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An evaluation of palbociclib as a breast cancer treatment option: a current update

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Abstract

Introduction: Patients with hormone receptor-positive/HER2-negative (HR+/HER2−) metastatic breast cancer have benefitted from treatment with palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor capable of selectively targeting mechanisms of cell cycle progression that contribute to tumor cell proliferation. Palbociclib use in this setting demonstrates improved progression-free survival when given in combination with aromatase inhibitors or fulvestrant.

Areas covered: The authors describe the current state of research surrounding palbociclib use in breast cancer, present evidence supporting a role for palbociclib in additional subtypes of metastatic breast cancer such as HER2-positive (HER2+) and triple-negative, report ongoing clinical trials aimed at expanding the scope of use for palbociclib, and discuss expected clinical results that will better inform decisions on including palbociclib as a part of breast cancer treatment strategies.

Expert opinion: Preclinical and clinical studies have shown promising evidence for palbociclib use in metastatic HER2+ and androgen receptor-expressing triple-negative breast cancer but mixed results in the adjuvant/neoadjuvant setting, where differences may only be detectable in high-risk disease. Palbociclib combinations may constitute viable replacements for chemotherapy in the neoadjuvant setting as part of de-escalation strategies. Investigation into synergy of palbociclib

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with immunotherapies is also ongoing based on non-canonical effects of CDK4/6 inhibition on the tumor immune microenvironment.

1. Introduction

Palbociclib is an orally available cyclin-dependent kinase (CDK) 4/6-specific inhibitor. Along with two other approved drugs of this class, ribociclib and abemaciclib, the CDK4/6 inhibitors have transformed the treatment of metastatic hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2−) breast cancer. Palbociclib is indicated for use as first-line therapy for metastatic HR+/HER2− breast cancer with the non-steroidal aromatase inhibitor letrozole or as second-line therapy with the selective estrogen receptor degrader fulvestrant [1]. Additional clinical trials have commenced investigating palbociclib use in HER2-positive (HER2+) and triple-negative receptor subtypes of metastatic breast cancer, in HR+/HER2− metastatic breast cancer resistant to CDK4/6 inhibitors, as adjuvant or neoadjuvant intervention in non-metastatic breast cancer, and in ductal carcinoma *in situ* (DCIS). In this review, we give a background of the biology of CDK4/6 inhibitors, explore clinical developments of palbociclib in HER2+ and triple-negative breast cancers, discuss palbociclib use in the adjuvant and neoadjuvant settings, and examine the clinical data regarding palbociclib and endocrine therapy use as an alternative to cytotoxic chemotherapy. Finally, we provide our expert opinion on the current and future state of palbociclib use in breast cancer.

1.1 Cyclin D-CDK4/6 activity at the G1/S checkpoint

During the early G1 phase of the cell cycle, mitogenic signaling converges upon the induction of expression of D-type cyclins, which assemble with CDK4 or CDK6 to phosphorylate retinoblastoma protein (RB) and its related family members [2–9]. The role of RB is to repress activity of the E2F family of transcription factors that would otherwise drive transcription of cell cycle-progression genes [10]. Active cyclin D-CDK4/6 complexes phosphorylate and inactivate RB, which permits E2F-driven transcription of cyclin E and forms a feed-forward loop as cyclin E joins with CDK2 to further phosphorylate and inactivate RB [5]. Subsequently, remaining inhibitory pressure from RB is mitigated and the full suite of E2F-regulated genes is transcribed to produce the proteins necessary to carry out DNA synthesis and progress to later stages of the cell cycle [11,12]. Cyclin-CDK complexes are regulated by endogenous inhibitory proteins and post-translational modification [13]. INK4 family proteins such as the prototypical $p16^{INK4A}$ directly bind CDK4 to inhibit cyclin D-CDK4 activity [14]. Cyclin D-CDK4 is also regulated by cyclin H-CDK7, which critically activates the complex by phosphorylation of CDK4 at the T172 residue [15]. $p21^{CIP1}$ and $p27^{KIP1}$ regulate cyclin E-CDK2 complexes, and sequestration of these inhibitors by cyclin D-CDK4/6 enables further phosphorylation of RB and RB-like family members at the G1/S checkpoint [14] (Figure 1).

1.2 Targeting CDK4/6 in breast cancer

Cyclin-dependent kinases present ideal targets for anti-cancer therapy as several cancers are growth-dependent on their activity. Although they play an integral role in cell cycle progression, CDKs are remarkably dispensable in many normal cell types. Systematic knock

out of CDK loci in mouse models revealed that the interphase CDKs (CDK2/4/6) are functionally redundant in most adult tissues, and their deficiency causes defects only in specialized cell types such as hematopoietic precursors [16]. However, cancer cells may be addicted to growth through CDK4/6. Work using the MMTV-Erbb2 mouse model of mammary carcinoma led to the discovery that intact CDK4 expression was required for tumorigenesis, though its ablation did not affect normal mammary gland development [17].

Given that cell cycle proteins serve a critical role in maintaining balance between proliferation and quiescence, it is unsurprising that aberrant cyclin D-CDK4/6 activity leads to dysregulated growth in a broad set of tumor types. In normal estrogen-responsive cells, active estrogen receptor (ER) can bind the *CCND1* promoter to cause transcription of cyclin D and mitogenesis through the cyclin D-CDK4/6 axis. Cyclin D can also directly bind ER and induce ER activity [18–20]. This pathway is often hijacked in breast cancer by *CCND1* amplification or cyclin D overexpression, aberrations that are associated with more aggressive disease, relapse, recurrence, and metastasis [21,22]. Palbociclib is a selective inhibitor of CDK4 and CDK6 developed to inhibit phosphorylation of RB by active CDK4/6 to induce G1 arrest in tumor cells [23] (Figure 1). An *in vitro* breast cancer cell line screen revealed that luminal-subtype cell lines are more likely to be sensitive to palbociclib than other subtypes, and that there is synergism when palbociclib is combined with tamoxifen [24]. RB pathway expression is typically intact in luminal-subtype breast cancers, which are characterized by estrogen and progesterone hormone receptor expression and HER2 non-amplification [25]. This has provided rationale for targeting HR+/HER2− breast cancer with CDK4/6 inhibition. Non-luminal tumors, such as those that are basal-like, are more likely to be resistant to palbociclib due to the increased frequency of lost RB protein expression in this subtype [25]. However, some basal-like breast cancer cell lines retain RB expression and are indeed sensitive to CDK4/6 inhibition *in vitro*, which lends to the complexity of predicting sensitivity or resistance to palbociclib or other CDK4/6 inhibitors [24–27].

1.3 Clinical development of palbociclib

Palbociclib is the first orally available CDK4/6-specific inhibitor approved by the FDA. Phase I trials demonstrated that the dose-limiting toxicities were neutropenia and thrombocytopenia and that treatment was tolerable in a schedule of three weeks of 125 mg daily followed by one week off [28,29]. Subsequently, the randomized, open-label phase II PALOMA-1/TRIO-18 clinical trial demonstrated that palbociclib in combination with letrozole was superior to letrozole alone in postmenopausal women with previously untreated HR+/HER2− metastatic breast cancer, leading to its accelerated approval by the FDA in 2015 [30]. A larger randomized phase III study, PALOMA-2, verified the results of the prior trial and indicated that median progression-free survival in the palbociclib plus letrozole group is increased to 24.8 months versus 14.5 months in the placebo plus letrozole group (hazard ratio 0.58, $p<0.001$), which was the primary study endpoint [31].

Palbociclib has also been approved for use in the second-line setting with fulvestrant based on the results of a second phase III study, PALOMA-3 [32]. Pre- and post-menopausal women with metastatic HR+/HER2− breast cancer were eligible to be enrolled in the study if their disease had progressed despite treatment with a prior line of endocrine therapy.

Median progression-free survival was increased in the palbociclib plus fulvestrant group to 9.5 months versus 4.6 months in the placebo plus fulvestrant group (hazard ratio 0.46, $p<0.0001$) [33]. Overall survival (OS) trended higher in the palbociclib plus fulvestrant group (34.9 months versus 28.0 months; $p<0.09$) but did not reach a statistically significant difference, perhaps due to the study becoming less powered for OS analysis after 16% of patients in the placebo-fulvestrant group received treatment with a CDK4/6 inhibitor following disease progression [34].

2. Expansion of use and future potential

2.1 Use in HER2-positive breast cancer

While palbociclib is not FDA-approved for use in HER2+ breast cancer, promising preclinical evidence exists of a role for CDK4/6 inhibition in this subtype. HER2+ breast cancers have been shown to depend on intracellular signaling via cyclin D-CDK4, which lies downstream from the activated HER2 receptor [35,36] (Figure 1). Synergy of CDK4/6 inhibition and anti-HER2 therapies was demonstrated in HER2+ breast cancer cell lines during the preclinical development of palbociclib [24]. An additional study using HER2+ cell lines found that sensitivity to lapatinib is augmented by palbociclib and that both drugs decrease DNA synthesis through disruption of E2F-target genes [37]. Unfortunately, a major shortcoming of targeted therapy in metastatic HER2+ breast cancer is the eventual development of therapeutic resistance. Evidence of a role for CDK4/6 inhibition in overcoming anti-HER2 therapy resistance was shown using another FDA-approved CDK4/6 inhibitor, abemaciclib. In a mouse model of inducible HER2-driven breast cancer, combined CDK4/6 inhibitor treatment and HER2 blockade acted synergistically on primary tumors growing *in vivo*, and intervention with abemaciclib at the outset of HER2 withdrawal significantly prolonged the time until tumor recurrence [38].

Clinical investigation of palbociclib in HER2+ breast cancer also includes intervention as adjuvant and neoadjuvant therapy in early breast cancer (Table 1). Only one ongoing clinical study has published interim results. The NA-PHER2 (NCT02530424) open-label phase II trial is investigating the combination of neoadjuvant trastuzumab, pertuzumab, palbociclib, and fulvestrant in women with non-metastatic invasive ER+/HER2+ breast cancer. Twenty-two patients were assessed at the interim analysis and their tumors were found to exhibit decreased expression of the proliferation marker Ki67 at the time of surgery compared to the pre-therapy baseline. The treatment regimen was deemed tolerable, as the most frequent grade 3 adverse events were neutropenia (29%) and diarrhea (14%) and no grade 4 events were recorded [39]. Other ongoing clinical trials involving palbociclib use in HER2+ breast cancer include PATRICIA II (NCT02448420), T-DM1 (NCT03530696), and PATINA/AFT-38 (NCT02947685).

2.2 Use in triple-negative breast cancer

Palbociclib use is also currently being investigated in the treatment of triple-negative breast cancer (TNBC), which is defined by the lack of expression of estrogen, progesterone, and HER2 receptors. TNBC is an aggressive subtype that is associated with a poor prognosis owing to several factors such as its increased tendency to metastasize and limited duration of

response to chemotherapy in the metastatic setting [40–42]. TNBC is often resistant to CDK4/6 inhibition [24], possibly due to the increased proportion of tumors that lack functional RB compared to other breast cancer subtypes [25]. Functional RB is a requirement for sensitivity to CDK4/6 inhibitors, though it does not necessarily rule in sensitivity [43] (Figure 1).

A phase II study investigated palbociclib monotherapy for patients with metastatic breast cancer that had progressed on prior lines of therapy and included four patients with RB-positive TNBC; however, these four patients rapidly progressed on treatment [44]. Elsewhere, a phase I study demonstrated feasibility of alternating paclitaxel and palbociclib in patients with advanced breast cancer and included nine patients with TNBC. Of the nine, one patient's disease was stable for over six months, though this response may have been from paclitaxel alone [45].

One promising area for use of palbociclib in TNBC is in the luminal androgen receptor (LAR) subtype, which expresses the androgen receptor (AR) and has been shown in cell line models to be sensitive both to bicalutamide, an AR antagonist, and to palbociclib [46,47]. A phase II clinical trial demonstrated that bicalutamide is safe and may be effective in patients with AR-positive (AR+) TNBC [40]. Subsequently, it was hypothesized that the addition of palbociclib will increase the efficacy of bicalutamide in patients with metastatic AR+ TNBC (Figure 1), and this is being investigated in an ongoing clinical trial (NCT02605486) [48] (Table 1).

2.3 Adjuvant and neoadjuvant use in HR+/HER2− breast cancer

Considerable interest has developed in expanding the use of palbociclib to earlier stages of HR+/HER2− breast cancer. Neoadjuvant treatment is used in cancer to improve surgical options, evaluate response to therapy, tailor individualized treatment approaches based on surgical tissue analyses, and obtain long-term disease-free survival [49]. Neoadjuvant palbociclib combined with endocrine therapies or compared to chemotherapy is being investigated in a number of clinical trials (Table 2).

Common primary outcome measures in the ongoing neoadjuvant clinical trials of palbociclib include histological evaluation of tumor proliferation markers such as Ki67 or the determination of the rate of pathological complete response (pCR), or residual cancer burden (RCB) at the time of surgery. For example, NeoPAL is a phase II clinical trial that evaluated the efficacy and safety of 20 weeks of chemotherapy or letrozole-palbociclib as neoadjuvant therapy in patients with HER2-negative stage II-IIIA invasive breast carcinoma who were not candidates for breast conserving surgery. Although the rate of pCR was low for both experimental arms, both groups demonstrated equivalent decreases in Ki67 levels. Additionally, patients in the letrozole-palbociclib arm experienced fewer serious adverse events than those in the chemotherapy arm, which provides promising evidence for replacing chemotherapy with targeted therapies in the future [50]. The PALLET trial is a phase II study that evaluated 14 weeks of combination palbociclib plus letrozole versus letrozole alone as neoadjuvant therapy in postmenopausal women with HR+ breast cancer. While the clinical response was not different between the two groups, the combination of palbociclib and letrozole significantly enhanced suppression of Ki67 in primary tumors [51].

A benefit of neoadjuvant intervention is that it facilitates the discovery and evaluation of biomarkers that can be correlated with response to treatment, vulnerability to additional therapies, or survival benefit. The phase II NeoPalAna trial evaluated the effects of neoadjuvant palbociclib and anastrozole on tumor cell proliferation and found that palbociclib enhanced cell cycle control, measured by reduced Ki67, regardless of luminal subtype [52]. Subsequent analysis from this trial found that drug-induced suppression of thymidine kinase 1, measured in peripheral serum, correlated with decreased Ki67 levels in these patients [53]. The phase II preoperative-palbociclib (POP) trial examined the effects of 14 days of preoperative palbociclib monotherapy in patients with early breast cancer. Tissue analyses from this trial found that short-term palbociclib treatment decreased protein levels of Ki67 in tumors compared to the no-treatment group, and decreased cyclin E2 mRNA expression correlated with decreased Ki67 levels [54].

While adjuvant endocrine therapy reduces the risk of breast cancer recurrence and death [55], disease recurrence after surgery remains a major issue in the treatment of breast cancer [56]. Several clinical trials examining the addition of adjuvant palbociclib to standard endocrine therapy are underway, with the unifying hypothesis that adding palbociclib to the standard-of-care treatments will prolong invasive disease-free survival time (Table 2). The phase III PENELOPE-B trial (NCT01864746), which is a post-neoadjuvant placebo-controlled study comparing palbociclib plus endocrine therapy to endocrine therapy alone, seeks to define a role for adjuvant palbociclib in the treatment of patients with residual disease after having received neoadjuvant chemotherapy. The phase III POLAR study (NCT03820830), compares palbociclib and endocrine therapy to endocrine therapy alone for the treatment of locoregional recurrent breast cancer. The phase III PALLAS study (NCT02513394), was designed to evaluate the addition of two years of palbociclib to standard adjuvant endocrine therapy in prolonging invasive disease-free survival time for patients with stage II-III HR+/HER2− early-stage breast cancer who received definitive surgery; however, at the interim analysis this trial was deemed unlikely to show a significant improvement and adjuvant palbociclib treatment was discontinued [57].

2.4 Palbociclib-based regimens compared to chemotherapy

The prospect of combining CDK4/6 inhibitors with cytotoxic chemotherapy remains challenging. DNA synthesis-targeting or mitosis-targeting agents are mechanistically at odds with CDK4/6 inhibitors, which cause cell cycle stasis at the G1/S checkpoint and prevent entry into the DNA synthesis and mitosis phases. Alternatively, a combination of palbociclib and additional agents could be administered instead of chemotherapy. In women with HR+/HER2− early breast cancer randomized to receive neoadjuvant palbociclib plus letrozole or chemotherapy, the palbociclib-letrozole combination caused fewer adverse effects than chemotherapy, though achievement of pathological complete response was poor in both groups (3.8% in the palbociclib-letrozole group versus 5.9% in the chemotherapy group) [50]. In premenopausal women with HR+/HER2− metastatic breast cancer whose disease had progressed after tamoxifen therapy, treatment with palbociclib plus exemestane with ovarian suppression resulted in an increased median progression-free survival of 20.1 months in the palbociclib plus exemestane group versus 14.4 months in the capecitabine group (hazard ratio 0.659, p=0.0235) [58]. In the PEARL study, women whose metastatic

disease had progressed on non-steroidal aromatase inhibitors were randomized to receive capecitabine or one of two treatment regimens: palbociclib plus exemestane (cohort 1) or palbociclib plus fulvestrant (cohort 2). Median progression-free survival was not significantly different between treatment groups in cohort 2 (n=305): 7.5 months in the palbociclib plus fulvestrant group versus 10 months in the capecitabine group (hazard ratio 1.09, p=0.537). The median progression free survival was also not different comparing endocrine therapy plus palbociclib with capecitabine in patients with pre-treatment *ESR1* wild type ctDNA. However, stratification by luminal subtype revealed that palbociclib plus fulvestrant is inferior to capecitabine in patients with non-luminal tumors, with median progression-free survival of 2.7 months in the palbociclib plus fulvestrant group versus 13.7 months in the capecitabine group (hazard ratio 3.19, p=0.013) [59]. Overall, the decision to employ palbociclib plus endocrine therapy or chemotherapy in treatment of HR+/HER2− disease remains complex. A recent meta-analysis has shown that no chemotherapy regimen is superior to palbociclib plus letrozole for progression-free survival in the HR+/HER2− metastatic setting [60]; therefore, when weighing the use of chemotherapy or CDK4/6 inhibitor plus endocrine therapy it is crucial to consider the receptor and molecular subtypes of the tumor, the previous lines of therapy the patient has received, the patient's tolerance for the toxicities of each therapy, and the financial impact of an additional targeted therapy.

3. Conclusion

The role of CDK4/6 inhibitors as first-line treatment for patients with metastatic HR+/HER2− breast cancer is firmly established. Palbociclib is under investigation in earlier clinical stages and other subtypes of breast cancer, and the combination of palbociclib with HER2-targeted therapies or with androgen receptor antagonists remains under evaluation. Combination palbociclib and endocrine therapy may provide an alternative to chemotherapy in early or advanced breast cancer, particularly in luminal subtype tumors, though strategies for appropriate patient selection must first be optimized. Investigation in the neoadjuvant and adjuvant settings is also ongoing. While a blanket-use scenario for palbociclib as a part of adjuvant therapy seems unlikely given the anticipated negative results of the PALLAS study, there may yet be subgroups that could benefit from treatment. Patient selection by less-than-optimal response to neoadjuvant therapy and correlative biomarker analyses of patient subgroups will inform future preclinical and clinical research alike.

4. Expert Opinion

Palbociclib is an effective, safe, and well-tolerated treatment for patients with HR+/HER2− metastatic breast cancer. Current clinical research is exploring the potential expansion of palbociclib use into new subtypes of breast cancer and earlier clinical stages, as well as in different sequences with existing approved therapies or in combination with experimental compounds. Anti-estrogen endocrine therapies for patients with metastatic HR+/HER2− breast cancer synergize with CDK4/6 inhibition owing to estrogen signaling biology (Figure 1). In HER2+ breast cancer, anti-HER2 therapy and CDK4/6 inhibition were shown to synergize in preclinical models, providing rationale for combining palbociclib with HER2-directed therapies such as anti-HER2 antibodies, receptor tyrosine kinase inhibitors and antibody-drug conjugates. In TNBC, combination treatment with enzalutamide provides

hope for targeted therapy against the LAR subtype, which is AR+; however, cytotoxic chemotherapy and immune therapy rather than palbociclib remain the mainstay of treatment in metastatic TNBC. Interestingly, the novel intravenous CDK4/6 inhibitor trilaciclib is under evaluation in combination with cytotoxic chemotherapy for its potential effects in preventing chemotherapy-induced myelosuppression and its potential to alter the tumor-immune microenvironment, in addition to a potential impact on response rates and survival [61].

A significant portion of patients will not benefit from the addition of palbociclib in first-line treatment of metastatic HR+/HER2− breast cancer but will endure its side effects, frequent follow-up requirements and elevated costs. Should all patients receive this CDK4/6 inhibitor in the first line? The answer may be provided by the SONIA study (NCT03425838), which is designed to evaluate if first-line treatment with a CDK4/6 inhibitor and endocrine therapy is superior to first-line treatment with endocrine therapy alone, followed by a CDK4/6 inhibitor in the second line. Also, a palbociclib monotherapy arm was not evaluated in the main phase II/III trials leading to its approval for patients with metastatic HR+/HER2− breast cancer. Palbociclib monotherapy as treatment of metastatic HR+/HER2− breast cancer was tested in the TREnd trial, which compared palbociclib alone to palbociclib given with the same endocrine therapy that was received prior to disease progression, with both arms being active in terms of clinical benefit ratio (54-60%), and a non-statistically significant progression free survival of 10.8 months in the combination group, compared to 6.5 months in the palbociclib group (Hazard Ratio 0.69; 95% CI: 0.4-1.1, exploratory p=0.12) [62]. In an exploratory analysis, a progression-free survival advantage in TREnd was identified in patients receiving combination palbociclib and endocrine therapy who had a history of receiving prior endocrine therapy for 6 months of greater (hazard ratio 0.53, p=0.02) [62]. Such a finding adds to the potential role for palbociclib in reversing acquired endocrine therapy resistance, a hypothesis which has also been discussed in a recent case series of 5 women with HR+/HER2− metastatic breast cancer who received palbociclib plus fulvestrant as second- or third-line therapy after disease progression on prior endocrine therapy [63].

In the adjuvant setting, palbociclib added to endocrine therapy in the PALLAS trial was deemed unlikely at interim analysis to show a significant improvement versus adjuvant endocrine therapy alone. A few weeks later, the interim results of the phase III MonarchE (NCT03155997) were reported, indicating that abemaciclib used in combination with adjuvant endocrine therapy had met the primary endpoint of increased invasive disease-free survival [64,65]. The differences in the selected population for these studies may hold the explanation for the discrepant results. PALLAS enrolled patients with stage II-III disease, while MonarchE selected a higher risk population based on tumor size, number of positive lymph nodes in the axilla and higher Ki67 at baseline. The full reports of these two studies are eagerly awaited. Additionally, the post-neoadjuvant phase III PENELOPE-B trial (NCT01864746) is also selecting a high-risk population for adjuvant palbociclib by requiring the presence of residual disease after neoadjuvant chemotherapy and surgery. Unfortunately, patient selection for therapy with CDK4/6 inhibitors cannot be based on surrogate biomarkers of benefit since none beyond ER+ has been validated to-date.

Finally, considerable interest has been generated in understanding the non-canonical effects of CDK4/6 inhibitors. The full mechanistic understanding of CDK4/6 inhibition in cancer is just beginning, as active cyclin D-CDK4/6 may phosphorylate over 300 targets in addition to RB [66]. Among other effects, CDK4/6 inhibitor therapies can alter immune activity within the tumor microenvironment, which creates an opportunity for these drugs to be combined with immune-modulatory therapies [67,68]. Based on promising preclinical evidence (reviewed in [69]), palbociclib is being tested clinically in combination with endocrine therapy and several PD-1 and PD-L1 immune checkpoint inhibitors (Table 3). Ultimately, palbociclib use in breast cancer is firmly established in the metastatic HR+/HER2− setting, and the large number of ongoing clinical trials involving palbociclib use in other types and stages of breast cancer will provide impactful guidance on the expansion of its use.

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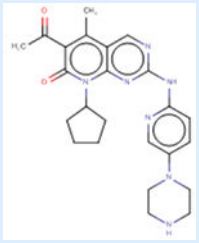
Drug Summary Box

Drug name	Palbociclib
Phase	Launched
Indication	Breast Cancer
Pharmacology description	Cyclin-dependent kinase 4 inhibitor Cyclin-dependent kinase 6 inhibitor
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	PALOMA-1/TRIO-18 [NCT00721409][30] PALOMA-2 [NCT01740427][31] PALOMA-3 [NCT01942135][32]

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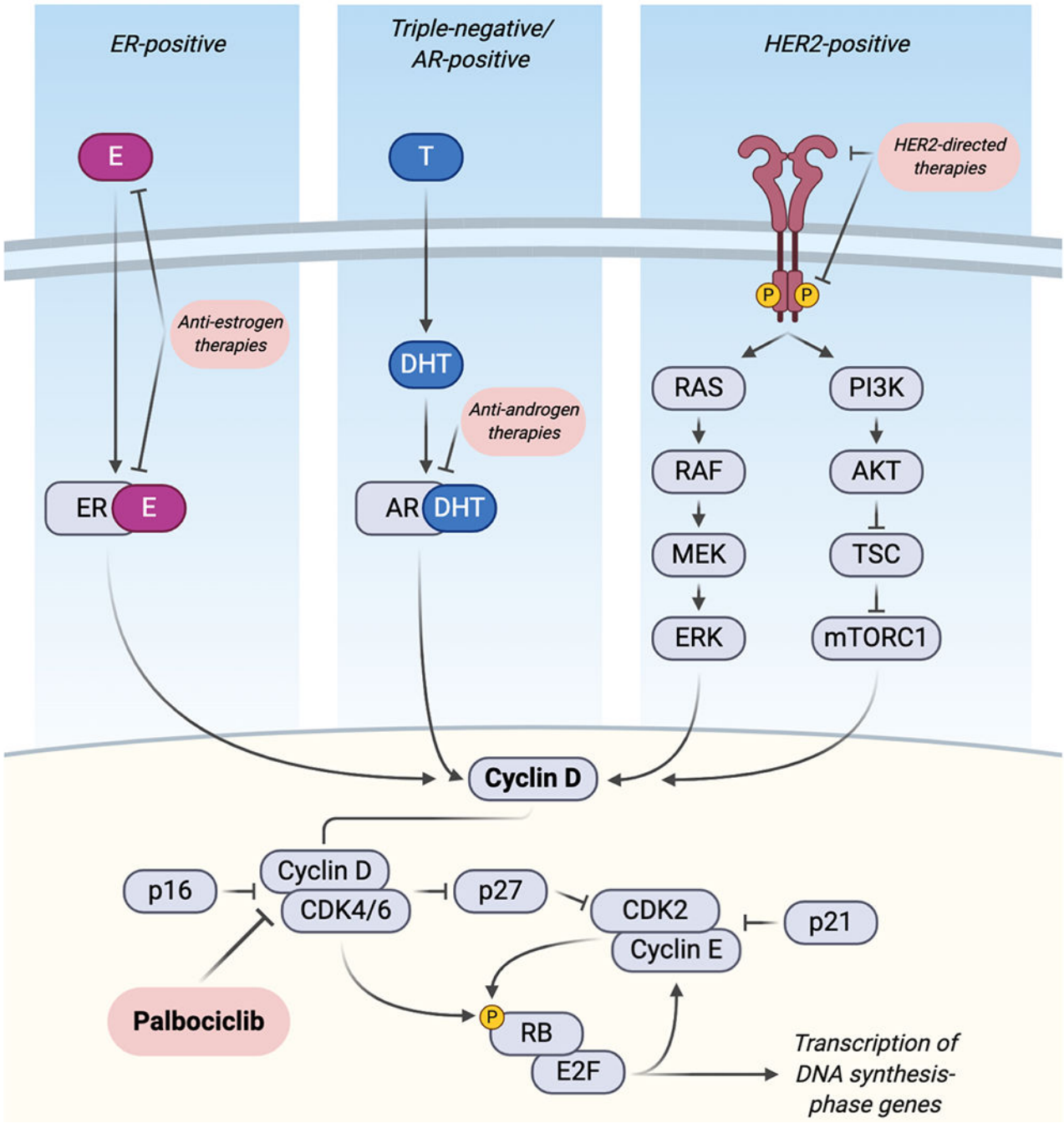

Figure 1:

Mitogenic signal transduction pathways converge on cyclin D-CDK4/6 activity across multiple breast cancer subtypes and can be inhibited by targeted therapies and palbociclib. Left panel: estrogen receptor (ER) interaction with estradiol (E) in ER-positive breast cancers. Middle panel: testosterone (T) and dihydroxytestosterone (DHT) activity with the androgen receptor (AR) in AR-positive triple negative breast cancer. Right panel: HER2-signaling stimulates the MAP kinase and PI3K pathways, which transduce extracellular growth factor signals. Downstream, endogenous cell cycle inhibitors in the p16, p21, and

p27 protein families negatively regulate CDK activity. Palbociclib inhibits cyclin D-CDK4/6-mediated phosphorylation of the retinoblastoma protein (RB) to prevent E2F-driven transcription of genes that commit the cell to DNA replication and cell division. This figure was created using BioRender.

Table 1:

Active clinical trials in metastatic breast cancer expanding the use of palbociclib to HER2-positive or triple-negative subtypes.

Name/Identifier	Phase	Subtype	Setting	Interventions	Primary Outcome Measures
NCT02530424 NA-PHER2	II	HER2+	NA	Palbociclib, trastuzumab, pertuzumab and fulvestrant	Serial measures of Ki67 Serial measures of apoptosis
NCT02907918 PALTAN	II	HER2+	NA	Palbociclib, letrozole, trastuzumab and goserelin if pre-menopausal	Rate of pCR
NCT03644186 TOUCH	II	HER2+	NA	Palbociclib, letrozole, trastuzumab and pertuzumab vs. paclitaxel, trastuzumab and pertuzumab	Rate of pCR
NCT01976169	I	HER2+	M	Palbociclib and T-DM1	Maximum tolerated dose Dose-limiting toxicities
NCT03054363	I/II	HER2+	M	Palbociclib, letrozole and tucatinib	Adverse events at 2.5 years Progression-free survival at 2.5 years
NCT03304080	I/II	HER2+	M	Palbociclib, anastrozole, trastuzumab and pertuzumab	Maximum tolerated dose Dose-limiting toxicities Clinical benefit rate
NCT03709082	I/II	HER2+	M	Palbociclib, letrozole and T-DM1	Rate of overall response at 5 years
NCT02448420 PATRICIA II	II	HER2+	M	Palbociclib and trastuzumab ± endocrine therapy Palbociclib, trastuzumab, and endocrine therapy vs. trastuzumab, T-DM1, and chemotherapy	PFS
NCT03530696 T-DM1	II	HER2+	M	T-DM1 ± palbociclib	PFS
NCT02947685 PATINA	III	HER2+	M	Trastuzumab, pertuzumab and endocrine therapy ± palbociclib	PFS
NCT02605486	I/II	TN (AR+)	M	Palbociclib and bicalutamide	Recommended phase II dose PFS

Abbreviations: (AR+) Androgen receptor-positive; (HER2+) HER2-positive; (M) Metastatic; (NA) Neoadjuvant; (pCR) Pathological complete response; (PFS) Progression-free survival; (T-DM1) Trastuzumab emtansine; (TN) Triple-negative

Table 2:

Active clinical trials expanding palbociclib use in the adjuvant or neoadjuvant settings of HR+/HER2− breast cancer.

Name/Identifier	Phase	Setting	Interventions	Primary Outcome Measures
NCT04130152	I	NA	Palbociclib, letrozole and goserelin	Rate of cell cycle arrest at 4 weeks post-surgery
NCT03774472	I/II	NA	Palbociclib, letrozole and hydroxychloroquine	Incidence of adverse events at 30 days Change in breast tumor proliferation index (Ki67) Change in autophagy, senescence, and cell cycle markers
NCT01723774 NeoPalAna	II	NA	Palbociclib, anastrozole and goserelin	Rate of cell cycle arrest in PI3K-mutant tumors or endocrine-resistant tumors
NCT02008734 POP (Completed)	II	NA	Palbociclib vs. no intervention	Change in Ki67 at time of surgery
NCT02296801 PALLET	II	NA	Letrozole Letrozole then palbociclib and letrozole Palbociclib then palbociclib and letrozole Palbociclib and letrozole	Change in Ki67 at 14 weeks Rate of cCR
NCT02400567 NeoPal	II	NA	Chemotherapy Palbociclib and letrozole	Number of patients with no residual cancer burden
NCT02592083 PREDIX LumA	II	NA	Endocrine therapy ± palbociclib	Rate of clinical and radiological response after 16 weeks of preoperative treatment
NCT02603679 PREDIX LumB	II	NA	Paclitaxel Palbociclib and tamoxifen Palbociclib and aromatase inhibitor Palbociclib, aromatase inhibitor and goserelin	Rate of radiological objective response rate after completion of 12 weeks of preoperative treatment
NCT02624973 PETREMAC	II	NA/A	Neoadjuvant palbociclib and endocrine therapy followed by adjuvant palbociclib	Evaluate predictive and prognostic value of mutations in 300 cancer-related genes
NCT02764541 PELOPS	II	NA	Tamoxifen Letrozole then tamoxifen Tamoxifen then palbociclib and tamoxifen Letrozole then palbociclib and tamoxifen	Anti-proliferative response rate after 2 years Rate of pCR after 2 years
NCT03065621 NeoRHEA	II	NA	Palbociclib and endocrine therapy	Identify biomarkers of resistance
NCT03535506	II	NA	Palbociclib vs. no intervention	Feasibility and comparison of histological findings between groups

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Name/Identifier	Phase	Setting	Interventions	Primary Outcome Measures
NCT03573648 ImmunoADAPT	II	NA	Avelumab and tamoxifen ± palbociclib	Rate of cCR at 2 years
NCT03628066 NSABP FB-13	II	NA	Palbociclib, letrozole, goserelin and Oncotype DX Breast Recurrence Score	Complete cell cycle arrest at 6 weeks
NCT03819010 DxCARTES (Completed)	II	NA	Palbociclib and letrozole	Difference in Oncotype DX Breast Recurrence Score® at the time of surgery between groups with high or low socres at the time of diagnosis
NCT04075604 CheckMate 7A8	II	NA	Palbociclib, anastrozole and nivolumab Palbociclib and anastrozole then palbociclib, anastrozole and nivolumab Palbociclib and anastrozole	Dose-limiting toxicity Residual cancer burden rate at 20 weeks
NCT03447132 SAFIA	III	NA	Palbociclib and fulvestrant vs. placebo and fulvestrant	Rate of pCR
NCT03969121	III	NA	Palbociclib and endocrine therapy vs. placebo and endocrine therapy	Change in Pre-operative Endocrine Prognostic Index score Change in EndoPredict™ EPclin Score
NCT02040857	II	A	Palbociclib and endocrine therapy	Treatment discontinuation rate
NCT03609047 Appalaches	II	A	Palbociclib Chemotherapy	Distant recurrence-free survival rate at 5 years
NCT04247633 HIPEx	II	A	Palbociclib and endocrine therapy	3-year event-free survival
NCT01864746 PENELOPE-B	III	A	Palbociclib vs. placebo	Invasive disease-free survival time
NCT02513394 PALLAS	III	A	Palbociclib and endocrine therapy vs. endocrine therapy alone	Invasive disease-free survival time
NCT03820830 POLAR	III	A	Palbociclib and endocrine therapy vs. endocrine therapy alone	Invasive disease-free survival time

Abbreviations: (A) Adjuvant; (cCR) Clinical complete response; (HR+/HER2−) Hormone receptor-positive/HER2-negative; (NA) Neoadjuvant; (pCR) Pathological complete response

Table 3:

Active clinical trials exploring palbociclib use with checkpoint inhibitors.

Name/Identifier	Phase	Setting	Interventions	Primary Outcome Measures
NCT03573648 ImmunoADAPT	II	NA	Palbociclib, tamoxifen and avelumab Tamoxifen and avelumab only	Rate of cCR at 2 years Safety and tolerability
NCT04075604 CheckMate7A8	II	NA	Palbociclib, anastrozole and nivolumab Palbociclib and anastrozole then palbociclib, anastrozole, and nivolumab Palbociclib and anastrozole	Residual cancer burden rate Dose limiting toxicity
NCT02778685	II	M	Letrozole, palbociclib and pembrolizumab	Response rate and duration of response
NCT03147287 PACE	II	M	Fulvestrant Palbociclib and fulvestrant Palbociclib, fulvestrant and avelumab	PFS at 2 years Overall response rate Safety and tolerability

Abbreviations: (cCR) Clinical complete response; (M) Metastatic; (NA) Neoadjuvant; (PFS) Progression-free survival