breast cancer. MONALEESA-3 is evaluating the addition of ribociclib to fulvestrant in patients with HR+ ABC who have received no or only one line of prior endocrine therapy. MONALEESA-7 is investigating the combination of ribociclib and tamoxifen or non-steroidal aromatase inhibitors plus goserelin in pre/perimenopausal women with HR+ ABC. MONALEESA-7 is the only trial entirely dedicated to investigating CDK4/6 inhibition in the pre/perimenopausal setting. In addition, based on preclinical rationale, a number of additional doublet and triplet combination studies are underway, including combinations of ribociclib with endocrine therapy and PI3K pathway inhibition (Supplementary Table 2).

**Ribociclib in perspective**

The clinical data for ribociclib adds to the wealth of emerging information supporting use of CDK4/6 inhibitors in the treatment of cancer. Certain differences among ribociclib, palbociclib, and abemaciclib, including PK factors, target selectivity, and toxicities, are likely to influence their activity or utility in individual settings. PK data with ribociclib demonstrate a long half-life compared with palbociclib and abemaciclib (Table 2). While the half-lives of ribociclib and palbociclib enable once-daily, 3-weeks-on/1-week-off dosing (14), the PK/pharmacodynamic profile of abemaciclib favors twice-daily, continuous dosing (29, 70). The convenience of intermittent versus continuous dosing and its impact on treatment adherence and outcomes remains to be explored. Once-daily, continuous dosing of ribociclib in combination with endocrine therapies is being evaluated in ongoing breast cancer trials (NCT02088684, NCT02712723, NCT02732119) (42). PK data indicate that ribociclib can be taken with or without food, whereas palbociclib must be administered with food (20, 33), and that ribociclib may be absorbed more rapidly than palbociclib and abemaciclib (Table 2) (70, 71). Preclinically, ribociclib appears to have less toxicity against bone marrow mononuclear cells compared with palbociclib and abemaciclib (Table 2) (26), which may potentially translate into fewer hematologic toxicities. Hematologic toxicities were reported with ribociclib plus letrozole in MONALEESA-2 and with palbociclib plus letrozole in PALOMA-2 (18, 46). Differences in target selectivity also lead to variations in safety: with abemaciclib demonstrating increased frequency of gastrointestinal AEs versus ribociclib or palbociclib (Table 1) (14). Ribociclib is generally well tolerated, with predictable AEs that are easily manageable by dose adjustment or treatments.
Finally, preclinical data suggest that both ribociclib and abemaciclib can cross the blood–brain barrier, supporting further exploration with central nervous system tumors (72, 73).

Conclusion

Ribociclib is a promising, selective CDK4/6 inhibitor in the late stages of clinical development, demonstrating preclinical and clinical activity across a range of tumor types, including HR+ breast cancer. The preclinical, clinical, and PK profiles of ribociclib in a variety of tumor types make it an important addition to the class of CDK4/6 inhibitors. Given the selectivity of ribociclib towards CDK4/6, the addition of ribociclib to existing anticancer therapies in doublet and triplet combinations has been successful, enhancing efficacy of existing therapies with minimal increases in toxicity in preclinical and clinical studies. This result is being explored extensively across a range of tumor types and in combination with a variety of anticancer agents (Supplementary Table 2). Establishing validated biomarkers of clinical response to ribociclib will help define patient populations who will benefit most from treatment, improve treatment outcomes, and identify effective drug combinations to mitigate treatment resistance. The comprehensive and robust portfolio of unique and ongoing clinical studies of doublet and triplet therapies containing ribociclib are likely to shape the future landscape of cancer therapeutics.

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Table 1. Key reported clinical trials with palbociclib and abemaciclib.

<table>
<thead>
<tr>
<th>Study name/ID</th>
<th>Combination drug</th>
<th>Phase</th>
<th>Population</th>
<th>Common Grade 3/4 AEs (≥10% of patients)</th>
<th>Clinical activity</th>
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<td><strong>Palbociclib</strong></td>
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<td><strong>Breast Cancer</strong></td>
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<tr>
<td>PALOMA-1/ NCT00721409 (74)</td>
<td>Letrozole</td>
<td>II</td>
<td>ER+ ABC with no prior treatment for ABC (N=165)</td>
<td>Neutropenia (54%), leukopenia (19%)</td>
<td>Median PFS 20.2 months vs 5.7 months for letrozole monotherapy (HR=0.488; P=0.0004)</td>
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<tr>
<td>PALOMA-2/ NCT01740427 (18)</td>
<td>Letrozole</td>
<td>III</td>
<td>ER+ ABC with no prior treatment for ABC (N=666)</td>
<td>Neutropenia (66%), leukopenia (25%)</td>
<td>Median PFS 24.8 months vs 14.5 months for letrozole monotherapy (HR=0.58; P&lt;0.000001)</td>
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<tr>
<td>PALOMA-3/ NCT01942135 (19)</td>
<td>Fulvestrant</td>
<td>III</td>
<td>HR+ ABC after progression on one line of endocrine therapy for ABC (N=521)</td>
<td>Neutropenia (62%), leukopenia (25%)</td>
<td>Median PFS 9.2 months vs 3.8 months for fulvestrant monotherapy (HR=0.42; P&lt;0.001)</td>
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<td>NCT01037790 (75)</td>
<td>None</td>
<td>II</td>
<td>Metastatic Rb+ breast cancer (N=37; n=33 HR+)</td>
<td>Neutropenia (54%), leukopenia (51%), lymphopenia (30%), thrombocytopenia (19%)</td>
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<td><strong>Solid tumors</strong></td>
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<td>NCT00141297 (71)</td>
<td>None</td>
<td>I</td>
<td>Rb+ advanced solid tumors (N=41)</td>
<td>Neutropenia (20%), leukopenia (10%) in Cycle 1</td>
<td>27% SD for ≥4 cycles, 16% SD for ≥10 cycles (n=37 evaluable)</td>
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<td>NCT004200056 (76)</td>
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<td>I</td>
<td>CD19+/CD20+, CD5+, CD23– MCL, with cyclin D1 positivity, t(11;14) translocation, or bcl-1/IgH rearrangement (N=17)</td>
<td>Neutropenia (35%), thrombocytopenia (24%), hypophosphatemia (12%)</td>
<td>6% CR, 12% PR, 41% SD, median PFS 4 months (90% CI 2.0–14.7 months) (n=16 evaluable)</td>
</tr>
<tr>
<td><strong>Liposarcoma</strong></td>
<td></td>
<td></td>
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<tr>
<td>Study ID</td>
<td>Cohort</td>
<td>Phase</td>
<td>Description</td>
<td>Side Effects</td>
<td>Efficacy</td>
</tr>
<tr>
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<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>NCT01209598 (77)</td>
<td>None</td>
<td>II</td>
<td>Advanced CDK4-amplified, Rb+ well-differentiated or dedifferentiated liposarcoma (N=30)</td>
<td>Neutropenia (50%), leukopenia (47%), thrombocytopenia (30%), lymphopenia (27%), anemia (17%)</td>
<td>3% PR, 12-week PFS 66% (90% CI 51–100%), median PFS 18 weeks (n=29 evaluable)</td>
</tr>
<tr>
<td>NCT01291017 (78)</td>
<td>None</td>
<td>II</td>
<td>Previously treated, advanced Rb+, CDKN2A inactivated NSCLC (N=19)</td>
<td>Neutropenia (16%)</td>
<td>50% SD, median PFS 12.5 weeks</td>
</tr>
<tr>
<td><strong>Abemaciclib</strong></td>
<td></td>
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<tr>
<td>Solid tumors</td>
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<tr>
<td>NCT01394016 (79)</td>
<td>None</td>
<td>I</td>
<td>Advanced solid tumors (whole study N=225; escalation phase n=33)</td>
<td>Leukopenia (10%), neutropenia (10%) (n=173)</td>
<td>Breast cancer (n=47): 23% PR, 47% SD, 23% ORR, 49% CBR, 70% DCR, median PFS 5.8 months NSCLC (n=68): 3% PR, 46% SD, 3% ORR, 49% DCR, median PFS 2 months Melanoma (n=26): 4% PR, 23% SD, 4% ORR, 27% DCR Glioblastoma (n=17): 0% PR, 18% SD, 0% ORR, 18% DCR CRC (n=15): 0% PR, 13% SD, 0% ORR, 13% DCR</td>
</tr>
<tr>
<td>NCT02014129 (80)</td>
<td>None</td>
<td>I</td>
<td>Japanese patients with advanced cancer (N=12)</td>
<td>200 mg BID (n=6): leukopenia (33%), neutropenia (17%)</td>
<td>Maximal percent change in tumor size from baseline: −35 to +25% &gt;30% tumor shrinkage in 2 patients (HR-, HER2+ breast cancer and small intestine neuroendocrine carcinoma)</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
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<tr>
<td>MONARCH-1/</td>
<td>None</td>
<td>II</td>
<td>HR+, HER2– ABC that has progressed on prior endocrine therapy and</td>
<td>Diarrhea (20%) and fatigue (13%), white blood cell decreased (28%), neutrophil count decrease (22%)</td>
<td>Confirmed PR 20%, confirmed ORR 20%, CBR 42%, median PFS 6 months</td>
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<tr>
<td>NCT02102490 (22)</td>
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<tr>
<td>Study ID</td>
<td>Treatment Description</td>
<td>Adverse Events</td>
<td>6-month PFS</td>
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<tr>
<td>NCT02057133 (81)</td>
<td>Endocrine and HER2-targeted therapies</td>
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<td></td>
<td>HR+ metastatic breast cancer (N=110)</td>
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<tr>
<td></td>
<td><strong>Combination with letrozole (n=20):</strong> diarrhea (45%), fatigue (20%), neutropenia (20%), nausea (15%), vomiting (10%)**</td>
<td></td>
<td>6-month PFS 76%</td>
<td></td>
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<tr>
<td></td>
<td><strong>Combination with anastrozole (n=16):</strong> diarrhea (31%), leukocyte count reduced (31%), neutrophil count reduced (25%), lymphocyte count reduced (25%), fatigue (19%)**</td>
<td></td>
<td>6-month PFS 87%</td>
<td></td>
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<tr>
<td></td>
<td><strong>Combination with tamoxifen (n=16):</strong> diarrhea (31%), fatigue (31%), lymphocyte count reduced (13%), leukocyte count reduced (13%)**</td>
<td></td>
<td>6-month PFS 73%</td>
<td></td>
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<tr>
<td></td>
<td><strong>Combination with tamoxifen (n=15):</strong> diarrhea (11%)</td>
<td></td>
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<tr>
<td></td>
<td><strong>Combination with tamoxifen + everolimus (150 mg BID dose; n=15):</strong> neutrophil count reduced (33%), lymphocyte count reduced (33%), diarrhea (27%), anemia (20%), fatigue (13%), stomatitis (13%), hypokalemia (13%)**</td>
<td></td>
<td>6-month PFS 100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Combination with trastuzumab (150 mg BID dose; n=18):</strong> neutrophil count reduced (75%), diarrhea (25%), leukocyte count reduced (25%), platelet count reduced (25%)**</td>
<td></td>
<td>6-month PFS 29% (HR+ breast cancer; n=11); 38% (HR- breast cancer; n=7)</td>
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<tr>
<td></td>
<td><strong>Combination with trastuzumab (200 mg BID dose; n=6):</strong> neutrophil count reduced (75%), diarrhea (25%), leukocyte count reduced (25%), platelet count reduced (25%)**</td>
<td></td>
<td>6-month PFS 50% (HR+ breast cancer; n=5); 0 (HR- breast cancer; n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study ID</td>
<td>Treatment</td>
<td>Phase</td>
<td>Cohort Description</td>
<td>All (N=47)</td>
<td>HR+ (n=36)</td>
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<tr>
<td>NCT01394016 (79)</td>
<td>None</td>
<td>I</td>
<td>Metastatic breast cancer expansion cohort (N=47)</td>
<td>-</td>
<td>23% PR, 47% SD, DCR 70%, median PFS 5.8 months</td>
</tr>
<tr>
<td>NCT01394016 (79)</td>
<td>Fulvestrant</td>
<td>I</td>
<td>HR+ ABC (N=19)</td>
<td>Antitumor activity against HR+ breast cancers</td>
<td>21% PR, ORR 21%, DCR 79%, CBR 63%</td>
</tr>
<tr>
<td>NSCLC</td>
<td>NCT01394016 (79)</td>
<td>None</td>
<td>NSCLC expansion cohort (N=68)</td>
<td>-</td>
<td>3% PR, 46% SD, 49% DCR, median PFS 2 months</td>
</tr>
</tbody>
</table>

Combination with trastuzumab (200 mg BID dose; n=6):
- diarrhea (83%), anemia (33%), neutrophil count reduced (33%), leukocyte count reduced (33%), lymphocyte count reduced (33%), platelet count reduced (17%), fatigue (17%), abdominal pain (17%)
BID, twice daily; CBR, clinical benefit rate; CDKN2A, cyclin-dependent kinase inhibitor 2A; CI, confidence interval; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR, hazard ratio; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; MCL, mantle cell lymphoma; MRT, malignant rhabdoid tumor; NSCLC, non-small cell lung cancer; ORR, overall response rate; Rb+, Rb-positive.
Table 2. Key characteristics of CDK4/6 inhibitors in clinical development for solid tumors.

<table>
<thead>
<tr>
<th></th>
<th>Ribociclib (LEE011) (26, 27, 31, 32)</th>
<th>Palbociclib (Ibrance®; PD-0332991) (20, 26, 28)</th>
<th>Abemaciclib (LY2835219) (26, 29, 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IC₅₀ (nM) – on target CDKs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDK4–cyclin D1</td>
<td>10</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>CDK6–cyclin D1/2/3</td>
<td>39</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td><strong>IC₅₀ (nM) – on other CDKs</strong></td>
<td></td>
<td></td>
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<tr>
<td>CDK1–cyclin B</td>
<td>113,000</td>
<td>&gt;10,000</td>
<td>1627</td>
</tr>
<tr>
<td>CDK2–cyclin A/E</td>
<td>76,000</td>
<td>&gt;10,000</td>
<td>504</td>
</tr>
<tr>
<td>CDK5–p25</td>
<td>43,900</td>
<td>&gt;10,000</td>
<td>355</td>
</tr>
<tr>
<td>CDK9–cyclin T</td>
<td>NR</td>
<td>NR</td>
<td>57</td>
</tr>
<tr>
<td><strong>Kinase partition index</strong></td>
<td>0.99</td>
<td>0.96</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Lipophilicity (cLogP)</strong></td>
<td>2.3</td>
<td>2.7</td>
<td>5.5</td>
</tr>
<tr>
<td><strong>IC₅₀ against bone marrow mononuclear cells (nM)</strong></td>
<td>1700 ± 231</td>
<td>240 ± 43</td>
<td>230 ± 27</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>33–42 hours</td>
<td>26–27 hours</td>
<td>17–38 hours</td>
</tr>
<tr>
<td><strong>Tₘ₉₉</strong></td>
<td>1–5 hours</td>
<td>6–12 hours</td>
<td>4–6 hours</td>
</tr>
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</table>

cLogP, calculated Log of the partition coefficient.
<table>
<thead>
<tr>
<th>Study name/ID</th>
<th>Combination drug</th>
<th>Phase</th>
<th>Population</th>
<th>MTD/RP2D/dose</th>
<th>Reported Grade 3/4 AEs</th>
<th>Clinical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR+, HER2– breast cancer</strong></td>
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<tr>
<td>CLEE011X2106/ NCT01857193 (44)</td>
<td>Exemestane</td>
<td>ib</td>
<td>Postmenopausal women with ER+, HER2– ABC previously treated with letrozole or anastrozole (N=14 treated with ribociclib + exemestane)</td>
<td><strong>Evaluated dose</strong>&lt;br&gt;Ribociclib: 600 mg/day (3-weeks-on/1-week-off)&lt;br&gt;Exemestane: 25 mg/day</td>
<td>Neutropenia (71%), leukopenia (36%), lymphopenia (14%), ALT elevation (14%), AST elevation (14%), and anemia (14%)</td>
<td>2 unconfirmed PR, 4 SD</td>
</tr>
<tr>
<td>CLEE011X2107/ NCT01872260 (45, 47)</td>
<td>Letrozole</td>
<td>ib</td>
<td>Pretreated and treatment-naïve postmenopausal women with ER+, HER2– ABC (N=47 treated with ribociclib + letrozole)</td>
<td><strong>RP2D:</strong>&lt;br&gt;Ribociclib: 600 mg/day (3-weeks-on/1-week-off)&lt;br&gt;Letrozole: 2.5 mg/day</td>
<td>All patients:&lt;br&gt;Neutropenia and neutrophil count reduced (60%), ALT elevation (4%), AST elevation (4%), asthenia (2%), Constipation (2%), nausea (2%), UTI (2%), fatigue (1%)&lt;br&gt;<strong>First line (n=28):</strong>&lt;br&gt;Neutropenia and neutrophil count reduced (64%), ALT elevation (4%), AST elevation (4%), asthenia (4%), nausea (4%)&lt;br&gt;<strong>Previously treated (n=19):</strong>&lt;br&gt;Neutropenia and neutrophil count reduced (53%), ALT elevation (5%), AST elevation (5%), constipation (5%), fatigue (5%), UTI (5%)</td>
<td>First line (n=28):&lt;br&gt;2 CR, 11 PR, 3 unconfirmed PR, 5 SD, 4 NCRNPD, ORR 46%, DCR 89%, CBR 79%, Median PFS 25.3 months&lt;br&gt;Previously treated (n=19):&lt;br&gt;Median PFS 5.5 months</td>
</tr>
<tr>
<td>CLEE011X2108/ NCT02088684 (42)</td>
<td>Fulvestrant</td>
<td>ib</td>
<td>Postmenopausal women with HR+, HER2– ABC (N=28).</td>
<td><strong>Ribociclib:</strong> 600 mg/day (3-weeks-on/1-week-off) or 400 mg/day (continuous)&lt;br&gt;Fulvestrant: 500 mg on Days 1 and 15 of Cycle 1</td>
<td><strong>Ribociclib 600 mg/day (3-weeks-on/1-week-off; n=13):</strong>&lt;br&gt;Neutropenia (62%), fatigue (15%), leukocyte count reduced (15%), ALT elevation (8%),</td>
<td>Ribociclib 600 mg/day (3-weeks-on/1-week-off; n=13):&lt;br&gt;3 PR, 9 SD,</td>
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<tr>
<td>Study</td>
<td>Treatment</td>
<td>Study Design</td>
<td>Population</td>
<td>Treatment Schedule</td>
<td>Toxicity</td>
<td>Response</td>
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<tr>
<td>CLEE011X2106/ NCT01857193 (52)</td>
<td>Everolimus + exemestane</td>
<td>Ib</td>
<td>Postmenopausal women with ER+, HER2– ABC previously treated with letrozole or anastrozole (N=77 treated with ribociclib + everolimus + exemestane)</td>
<td>Ribociclib 400 mg/day (continuous; n=15): Neutropenia (33%), leukocyte count reduced (7%), ALT elevation (7%), AST elevation (7%)</td>
<td>Neutropenia (31%), neutrophil count reduced (18%), leukocyte count reduced (12%), anemia (7%), thrombocytopenia (7%), lymphopenia (7%), ALT elevation (5%), AST elevation (4%), and lymphocyte reduced (4%)</td>
<td>ORR 9%, DCR 73%, CBR 26%</td>
</tr>
<tr>
<td>CLEE011X2107/ NCT01872260 (51)</td>
<td>Alpelisib + letrozole</td>
<td>Ib</td>
<td>Pretreated and treatment-naïve postmenopausal women with ER+, HER2– ABC (N=46 treated with ribociclib + alpelisib + letrozole)</td>
<td>Ribociclib 300 mg/day (3-weeks-on/ 1-week-off)</td>
<td>Increased ALT (30%), increased AST (26%), hyperglycemia (17%), neutropenia (17%), fatigue (13%), reduced neutrophil count (4%), anemia (4%), thrombocytopenia (2%), vomiting (2%), and nausea (2%)</td>
<td>ORR 16%, DCR 70%, CBR 26%</td>
</tr>
<tr>
<td>CLEE011A2201/ NCT01919229 (43)</td>
<td>Letrozole</td>
<td>II</td>
<td>Postmenopausal women with HR+, HER2– Grade II/III, invasive, early breast cancer who have received no prior breast cancer treatment (N=14)</td>
<td>Ribociclib 600 mg/day or 400mg/day Letrozole: 2.5 mg/day</td>
<td>All AEs were mild/moderate with no Grade 3/4 AEs</td>
<td>Ribociclib 400 mg/day + letrozole: 96% decrease in Ki67 Ribociclib 600 mg/day + letrozole: 92% decrease in Ki67 Letrozole only: 69% decrease in Ki67</td>
</tr>
<tr>
<td>MONALEESA-2/ NCT01958021 (46)</td>
<td>Letrozole</td>
<td>III</td>
<td>Postmenopausal women with HR+, HER2– ABC who have received no prior treatment for advanced disease (N=668)</td>
<td>Ribociclib 600 mg/day (3-weeks-on/ 1-week-off) Letrozole: 2.5 mg/day</td>
<td>Ribociclib + letrozole arm vs placebo + letrozole arm: Neutropenia (50% vs 1%), leukopenia (21% vs 1%), hypertension (10% vs 11%), increased ALT (9% vs 1%), lymphopenia (7% vs 1%), and Ribociclib + letrozole arm vs placebo + letrozole arm: Median PFS NR (95% CI, 19.3–NR) vs 14.7 months (95% CI, 13.0–16.5); HR=0.56; P=3.29x10^-6</td>
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### NRAS- or BRAF-mutant melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Study Design</th>
<th>Patients</th>
<th>MTD</th>
<th>RP2D</th>
<th>Dose Schedule</th>
<th>Adverse Events</th>
<th>Clinical Response</th>
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</thead>
<tbody>
<tr>
<td>CMEK162X2114/ (62)</td>
<td>Binimetinib Ib/ll</td>
<td>Patients with advanced NRAS-mutant melanoma (N=22 received ribociclib + binimetinib)</td>
<td>Ribociclib: 200 mg/day (3-weeks-on/1-week-off)</td>
<td>Binimetinib: 45 mg BID</td>
<td>MTD:</td>
<td>CPK elevation (18%), neutropenia (9%), acneiform (4%), dermatitis (4%), and rash (4%)</td>
<td>7 PR, 11 SD, 33% had 20–30% tumor shrinkage, CBR 86%</td>
<td></td>
</tr>
<tr>
<td>CLEE011X2105/ (61)</td>
<td>Encorafenib Ib/ll</td>
<td>Patients with advanced BRAFV600E-mutant melanoma (N=28 received ribociclib + encorafenib)</td>
<td>MTD: ongoing</td>
<td>RP2D: ongoing</td>
<td>Hand–foot syndrome (11%), rash (4%), and myalgia (4%)</td>
<td>2 confirmed PRs, 3 unconfirmed PRs, 1 SD, 1 SD &gt;9 cycles</td>
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</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; NCRNPD, not complete response nor progressive disease; NR, not reached; ORR, overall response rate; UTI, urinary tract infection.
Figure legends

Figure 1. The role of cyclin–CDK complexes and the cyclin D–CDK4/6–p16–Rb pathway in the cell cycle

The cell cycle is regulated by cyclins and checkpoints, with different cyclins (and cyclin–CDK combinations) and checkpoints acting at phase transition of the cell cycle. At the G1–S cell cycle checkpoint, multiple mitogenic pathways including ER and PI3K/AKT/mTOR promote the synthesis of cyclin D, which associates with and activates CDK4/6. Activated CDK4/6 phosphorylates the Rb protein to disrupt its sequestering interaction with E2F, releasing its transcription effect and allowing the expression of genes necessary for cell cycle progression, including cyclin E. Cyclin E associates with CDK2, which further phosphorylates Rb, resulting in progression of the cell cycle past the restriction point and irreversible S phase entry. Additional cyclin–CDK complexes act at further cell cycle checkpoints; cyclin A–CDK2 enables the S–G2 transition, and cyclin A–CDK1 and cyclin B–CDK1 facilitate the onset and progression of mitosis, respectively (82). Selective inhibitors of CDK4/6, such as ribociclib, act directly on the cyclin D–CDK4/6–p16–Rb pathway to block cell cycle progression. The pathway may also be impacted by inhibitors of other pathways acting upstream of CDK4/6, providing a rationale for dual inhibition.

CDK, cyclin-dependent kinase; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; IGF1R, insulin-like growth factor 1 receptor; MAPK, mitogen-activated protein kinase; RTK, receptor tyrosine kinase.
References


Figure 1:

Aromatase inhibitors (e.g., letrozole, anastrozole, exemestane)→ Estradiol → RTK (e.g., IGFR-1) → PI3K (e.g., alpelisib, pictilisib, buparlisib, taselisib) → AKT → ER → mTOR → mTOR inhibitors (e.g., everolimus) → PI3K inhibitors (e.g., alpelisib, pictilisib, buparlisib, taselisib) → CDK4/6 inhibitors (e.g., ribociclib, palbociclib, abemaciclib)

ER modulators (e.g., tamoxifen, fulvestrant) → CDK1 → Cyclin B → CDK1

Cyclin A → CDK1 → Cyclin A → CDK2

Cyclin E → CDK2 → E2F → Rb

Restriction point

RTK (e.g., IGFR-1)

ER

mTOR

mTOR inhibitors (e.g., everolimus)

PI3K inhibitors (e.g., alpelisib, pictilisib, buparlisib, taselisib)

CDK4/6 inhibitors (e.g., ribociclib, palbociclib, abemaciclib)
Clinical Cancer Research

Ribociclib (LEE011): mechanism of action and clinical impact of this selective cyclin-dependent kinase 4/6 inhibitor in various solid tumors

Debu Tripathy, Aditya Bardia and William R. Sellers

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