Review Article

Cyclin-dependent kinase 4 and 6 inhibitors at the crossroads: the combinational therapeutic strategies in breast cancer—a narrative review

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Abstract: The successful development of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors is of milestone significance. Since 2015, three CDK4/6 selective inhibitors (palbociclib, ribociclib, abemaciclib) have been developed by virtue of their outstanding performance in a series of studies, such as PALOMA, MONALEESA, and MONARCH. As CDK4/6 inhibitor monotherapy shows limited effectiveness, besides endocrine therapy (tamoxifen, AI, fulvestrant), an increasing number of laboratories and clinical researches exploring CDK4/6 inhibitor in combination with targeted therapy (HER2 targeted therapy, PI3K-mTOR/AKT/FGFR/PARP inhibitors), chemotherapy, immunotherapy, and radiotherapy, have emerged and exhibited broad prospects in breast cancer treatment, indicating that the use of CDK4/6 inhibitors does not restrict to hormone receptor-positive and HER2-negative advanced breast cancers. This review summarizes and discusses the advances in combinational strategies of CDK4/6 inhibitors for the treatment of breast cancer to further expand its clinical efficacy, overcoming endocrine and even CDK4/6 inhibitors resistance. The combined therapies have achieved favorable clinical efficacy with tolerable adverse effects. However, more efforts are warranted to investigate the better combinations for individuals. The precise choice of target population, the extensive search of predictive biomarkers, and the deep exploration of resistance mechanisms might be the future directions, which will assist us in seeking more beneficial strategies of combined therapy for individuals to improve survival.

Keywords: Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6 inhibitors); breast cancer; combination therapy; endocrine resistance

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Introduction

Breast cancer is the leading cause of cancer death among women, and hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2–) breast cancer is the most common subtype accounts for 70% of all invasive breast cancer (1,2). Endocrine therapy is the cornerstone of the treatment against hormone receptor-positive breast cancer, while endocrine resistance has been a critical clinical problem (3). The cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6) have

effectively improved the survival of advanced/metastatic HR+/HER2– breast cancer patients with tolerable adverse effects, especially when combined with endocrine therapies, and could reverse the endocrine resistance to some extent (4). Palbociclib, ribociclib, and abemaciclib are the three selective CDK4/6 inhibitors approved by the US Food and Drug Administration (FDA) since 2015, which has changed the treatment pattern of hormone receptor-positive advanced breast cancer and has become the new standard of treatment. However, we are confronted with the problem of resistance to CDK4/6 inhibitors. In this review, we summarize the crucial advances in combined strategies of CDK4/6 inhibitor to provide ideas to this puzzle, exploring its maximized therapeutic effects to improve the survival further for breast cancer patients. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tbcr-20-54).

Methods

We searched the relevant studies published in English in the PubMed database from inception to Sep 30, 2020, using the search terms "breast cancer", "CDK4/6", "CDK 4/6", "cyclin-dependent kinases 4 and 6", and "palbociclib or ribociclib or abemaciclib". A total of 1,274 results were found. Articles in reference lists of key papers were also reviewed. Besides, pivotal oncology meetings were searched from Jan 1, 2017, to Sep 30, 2020.

CDK4/6 inhibitors plus endocrine therapy

Retinoblastoma protein (RB1) is a tumor suppressor, binding the E2F transcription factors to prevent G1 transition (5). CDK4 and CDK6 are considered pivotal regulatory factors in the cell cycle, complex with cyclin D, phosphorylating RB1, deactivating RB1 function and releasing E2F successively, and then drive the cell cycle transiting from G1 phase to S phase (5). Meanwhile, E2F promotes the expression of cyclin E, which binds to CDK2, and then hyper-phosphorylates Rb1, releasing E2F, and further facilitating the G1-S phase transition (6,7) (*Figure 1*). However, this process is often dysregulated in cancer cells, which is one of the key properties of breast cancer cells, due to overexpression of cyclin D1 and loss of Rb (8,9). Mouse models lacking cyclin D1 and CDK4 prevent breast tumorigenesis (10,11). Therefore, inhibitors of CDK4/6 halt the cell cycle at the G1 phase, preventing tumor progression.

Furthermore, cyclin D1 expression induced by estrogen activating CDK4/6 is characteristic in ER-positive breast cancer (12). Finn and colleagues find that luminal estrogen receptor-positive cell lines, as well as the ones with HER2 amplified, which usually have a functional RB1, are most sensitive to palbociclib (PD 0332991) (13). They also discover the synergistic effect of palbociclib and tamoxifen (13), which leads to multiple pivotal clinical trials verifying the therapeutic effects of CDK4/6 inhibitors plus endocrine therapy in hormone receptor-positive breast cancer.

CDK4/6 inhibitors plus tamoxifen/aromatase inhibitors (AI)

Palbociclib is the first selective CDK4/6 inhibitor that reveals the results of clinical studies. In phase III PALOMA-2 trial (14), for postmenopausal patients who are sensitive to endocrine therapy, the median progression-free survival (PFS) of palbociclib plus letrozole group is significantly higher than that of the letrozole monotherapy group (24.8 *vs.* 14.5 months, HR =0.58, P<0.001), which establishes the position of palbociclib combined with aromatase inhibitors (AIs) in the first-line treatment of hormone receptor-positive breast cancer. The favorable results are also seen in patients with visceral metastases (15). Subsequently, the MONALEESA-2 (16) and MONARCH 3 (17) trials report similar results as PALOMA-2, with the addition of ribociclib and abemaciclib to non-steroidal AIs (NSAI) respectively, which further consolidate the first-line treatment place of CDK4/6 inhibitor plus AI in advanced breast cancer.

Due to the difference in morbidity crowd, patients under the age of 50 account for 42% of breast cancer patients in the Asia-Pacific region (18), and is about 50% in the Middle East (19) and Latin American (20), while 20% in the USA (21), but there is limited data about the use of CDK4/6 inhibitors in previous studies in the premenopausal population. The MONALEESA-7 (22,23) trial, for the first time, compares an NSAI or tamoxifen plus goserelin in combination with CDK4/6 inhibitor or placebo in premenopausal and perimenopausal patients with HR+/HER2– advanced breast cancer. The result shows that the median PFS of the ribociclib combined with the endocrine therapy group reaches 23.8 months, which is much longer than 13.0 months in the placebo group, suggesting that ribociclib reduces the risk of disease progression by nearly half (HR =0.55, P<0.001) (22). Compared with

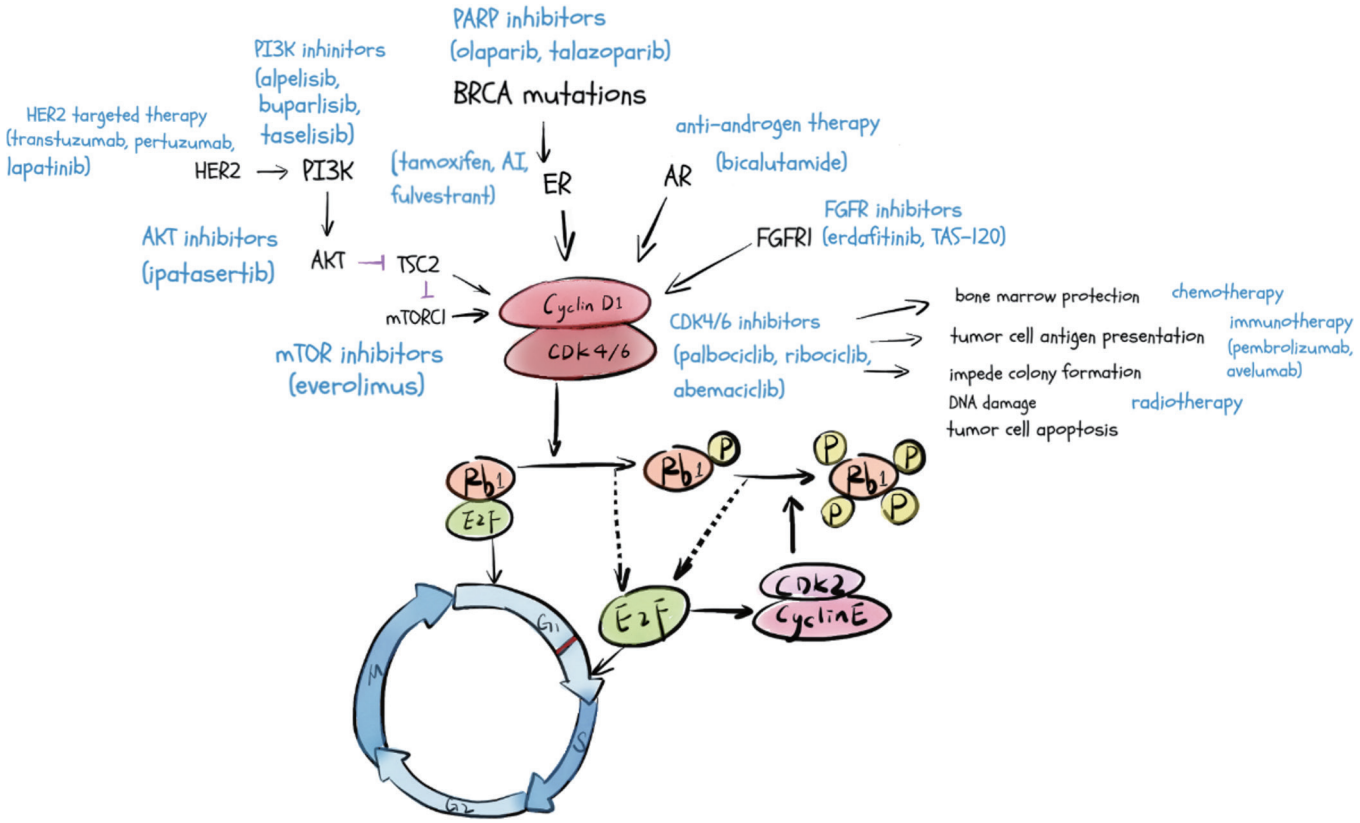

Figure 1 The cyclin D1-CDK4/6-Rb pathway and the combinational strategies of CDK4/6 inhibitors are indicated.

placebo, the addition of ribociclib significantly prolongs overall survival (not reached *vs.* 40.9 months, HR =0.712, P=0.00973) as well (23). Therefore, the study confirms that for premenopausal or perimenopausal patients, ribociclib combined with AI or tamoxifen as first-line therapy has excellent effects after ovarian function suppression.

Which is better for HR+ advanced breast cancer, chemotherapy, or endocrine plus target therapy? The KCSG-BR 15-10 trial (NCT02592746) (24) compares the anti-tumor activity between capecitabine and endocrine therapy combination (exemestane, palbociclib, and GnRH agonist). The trial includes premenopausal HR+/HER2– advanced breast cancer patients who have received tamoxifen or at most one line of chemotherapy for metastasis. Palbociclib, combined with exemestane and ovarian function suppression, prolongs PFS by 7.7 months compared to capecitabine (19.0 *vs.* 11.3 months, HR =0.659, P=0.0469) (25). However, the subsequent PEARL study (NCT02028507) (26) shows that palbociclib plus endocrine therapy do not improve the PFS of postmenopausal patients with AI resistance compared to capecitabine (7.5 *vs.* 10.0 months, HR =1.09, P=0.537), neither in the ESR1 wild-type sub-settings (8.0 *vs.* 10.6 months, HR =1.08, P=0.526). These two studies compare CDK4/6 inhibitor plus endocrine therapy with capecitabine single-agent chemotherapy, but the results are inconsistent, probably attributed to the distinct enrolled population. The patients included in the KCSG-BR 15-10 trial are relatively sensitive to AI, while patients with endocrine-resistance breast cancer in the PEARL study account for the vast majority. It suggests that the combination of CDK4/6 inhibitor and endocrine therapy will achieve better efficacy in endocrine-sensitive patients of early lines.

CDK4/6 inhibitors plus fulvestrant

The PALOMA-3 trial (27,28) reports that the median PFS of the fulvestrant plus palbociclib treatment group is significantly improved compared with the fulvestrant group (9.5 *vs.* 4.6 months, HR =0.46, P<0.0001), and the median OS is extended by 6.9 months from 28.0 months (95% CI, 23.6–34.6) in the control group to 34.9 months (95% CI,

28.8–40.0) in the treatment group yet with no statistical difference (HR =0.81, P=0.09). In the MONARCH 2 trial (29,30), the addition of abemaciclib significantly improves PFS and OS compared with fulvestrant alone: median PFS is 16.4 *vs.* 9.3 months (HR =0.55, P<0.001); median OS is 46.7 *vs.* 37.3 months (HR =0.76, P=0.01). Given the premenopausal/perimenopausal subgroups, PALOMA-3 and MONARCH 2 trials both report significant improvements in PFS with the addition of CDK4/6 inhibitors to fulvestrant (27,29).

MONALEESA-3 (31,32) includes 726 postmenopausal HR+/HER2– advanced breast cancer patients and the results indicate that ribociclib significantly improves the PFS (20.5 *vs.* 12.8 months, HR =0.59, P<0.001) and the OS as well (40.0 months *vs.* not reached, HR =0.72, P=0.00455). This study also demonstrates that CDK4/6 inhibitor combined with fulvestrant is effective for newly diagnosed (*de novo*) advanced breast cancer and patients relapse after completing adjuvant/neoadjuvant endocrine therapy for at least 12 months, which suggests that fulvestrant plus ribociclib becomes a favorable choice for first-line/second-line treatment of postmenopausal HR+/HER2– breast cancer (31,32).

Partner conundrum: AI or fulvestrant?

Which is the better partner of CDK4/6 inhibitor, AI or fulvestrant? The PARSIFAL trial (33) (NCT02491983) answers this question, which compares the efficacy and safety of CDK4/6 inhibitors combined with fulvestrant or letrozole in endocrine-sensitive metastatic breast cancer patients of the first line. The trial reports no statistical difference in survival or incidence of severe adverse events between the fulvestrant and the letrozole groups (27.9 *vs.* 32.8 months, HR =1.1, P=0.321), and the non-inferiority hypothesis does not have a definitive conclusion (33). No difference is observed in pre-defined subgroups as well, such as with or without visceral involvement, newly diagnosed or metastatic breast cancer (33).

CDK4/6 inhibitors plus anti-androgen therapy

As regards androgen receptor (AR) expressing in one-third of triple-negative breast cancer (TNBC), anti-androgen enzalutamide has become a promising target therapy in AR-positive TNBC (34). Additionally, AR stimulates DNA replication through CDK activation and Rb hyperphosphorylation in prostate cancer (35). The luminal AR (LAR) subgroup of TNBC is highly sensitive to CDK4/6 inhibitors compared to the basal-like subtype. The LAR subtype cells, which show sensitivity to palbociclib, exit mitosis into a quiescent state requiring CDK4/6 activity to reenter the cell cycle. In contrast, basal-like subtype cells exit mitosis bypassing the restriction point that requires CDK4/6 activity straight into a proliferative state (36). AR antagonist enhances the activity of palbociclib in AR-positive and RB proficient TNBC cells (37). Moreover, AR antagonist coupled with palbociclib re-sensitizes CDK4/6 inhibitor-resistant breast cancer cells (38). Clinical trials exploring the efficacy of this combination therapy are undergoing, such as a study exploring the efficacy of ribociclib with bicalutamide (NCT03090165) and palbociclib with bicalutamide (NCT02605486) in AR-positive TNBC.

CDK4/6 inhibitors plus targeted therapy

CDK4/6 inhibitors plus HER2 targeted therapy

HER2 amplified breast cancer cell lines representing the luminal subtype are also sensitive to CDK4/6 inhibitors, similar to ER+/HER2– subtype (13). Preclinical studies indicate that CDK4/6 inhibitors target cyclin D1, which relates to the acquired resistance to HER2 inhibition, suppress Rb and TSC2 phosphorylation, attenuate mTORC1 activity, and thus augment the efficacy of HER2-targeted therapies (39,40). Such results are verified in clinical trials. The monarcHER trial (NCT02675231) includes breast cancer patients with previously at least 2 HER2-targeted therapies for advanced disease (41). The results reveal that abemaciclib in combination with fulvestrant and trastuzumab improves the PFS significantly compared to the group treated with chemotherapy and trastuzumab (8.3 *vs.* 5.7 months, HR =1.1, P=0.051) (41). Trastuzumab and pertuzumab plus palbociclib and fulvestrant are used as neoadjuvant therapy without chemotherapy in the NA-PHER2 study (42), which lead to a significant reduction of Ki67, and 27% of patients have a pathological complete response (pCR) in breast and axillary nodes, higher than pCR rate of 21% in TR006 trial (43) with the combination of lapatinib, trastuzumab, and letrozole. Various studies are ongoing, exploring the combinational therapeutic effects of CDK4/6 inhibitors and anti-HER2 therapy at different stages of breast cancer (*Table 1*).

Table 1 Selected clinical trials exploring combination therapy of CDK4/6 inhibitors in breast cancer

Study	CDK4/6 inhibitor	Combination therapy	Phase	Sample size and study population	Primary endpoint	Results
CDK4/6 inhibitors plus tamoxifen/aromatase inhibitors						
PALOMA-2 (NCT01740427)	Palbociclib	Letrozole	3	666, postmenopausal AI sensitive/treatment naïve ER+/HER2– MBC	PFS	Palbociclib + letrozole *vs.* placebo + letrozole (24.8 *vs.* 14.5 months, HR =0.58, P<0.001) (14)
PALOMA-4 (NCT02297438)	Palbociclib	Letrozole	3	340, ER+/HER2– Asian MBC	PFS	Not reported
MONALEESA-2 (NCT01958021)	Ribociclib	Letrozole	3	668, postmenopausal AI sensitive/treatment naïve ER+/HER2– MBC	PFS	Ribociclib + letrozole *vs.* placebo + letrozole (25.3 *vs.* 16.0 months, HR =0.57, P<0.001) (16)
MONARCH 3 (NCT02246621)	Abemaciclib	Nsai	3	493, postmenopausal AI sensitive/treatment naïve ER+/HER2– MBC	PFS	Abemaciclib + NSAI *vs.* placebo + NSAI (not reached *vs.* 14.7 months, HR =0.54, P<0.001) (17)
MONARCH plus (NCT02763566)	Abemaciclib	Anastrozole/ letrozole	3	306, AI sensitive ER+/ HER2– MBC	PFS	Abemaciclib + NSAI *vs.* placebo + NSAI (not reached *vs.* 14.73 months, HR =0.499, P=0.001) (44)
MONALEESA-7 (NCT02278120)	Ribociclib	NSAI/tamoxifen	3	672, premenopausal ER+/HER2– MBC with endocrine treatment naïve for advanced disease	PFS	Ribociclib + NSAI/tamoxifen *vs.* placebo + NSAI/tamoxifen (23.8 *vs.* 13.0 months, HR =0.55, P<0.001) (22)
nextMONARCH 1 (NCT02747004)	Abemaciclib	Tamoxifen	2	234, ER+/HER– MBC previously treated	PFS	Abemaciclib + tamoxifen *vs.* abemaciclib (9.1 *vs.* 7.4 months, HR =0.815, P=0.293) (45)
NeoPAL (NCT02400567)	Palbociclib	Letrozole	2	106, ER+/HER– BC	RCB 0-I rate	Letrozole + palbociclib *vs.* chemotherapy (7.7% *vs.* 15.7%) (46)
PELOPS (NCT02764541)	Palbociclib	Tamoxifen	2	195, early-stage lobular and ductal BC	Ki67, pCR	Not reported
FELINE	Ribociclib	Letrozole	2	121, ER+/HER2– early-stage BC	Rate of PEPI score 0 at surgery	Not reported
KCSG-BR 15-10 (NCT02592746)	Palbociclib	Exemestane	2	182, ER+/HER2– premenopausal MBC	PFS	Palbociclib + exemestane *vs.* capecitabine (20.1 *vs.* 14.4 months, HR =0.659, P=0.0469) (24)
PARSIFAL	Palbociclib	Fulvestrant/ letrozole	2	486, AI sensitive ER+/ HER2– MBC	PFS	Palbociclib + fulvestrant *vs.* palbociclib + letrozole groups (27.9 *vs.* 32.8 months, HR =1.1, P=0.321) (33)

Table 1 (*continued*)

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Study	CDK4/6 inhibitor	Combination therapy	Phase	Sample size and study population	Primary endpoint	Results
CDK4/6 inhibitors plus fulvestrant						
PALOMA-3 (NCT01942135)	Palbociclib	Fulvestrant	3	521, endocrine resistant ER+/HER2– MBC	PFS	Palbociclib + fulvestrant *vs.* placebo + fulvestrant (9.5 *vs.* 4.6 months, HR =0.46, P<0.0001) (27)
MONALEESA-3 (NCT02422615)	Ribociclib	Fulvestrant	3	726, ER+/HER2– postmenopausal MBC	PFS	Ribociclib + fulvestrant *vs.* placebo + fulvestrant (20.5 *vs.* 12.8 months, HR =0.59, P<0.001) (31)
MONARCH 2 (NCT02107703)	Abemaciclib	Fulvestrant	3	669, AI resistant, chemotherapy naïve ER+/HER2– MBC	PFS	Abemaciclib + fulvestrant *vs.* placebo + fulvestrant (16.4 *vs.* 9.3 months HR =0.55, P<0.001) (29)
MONARCH plus (NCT02763566)	Abemaciclib	Fulvestrant	3	157, AI resistant ER+/HER2– MBC	PFS	Abemaciclib + fulvestrant *vs.* placebo + fulvestrant (11.4 *vs.* 5.59 months, HR =0.376, P<0.001) (44)
PEARL (NCT02028507)	Palbociclib	Fulvestrant	3	601, ER+/HER2– MBC	PFS	Palbociclib + fulvestrant *vs.* capecitabine (7.5 *vs.* 10.0 months, HR =1.09, P=0.537) (26)
MAINTAIN (NCT02632045)	Ribociclib	Fulvestrant	2	132, ER+/HER2– MBC with progression on AI + palbociclib/ribociclib	Percent of progression-free at 24 weeks	Not reported
SAIFA (NCT03447132)	Palbociclib	Fulvestrant	3	400, operable BC responding to Fulvestrant	PFS	Not reported
PARSIFAL (NCT02491983)	Palbociclib	Fulvestrant/ letrozole	2	486, AI sensitive ER+/ HER2– MBC	PFS	Palbociclib + fulvestrant *vs.* palbociclib + letrozole groups (27.9 *vs.* 32.8 months, HR =1.1, P=0.321) (33)
CDK4/6 inhibitors plus anti-androgen therapy						
NCT03090165	Ribociclib	Bicalutamide	1/2	11, AR+ MBC	MTD, CBR	Not reported
NCT02605486	Palbociclib	Bicalutamide	1/2	51, AR+ MBC	Dose, PFS	Not reported
CDK4/6 inhibitors plus HER2 targeted therapy						
NA-PHER2 (NCT02530424)	Palbociclib	Trastuzumab + pertuzumab + fulvestrant	2	36, early invasive BC with HR+/HER2+ not previously treated	Ki67, pCR	The expression of Ki67 is significantly reduced (42)
MonarcHER (NCT02675231)	Abemaciclib	Trastuzumab + fulvestrant	2	237, ER+/HER2– locally advanced or metastatic BC with ≥2 HER2– targeted therapies for advanced disease	PFS	Abemaciclib + fulvestrant + trastuzumab *vs.* standard-of-care chemotherapy + trastuzumab (8.3 *vs.* 5.7 months, HR =1.1, P=0.051) (41)

Table 1 (*continued*)

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Study	CDK4/6 inhibitor	Combination therapy	Phase	Sample size and study population	Primary endpoint	Results
TOUCH (NCT03644186)	Palbociclib	Trastuzumab + pertuzumab + letrozole	2	144, ER+/HER2+ early BC	pCR	Not reported
PATRICIA (NCT02448420)	Palbociclib	Trastuzumab ± letrozole	2	232, ER±/HER2+ locally advanced or metastatic BC	PFS	Not reported
PATINA (NCT02947685)	Palbociclib	Anti-HER2 + endocrine therapy	3	ER+/HER2+ MBC with previous CT containing anti-HER2 based induction therapy	PFS	Not reported
NCT03530696	Palbociclib	T-DM1	2	132, HER2+ MBC	PFS	Not reported
CDK4/6 inhibitors plus PI3K-mTOR inhibitors						
TRINITI-1 (NCT02732119)	Ribociclib	Everolimus + exemestane	1/2	95, ER+/HER2– MBC that progressed on prior CDK4/6 inhibitor	MTD, CBR	CBR in week 24 is 41.1%, exceeding the predefined threshold (47)
NCT02088684	Ribociclib	Buparlisib/ alpelisib + fulvestrant	1/2	70, HR+/HER2+ locally recurrent or advanced MBC	DLT, PFS	Not reported
NCT03128619	Palbociclib	Copanlisib + letrozole	1/2	102, HR+/HER2– BC	Ki-67, DLT	Not reported
CDK4/6 inhibitors plus AKT inhibitors						
TAKTIC (NCT03959891)	Palbociclib	Ipatasertib + fulvestrant	1	60, HR+/HER2– MBC	TEAE	The combination therapy is well tolerated (48)
CDK4/6 inhibitors plus FGFR inhibitors						
NCT03238196	Palbociclib	Erdafitinib + fulvestrant	1	32, FGFR-amplified ER+/HER2– MBC	safety and tolerability	Not reported
CDK4/6 inhibitors plus PARP inhibitors						
NCT03685331	Palbociclib	Olaparib + fulvestrant	1/2	54, BRCA-mutated HR+/HER2– MBC	PFS	Not reported
CDK4/6 inhibitors plus chemotherapy						
NCT02978716	Trilaciclib	Gemcitabine and carboplatin	2	102, metastatic TNBC	TRAE	Trilaciclib + gemcitabine + carboplatin *vs.* gemcitabine + carboplatin (No significant differences in myelosuppression endpoints) (49)

Table 1 (*continued*)

Table 1 (*continued*)

Study	CDK4/6 inhibitor	Combination therapy	Phase	Sample size and study population	Primary endpoint	Results
CDK4/6 inhibitors plus immunotherapy						
NCT02779751	Abemaciclib	Pembrolizumab	1	28, endocrine-resistant HR+/HER2– MBC	AE	The combination is generally tolerable with a numerically higher rate of transaminase elevations than reported for the individual treatments (50)
PAveMenT (NCT04360941)	Palbociclib	Avelumab	1	45, metastatic AR+ TNBC	MTD, ORR	Not reported
ImmunoADAPT (NCT03573648)	Palbociclib	Avelumab + tamoxifen	2	40, early stage ER+ BC	cCR	Not reported
PACE (NCT03147287)	Palbociclib	Avelumab + fulvestrant	2	220, ER+/HER2– MBC with prior progression on palbociclib and endocrine therapy	PFS	Not reported
CDK4/6 inhibitors plus radiotherapy						
ASPIRE (NCT03691493)	Palbociclib	Radiotherapy + endocrine therapy	2	42, HR+/HER2– MBC with bone metastases	Response rate	Not reported

BC, breast cancer; MBC, metastatic breast cancer; HR+, hormone receptor-positive; HER2, humane epidermal receptor 2; TNBC, triple-negative breast cancer; AR+, androgen receptor-positive; AI, aromatase inhibitor; NSAI, non-steroidal aromatase inhibitor; CT, chemotherapy; PFS, progression-free survival; pCR, pathological complete response; cCR, clinical complete response; RBC, residual cancer burden; PEPI, pre-operative endocrine prognostic index; ORR, objective response rate; MTD, maximum tolerated dose; CBR, clinical benefit rate; DLTs, dose-limiting toxicities; AE, adverse events; TEAE, treatment-emergent adverse events; TRAE, treatment-related adverse event.

CDK4/6 inhibitors plus PI3K-mTOR inhibitors

Thirty percent of ER+/HER2– metastatic breast cancers have activating PIK3CA mutations (51). *In vivo* and *in vitro* studies evince that CDK4/6 inhibitors synergize with PI3K inhibition by partially attenuating mTORC1 activity (40), sensitizing PIK3CA-mutated cells (52), and triggering cancer cell apoptosis (53). These findings lead to a multi-center, open-label phase Ib/II study (NCT02088684) (54) investigating LEE011 (ribociclib), BKM120 (buparlisib, PI3K-pan class I-inhibitor) or BYL719 (alpelisib, PI3K-alpha specific class I inhibitor) in combination with fulvestrant, with the results not opened yet. Furthermore, Herrera-Abreu indicates that a combination of endocrine therapy, CDK4/6, and PI3K inhibition is more effective than the combination without endocrine therapy in a PDX model (53). This synergistic effect is also recognized in PIK3CA-mutant TNBC cell lines and TNBC tumors *in vivo* (36,55). We look forward to the results of the joint effect.

CDK4/6 inhibitors plus AKT inhibitors

A proportion of 1.4–8% of breast cancer patients have AKT1 mutations, restricted to hormone receptor-positive breast cancers (56,57). However, AKT activation is associated with a worse clinical outcome and induces endocrine resistance among patients treated with endocrine therapy (58,59). Preclinical studies suggest that AKT1 activation can drive resistance to CDK4/6 inhibitors (60). The phase Ib trial TAKTIC (NCT03959891) (48) exploring the anti-tumor activity of palbociclib in combination with fulvestrant and ipatasertib, an AKT1 inhibitor, following CDK4/6 inhibitors progression demonstrates clinical benefit. The combination is well tolerated and does not affect the pharmacokinetics of ipatasertib (48).

CDK4/6 inhibitors plus FGFR inhibitors

Formisano and colleagues (61,62) identify FGFR1 signaling as a potential mechanism of resistance to CDK4/6 inhibitors

in combination with endocrine therapy in preclinical studies, while the resistance can be blocked by lucitanib, the FGFR tyrosine kinase inhibitor (61); 41% (14/34) specimens progressing on CDK4/6 inhibitors are identified FGFR1/2 amplification or activating mutations. Patients in MONALEESA-2 with higher FGFR1 mRNA expression levels exhibit a significantly shorter PFS compared to patients with lower levels (61). Recent studies are worth waiting that exploring the treatment of FGFR-amplified/hormone receptor-positive metastatic breast cancer with erdafitinib plus fulvestrant plus palbociclib (NCT03238196) and an oral FGFR inhibitor, TAS-120, from FOENIX-MBC2 trial (NCT04024436).

CDK4/6 inhibitors plus PARP inhibitors

ER-positive breast cancers account for 22% and 77% of breast cancer patients with BRCA1 and BRCA2 mutations, respectively (63). ER-positive breast cancers with BRCA mutations are often characterized by more aggressive tumor statues, which result in a higher risk of distance recurrence and death (64,65). Studies investigating the relationship between BRCA1 and ERα suggest that BRCA1 mutation releases the brake on ERα-driven proliferation, which is functioned by wild-type *BRCA1* gene (66,67). BRCA1 knockdown also promotes aromatase expression and thus may cause an elevated estrogen level (68). In addition, BRCA1 mutation abolishes the antiproliferative property of BRCA1 which binds to phosphorylated Rb and is involved in cell cycle arrest (69). Moreover, cyclin D1 that activates CDK4 and CDK6 plays a kinase-independent role in DNA repair, and the recruitment of cyclin D1 to DNA damage sites is through BRCA2 (70). Furthermore, CDK4/6 inhibition increases error-prone DNA repair, which suggests the synthetic lethal effect in BRCA mutated breast cancer (71,72).

Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor prevents the participation of PARP1 and PARP2 in DNA repair, which indicates the potential clinical use in germline BRCA mutated breast cancer based on the rationale of synthetic lethality (73,74). The phase III OlympiAD and EMBRACE trials report significant PFS improvement in PARP inhibitor olaparib and talazoparib groups over standard-therapy groups in HER2-negative metastatic breast cancer patients with germline BRCA mutation (75,76). The study has recently started exploring olaparib, palbociclib, and fulvestrant in patients BRCA-mutated hormone receptor-positive, HER2-negative metastatic breast cancer (NCT03685331).

CDK4/6 inhibitors plus chemotherapy

Cell cycle arrest induced by CDK4/6 inhibitors antagonizes cytotoxic therapeutic strategies and result in reduced anti-tumor efficacy when combined with DNA-damaging chemotherapy, such as carboplatin and doxorubicin (71,77). On the other hand, CDK4/6 inhibitors show bone marrow protection on chemotherapy- or ionizing radiation-induced myelosuppression *in vitro* even in CDK4/6-resistant tumors without dose reduction (77,78), so as not to compromise distant survival (79). A phase II randomized clinical trial (NCT02978716) finds that the addition of trilaciclib to gemcitabine and carboplatin makes fewer patients have anemia who need red blood cell transfusions and improves the overall survival markedly (17.8 *vs.* 12.6 months, P=0.0023) (49).

CDK4/6 inhibitors plus immunotherapy

Selective CDK4/6 inhibitors not only induce G0 and G1 cell-cycle arrest but also enhance tumor cell antigen presentation as well as suppress regulatory T cell proliferation, which reduce the transcription of DNA methyltransferase 1, the target of E2F. In general, these factors lead to the enhanced clearance of tumor cells mediated by cytotoxic T cells with the combined therapy of CDK 4/6 inhibitors and immunotherapy (80). Also, CDK 4/6 inhibitors increase the infiltration of tumor cells and activate effector T cells via de-repression of the nuclear factor of activated T cell (NFAT) proteins, which synergize with immunotherapies (81). Moreover, CDK4/6 inhibitors hinder the phosphorylation of speckle-type POZ protein (SPOP), promote its degradation, and increase the PD-L1 protein levels (82). By combining a CDK4/6 inhibitor with immunotherapy, tumor regresses, and overall survival rates improve significantly *in vivo* (82). Additional immune checkpoint inhibitor combined with PI3K-alpha and CDK4/6 inhibition induces consistent tumor regression in the TNBC mouse model by enhancing tumor immunogenicity and T-cell cytotoxicity responses (55). The combination of abemaciclib and pembrolizumab shows numerically higher but not significantly better outcomes in 28 HR+/HER2– metastatic breast cancer patients from a phase Ib study (NCT02779751) (50), compared to previous data of abemaciclib monotherapy. More ongoing studies validating the efficacy of combination therapies with

immunotherapy have the potential to fortify the clinical benefits of combined treatment.

CDK4/6 inhibitors plus other agents

CDK4/6 inhibitors plus lysosome-destabilizing compounds

CDK4/6 inhibitors are found to be absorbed into tumor cell lysosomes, which brings about the resistance of a subgroup TNBC to CDK4/6 inhibitors. Fassl and colleagues (83) develop new CDK4/6 inhibitor compounds evading the sequestration of lysosomal and reversing the drug resistance in TNBC cells.

CDK4/6 inhibitors plus radiotherapy

Brain metastases are common during the extending lifespan of breast cancer patients and are usually treated with surgery, radiotherapy, and systemic therapy (84-86). Preclinical studies indicate that abemaciclib penetrates the blood-brain barrier (87). A phase II clinical trial shows the anti-tumor activity of abemaciclib in hormone receptor-positive breast cancer patients with brain metastases (88). The combined use of palbociclib and radiotherapy impedes colony formation, inhibits DNA damage repair, and promotes tumor cell apoptosis synergistically in glioblastoma cell lines (89,90). A retrospective study analyzes patients who receive stereotactic radiotherapy to brain metastases alongside palbociclib/abemaciclib (91). Fifteen patients with 42 metastatic brain lesions are included (91). The radiotherapy is well-tolerated in combination with CDK4/6 inhibitors, two lesions developing radionecrosis managed with steroids and bevacizumab (91). Six- and 12-month local brain control is both 88%, and distant brain control is 61% and 39% respectively, similar to the previous data (91). However, there is an improvement in overall survival (36.7 months) from the date of brain metastases diagnosis (91). Besides, the phase II ASPIRE trial (NCT03691493) is evaluating the response rate of concurrent palbociclib and radiotherapy for hormone receptor-positive patients with bone metastasis.

Conclusions

Over the past decades, CDK4/6 inhibitors have altered the therapeutic landscape, and endocrine therapy combined with CDK4/6 inhibitors become the standard first-line treatment against hormone receptor-positive breast cancer. The potential synergistic effect of CDK4/6 inhibitors with other medical treatments has drawn more attention (*Figure 1*), at the crossroads of endocrine therapy and CDK4/6 inhibitor resistance. Plenty of ongoing clinical studies investigating the combinational strategies of CDK4/6 inhibitors has set off (*Table 1*) and promised an encompassing clinical profit to breast cancer patients. However, to enhance the efficacy of combination treatment, well-designed research and concrete answers about signaling mechanisms are urgently needed and require more scientific effort. Exploratory research in the predictive biomarkers and resistance mechanisms might be the future directions, and the precise choice of the target population will assist us in seeking a more appropriate combination therapy for individuals to improve survival.

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Footnote

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