Review Article

Potential biomarkers of resistance to CDK4/6 inhibitors: a narrative review of preclinical and clinical studies

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Abstract: Cyclin-dependent kinase (CDK) 4/6 inhibitors are a class of novel oral drugs which have been approved for treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) metastatic breast cancer (mBC) patients since 2015. These drugs share a common mechanism by blocking cell cycle progression from the G1 to the S phase through regulation of retinoblastoma protein (Rb) phosphorylation. Several large, prospective, randomized clinical trials (RCTs) have evaluated the clinical efficacy and safety profile of selective CDK4/6 inhibitors in combination with endocrine therapy (ET), which have delivered promising results with significantly prolonged progression-free survival (PFS) and overall survival (OS). However, owing to primary and secondary resistance, still some patients failed during the course of treatment. Recent studies attempted to investigate potential subgroup of HR+/HER2– mBC patients might benefit from CDK4/6 inhibition in both biomarker-driven RCTs and real-world data. The following review gives an overview of the pharmacological mechanism of CDK4/6 inhibitors in BC treatment and highlight current studies with regard to the potential biomarkers of resistance to CDK4/6 inhibitors.

Keywords: CDK4/6 inhibitors; mechanism; biomarker; resistance; breast cancer

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Introduction

Breast cancer (BC) is the most common cancer diagnosed in women with the morbidity ranging from 27/100,000 to 94/100,000 (1), which accounts for 25% of all malignancies worldwide (2). BC is generally categorized into 3 subtypes: hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative BC (HR+/HER2– BC), HER2-positive (HER2+) BC and triple negative BC (3). Of all BC cases, approximately 60–70% of women are diagnosed as HR+/HER2– BC (4). In the past decades, the standard of care for HR+/HER2– BC is blocking the estrogen receptor signaling pathway, which is so-called endocrine therapy (ET) (5). Although the overall 5-year survival has increased to 90%, remains incurable with an estimated 5-year survival rate was only 25% in metastatic or advanced BC (mBC/ABC) (6). Thus, new therapeutic regimens are continuously explored to extend the overall survival (OS) of BC patients.

With the discovery of cyclin-dependent kinase (CDK) 4/6 inhibitors, the progression-free survival (PFS) is almost doubled when combination of CDK4/6 inhibitors and aromatase inhibitors (AIs) as the first line treatment of HR+/HER2– mBC/ABC patients (*Table 1*) (7-9). Even in patients progressed with previously ET, the PFS is significantly prolonged in combination with fulvestrant (10-12). In addition, the statistically significant OS data were also reported in MONALEESA-3 (13),

Table 1 Randomized clinical trials of CDK4/6 inhibitors in HR+/HER2– advanced breast cancer

Study name	Phase	NCT No.	PFS	OS
First line treatment (CDK4/6 inhibitors + AI)				
PALOMA-1 (1,2)	II	NCT00721409	20.2	–
PALOMA-2 (3,4)	III	NCT01740427	27.6	–
MONALEESA-2 (5,6)	III	NCT01958021	25.3	–
MONARCH 3 (7,8)	III	NCT02246621	28.2	–
ET-resistance (CDK4/6 inhibitors + Fulvestrant)				
PALOMA-3 (9,10)	III	NCT01942135	9.5	34.9
MONALEESA-3 (11,12)	III	NCT02422615	20.5	NR
MONARCH 2 (13,14)	III	NCT02107703	16.4	46.7
Premenopausal				
MONALEESA-7 (15,16)	III	NCT02278120	23.8	NR
Young PEARL (17)	II	NCT02592746	20.1	–

NCT, ClinicalTrials.gov identifier; LOT, line of therapy; mPFS, median progression-free survival (months); mOS, median overall survival (months); AI, aromatase inhibitor; ET, endocrine therapy; NR, not reached.

MONALEESA-7 (14) and MONARCH 2 (*Table 1*) (15). These promising results make the combination of CDK4/6 inhibitors and ET as a standard of care for treatment of HR+/HER2– mBC/ABC, which is highly recommended in various BC guidelines (16,17).

However, not all HR+/HER2– BC patients achieved clinical benefits from CDK4/6 inhibitor-based therapy and almost all the patient would gained the acquired resistance finally (18). The mechanisms of resistance to CDK4/6 inhibitors is still unclear and there were no predictive biomarkers indicating the clinical efficacy of CDK4/6 inhibitors. This review mainly discussed the pharmacological mechanism of CDK4/6 inhibitors and the potential biomarkers of resistance to CDK4/6 inhibitors (*Table 2*), aiming to provide some insights to overcome the resistance to CDK4/6 inhibitors. We present the following review in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tbcr-20-52).

Pharmacological mechanism of CDK4/6 inhibitors

In normal physiological conditions, cell cycle is tightly controlled to maintain the normal process of cell proliferation. Dysregulation of cell cycle involved in many pathological process, including cancers (19). Cell cycle is classically divided into four phases: G1 (pre-DNA synthesis), S (DNA synthesis), G2 (pre-division), and M (cell division) (20). Many signaling pathways have involved into cell cycle regulation and CDK4/6 is one of the most important kinase initiating cell cycle transition from G1 phase to S phase (21). In G1 phase of cell cycle, activation of upstream signaling pathways promotes the combination of CDK4/6 with cyclin D (*Figure 1*) (22). The formation of cyclin D-CDK4/6 complex released adenosine triphosphate (ATP), which provides energy for phosphorylation of retinoblastoma (Rb) (23,24). Inactivated Rb is tightly binding to E2 transcription factor (E2F) to repress the E2F function (25). When phosphorylated, Rb releases E2F from Rb-E2F complex and then the dissociated E2F induced the upregulation of target genes and initiating DNA replication, resulting in cell cycle transition from G1 phase to S phase (20,26).

CDK4 and CDK6 are expressed in most cell types and share 71% amino acid identity (27). The functions of CDK4 and CDK6 are largely overlapped and both of them can partner with all 3 D-type cyclins (D1, D2 and D3) (27). Intrinsically, CDK4/6 activity is inhibited by the INK4 family (p16, p15, p18, and p19) and by the Cip (p21) and Kip (p27) family (28). In BC, cyclin D-CDK4/6-Rb signaling cascade was dysregulated, which accelerated the unchecked cell proliferation (29,30). Amplification of cyclin D1 gene was observed in ~15% of BC cases and cyclin D1 mRNA and protein was overexpressed in up to 50% of primary breast cancers, mostly ER-positive and well-

Table 2 Potential biomarkers of resistance to CDK4/6 inhibitors

Gene	Status	Function	Ref.
Cell cycle specific			
p16	Amplification	Intrinsic inhibitor of CDK4/6	(18-20)
CCND1	Amplification	Release E2F via phosphorylating Rb	(21,22)
CDK4/6	Amplification	Release E2F via phosphorylating Rb	(21,22)
CCNE1-CDK2	Amplification	Release E2F via phosphorylating Rb	(23)
CDK7	Amplification	Transcriptional regulator	(24)
CDK9	Amplification	Transcriptional regulator	(24)
Rb	Loss	Intrinsic inhibitor of E2F	(25)
E2F	Amplification	E2 transcription factors to regulate gene expression	(26,27)
Cell cycle non-specific			
TK1	Overexpression	Catalyze DNA precursor synthesis	(28)
FAT1	Loss	Intrinsic tumor suppressor	(29)
FGFR	Amplification	Tyrosine kinase receptors	(30)
PI3K/Akt/mTOR	Activation	Regulate mRNA translation, protein synthesis and cell proliferation	(31)
PD-1	Overexpression	drive T cell dysfunction	(32)

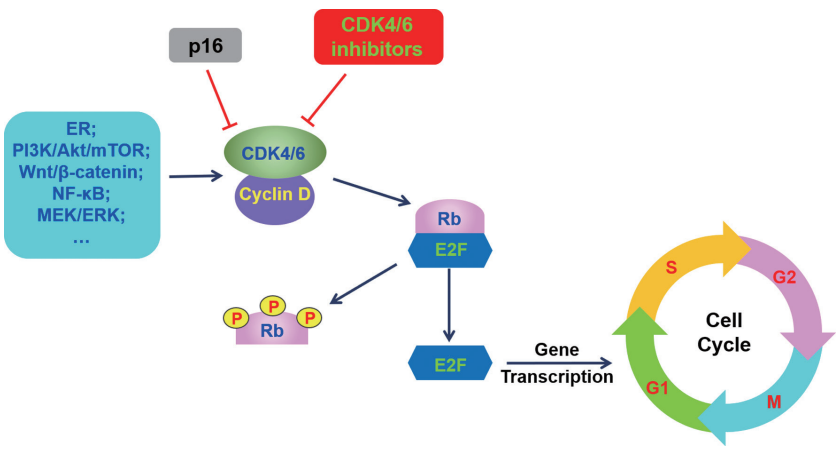

Figure 1 Pharmacological mechanism of CDK4/6 inhibitors. Activation of upstream signaling pathways promotes the formation of cyclin D-CDK4/6 complex, which phosphorylates Rb protein and releases E2F from Rb-E2F complex. As a transcription factor, released E2F initiates gene transcription, resulting in cell cycle into S phase from G1 phase. External CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib), as well as the intrinsic tumor-suppressor (p16) prevent the activation of CDK4/6 to cause cell cycle arrest at G1 phase. CDK, cyclin-dependent kinase; Rb, retinoblastoma protein; E2F, E2 transcription factor.

differentiated tumors (31,32). In breast cancer cell lines, upregulation of cyclin D induced cell cycle progressing from G1 to S phase (33). In transgenic mice, excessive expression of cyclin D accelerated cell proliferation, contributing to the progression of mammary carcinomas (34). Cyclin D is often overexpressed in many cancers and correlated with poor prognosis and high metastasis of tumor (31,35,36). Similarly, upregulation of CDK4 expression is positively

correlated with high tumor cell proliferation in sporadic breast carcinomas (37). Suppression of cyclin D3-CDK6 signaling resulted in tumor cell apoptosis (38). Therefore, both CDK4/6 and cyclin D play a crucial role in caner progression and could be the therapeutic targets for cancer treatment.

So far, there are three CDK4/6 inhibitors approved by U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA): palbociclib (Ibrance, Pfizer, USA), ribociclib (Kisqali, Novartis, Switzerland) and abemaciclib (Verzenio, Lilly, USA). The indications of these 3 CDK4/6 inhibitors approved by FDA and EMA are: (I) in combination with an AI as initial therapy in postmenopausal women with HR+/HER2– ABC/mBC; (II) in combination with fulvestrant for women who have previously treated with ET (39). Moreover, abemaciclib is the only CDK4/6 inhibitor that can be used as a monotherapeutic drug and palbociclib is the only one which is approved to treat male patients with HR+/HER2– mBC on the basis of real-world data on April 4, 2019 by FDA (40). In China, only palbociclib has been approved by National Medical Products Administration (NMPA) in 2017 and is orally administered in combination with AI as initial therapy in postmenopausal women with HR+/HER2– ABC/mBC.

Potential biomarkers of resistance to CDK4/6 inhibitors

Resistance to CDK4/6 inhibitors: regulation of cell cycle (Table 2)

p16 amplification

$p16^{INK4A}$, encoded by the *CDKN2A*^{ink4a}, is an intrinsic tumor-suppressor which can bind to CDK4/6 to block the interaction between CDK4/6 and cyclin D, resulting in the inactivation of the downstream signaling pathway (*Figure 1*) (41-43). The expression of p16 is upregulated during oncogenic stress. When p16 amplification is concurrent with Rb mutation, resistance to CDK4/6 inhibitor was observed due to loss of Rb function (44). In the presence of Rb, overexpression of p16 demonstrated resistance to CDK4/6 inhibitor through downregulation of CDK4 in breast cancer cells (18,45). In melanoma cell lines, downregulation of *CDKN2A*^{ink4a} expression is associated with the sensitivity to palbociclib (46). Deletion of p16 demonstrated a significant repression of cell cycle in G1 phase and inhibited cell proliferation by palbociclib in glioblastoma xenograft cells (47). All these preclinical evidences indicated that p16 amplification should be an effective biomarker of resistance to CDK4/6 inhibitors. However, the data of PALOMA-1 study did not present any significant difference in PFS between the unselected cohort and the loss of p16/CCND1 amplification cohort (48). Similar results were also observed from the biomarker analysis of PALOMA-2 and PALOMA-3 (49,50). Therefore, it is controversial to use p16 amplification as a biomarker.

CCND1 amplification

There are 3 isoforms of D cyclins, cyclins D1, D2 and D3, all of which could form a complex with CDK4/6, driving cell cycle transition from G1 to S phase (51). Cyclins could allosterically activate the cognate CDKs through formation of cyclin-CDK complexes, which contribute to cell cycle progression (32,52). Overexpression of D cyclins can promote cell proliferation and induce tumor growth (32). Among these 3 D cyclins, cyclin D1 is more frequently overexpressed than cyclin D2 and D3 in human cancers (52). The cyclin D1 encoding gene, CCND1 have been found to upregulated in ER+ BC (cyclin D1; 58% in luminal B *vs.* 29% in luminal A) (53). Therefore, CCND1 amplification or cyclin D1 overexpression would be an indicator of resistance of CDK4/6 inhibitor. Unfortunately, the biomarker analysis of PALOMA studies did not show any significant difference on PFS according the expression level of CCND1 (49,50,54). The role of CCND1 in CDK4/6 inhibition should be further explored.

CDK4 or CDK6 amplification

Both CDK4 and CDK6 are the major components of cyclin D-CDK4/6-Rb signaling pathway (55). As mentioned above, CDK4 and CDK6 are expressed in most cell types and share 71% amino acid identity and their functions are largely overlapped (27). Previous studies have revealed that the cell proliferation of mouse embryonic fibroblast was normal but have a delayed S phase in the CDK4 null mouse model (56). In $CDK4^{-/-}$ mice, the expression of CDK6 was upregulated in lung (57). Thus, lack of CDK4 function might be compensated by increased level of CDK6 in these models. On the basis of these observations, CDK6 seems to be more important than CDK4. In CDK4-amplified glioblastoma cells, pRb is persistent even if the cells were treated with palbociclib (47). Reduction of sensitivity to ribociclib was also observed in fusion-positive rhabdomyosarcoma with CDK4 amplification and overexpression (58). These preclinical data suggested that CDK4 amplification might indicate a poor response to

CDK4/6 inhibitors. In HR+ breast cancer cells, prolonged exposure to abemaciclib induced amplification of CDK6, which reduced pRb and sensitivity to all the three CDK4/6 inhibitors, demonstrating that CDK6 amplification could be the mechanism of acquired resistance to CDK4/6 inhibitors (59). However, biomarker analysis of PALOMA-2 and PALOMA-3 did not support these preclinical findings that amplification of CDK4 or CDK6 was a biomarker to predict the prognosis of mBC/ABC patients treated with CDK4/6 inhibitors (49,50). But the data of ECLIPS study showed that high baseline CDK4 expression indicated a longer PFS compared with patients who had a low baseline CDK4 expression (low *vs.* high: 6.45 months *vs.* not reached, P=0.01) in patients treated with palbociclib plus fulvestrant (60). Therefore, the predicted value of CDK4 or CDK6 amplification in early BC should be investigated in future.

CCNE1-CDK2 amplification

In addition to cyclin D-CDK4/6 complex, cyclin E-CDK2 complex could also release E2F via phosphorylating Rb (61). Cyclin E is expressed in the late G1 phase until the end of S phase of cell cycle (62). It can bind and activate the kinase CDK2 to control the entry of S phase (63). Activation of cyclin E-CDK2 complex phosphorylates Rb and activate E2F to upregulate the target gene expression, which is required for S phase (64). Upregulation of cyclin E expression was associated with tumorigenesis of human cancers, especially BC (62). CCNE1 expression was amplified in CDK4/6 inhibitor resistance cell lines (65) and upregulation of Cyclin E1 indicated the reduction of the inhibitory effects of CDK4/6 inhibitors on cell cycle progression (66). Biomarker analysis of PALOMA-3 demonstrated that overexpression of CCNE1 mRNA is associated with a shorter PFS in patients treated with the combination of palbociclib and fulvestrant (50) while this was not found in PALOMA-2 study (49), suggesting that upregulation of cyclinE1 mRNA was one of the mechanisms of resistance to CDK4/6 inhibitors in previously treated HR+/HER2– mBC.

CDK7 amplification

Unlike CDK4/6, CDK7 has downstream effects as transcriptional regulators and cell cycle regulator through formation of complex with cyclin H or MAT1 (67,68). Evidence has been revealed that CDK7-cyclin H complex also functioned as CDK activating kinase (CAK) (69), which can activate cyclin T1-CDK9 and cyclin K-CDK12/13 resulting in a pause of transcription (70). Furthermore, as a CAK, CDK7 can activate CDK4/6 to regulate G1 phase transition, maintain CDK1 and CDK 2 activity to involve into G2/M phase (68). After treated with palbociclib, the expression of CDK7 was increased by 27.27% in hematopoietic stem cells in mice (71). Upregulation of CDK7 demonstrated the resistance to palbociclib in MCF7 cells (72). Thus, overexpression of CDK7 might be a biomarker of acquired resistance to CDK4/6 inhibitors. However, neither PALOMA-2 nor PALOMA-3 results analyzed the change of CDK7 expression as a biomarker of CDK4/6 inhibitors. More clinical evidence is required to verify the role of CDK7 in resistance to CDK4/6 inhibitors.

CDK9 amplification

Similar to CDK7, CDK9 also has downstream effects as transcriptional regulators (67), which is crucial to RNA Polymerase II (Pol II) transcription initiation, elongation, and termination (73). Activation of CDKs is mainly dependent on the formation of heterodimers with cyclin proteins (74). CDK9 interacts with cyclin T to form the Positive Transcription Elongation Factor b (P-TEFb) (75,76), resulting in activating the transcription elongation of the target genes in nucleus, including MYC, MCL1 and NF-κB (77,78). CDK9 is constitutively expressed throughout cell cycle and overexpressed in many cancers, such as lung cancer, ovarian cancer, leukemia, prostate cancer, as well as breast cancer (79,80). Results from ECLIPS study have shown that the increased number of copies/mL of CDK9 in plasma-derived exosomes was observed after 3 months of treatment compared with before treatment (3,800 *vs.* 7,500 copies/mL, P=0.03) in HR+/HER2– mBC patients whose disease has progressed after treated with palbociclib plus ET (60), indicating that overexpression of CDK9 is positively correlated with clinical resistance of CDK4/6 inhibitors.

Loss of Rb function

Rb, as the downstream protein of CDK4/6, is considered as the most important biomarker indicating the clinical activity to CDK4/6 inhibitors (81). Preclinical studies have proved that loss of Rb function was detected in palbociclib resistance cell lines (82). A phase II RCT study, POP study, aimed to investigate the effects of palbociclib on cell proliferation in the neoadjuvant setting in BC patients (83). The results manifested that early decreased of Rb phosphorylation (pRb) was associated with antiproliferative response to palbociclib, suggesting that pRb would be

a potential indicator to identify patients with primary resistance. Somatic *Rb1* mutations were found when disease was progressed in mBC patients who had received the treatment with palbociclib or ribociclib (84), suggesting that Rb mutation might be an effective indicator to the acquired resistance to CDK4/6 inhibitors. However, there were only 3 patients in this publication. More patients and real-world data were warranted to confirm this conclusion.

E2F amplification

As mentioned above, CDK-Rb-E2F axis is critical for driving cell cycle progression. Expression and activity of E2E is strictly controlled in the normal physiological process at different levels, including transcription, mRNA stability, post-translational modifications, interaction with regulatory proteins and protein stability (85). Upregulation of E2F and E2F target in cancer is associated with poor prognosis (85). The dissociation of Rb-E2F complex is regulated by cyclin D-CDK4/6 and cyclin E-CDK2 (86). In turn, cyclin D3 and cyclin E are the target gene of E2F (87-89). As the downstream signaling, activation of E2F by the bypass of cyclin D-CDK4/6, such as cyclin E-CDK2, might be the mechanism of resistance to CDK4/6 inhibitors.

Resistance to CDK4/6 inhibitors: regulation beyond cell cycle (Table 2)

TK1

Thymidine kinase-1 (TK1) is a key regulator of cell cycle, which is highly expressed in S/G2 phase, and functioned as an enzyme to catalyze the synthesis of DNA precursor (90). Serum TK1 level and activity was significantly increased in solid tumors, including breast cancer, lung and colorectal (91). In primary BC patients, increased TK1 levels and activity is positively correlated with large tumor size and poor outcomes (92,93). In HR+/HER2– mBC patients, lower baseline TK1 activity was associated with a longer PFS and reduction of TK1 activity after one month of treatment was also associated a significantly prolongation of PFS (94). Thus, TK1 might be a meaningful prognostic biomarker for HR+/HER2– mBC. The prospective, pharmacogenetic study, ECLIPS, aims to explore the predictive biomarkers of responsive/resistant to the combined treatment of palbociclib and ET (letrozole or fulvestrant) (60). The data demonstrated that the number of copies/mL of TK1 was significantly increased after 3 months of treatment compared with before treatment (1,200 *vs.* 3,350 copies/mL, P=0.01) in disease progressed patients. In addition, results of TREnd trial showed that increased level of TK1 mRNA is linked to shorter PFS (95). These data supported that TK1 level might be a significant biomarker of acquired resistance to CDK4/6 inhibitors.

Loss of FAT1

FAT1 is a tumor-suppressor belonging to the cadherin superfamily and interacts with the Wnt/β-catenin and Hippo signaling pathways (96-98). Loss of FAT1 function contributed to the development and progression of cancers (96). Gene sequencing results manifested that FAT1 mutation accounted for ~2% in primary and ~6% in metastatic tumors in HR+/HER2– BC patients (99). Preclinical data demonstrated that loss of FAT1 resulted in excessive expression of CDK6 through activation of Hippo pathway, contributing to resistance to CDK4/6 inhibitors (100). Gene analysis results from 348 ER+/HER2– BC patients previously treated with CDK4/6 inhibitors, manifested that loss of FAT1 was linked with poor prognosis of CDK4/6 inhibitor-based therapy, with a shorter PFS (2.4 months) than that in FAT1 wild type arm (PFS: 10.1 months; $P=2.2\times10^{-11}$) (100). Therefore, loss of FAT1 might be an effective biomarker of resistance to CDK4/6 inhibitors.

Activation of the PI3K/Akt/mTOR pathway

Phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway is activated in ~30–40% of BC, especially in HR+ BC (65,101). PI3K interacts with phosphorylated tyrosines on IRS molecules, which further phosphorylates and activates Akt (102). Phosphorylation of Akt can activate mTOR, a serine/threonine kinase laying downstream of the PI3K/Akt/mTOR pathway, leading to the upregulation of mRNA translation, protein synthesis, as well as cell proliferation (103). Kinome-wide siRNA screen results has revealed that Akt pathway was excessively activated via phosphorylation of Ak at S477/T479 in ribociclib-resistance breast cancer cells and that the level PDK1, a downstream kinase of Akt was increased after short- and long-term treatment with ribociclib in MCF-7 cells, indication that Akt-PDK1 pathway mediated acquired resistance to ribociclib (104). Dual blockade of mTOR and CDK4/6 has a synergistically inhibitory effects on E2F-dependent transcription (105). In a PDX model, the acquired resistance to ribociclib was attenuated by combination of ribociclib and alpelisib. Triple combination of fulvestrant, ribociclib and alpelisib was a better effect on repressing rapid tumor progression that

paired combinations (65). All these results indicated that inhibition of PI3K/Akt/mTOR signaling pathway may overcome the acquired resistance to CDK4/6 inhibitors.

FGFR amplification

Fibroblast growth factor receptor (FGFR) is a type of tyrosine kinase receptors (106). Activation of FGFR signaling can transduce the activation of PI3K/Akt/mTOR pathway, MAPK/ERK pathway, STAT3 pathway, as well as ribosomal protein S6 kinase 2, leading to cell survival, proliferation, differentiation, etc. (106). Overexpression of FGFR was associated with poor prognosis with the reduction of OS and also involved in treatment resistance in various cancers, including breast cancer (107,108). Palbociclib resistant cells showed the increased activity of EKR1/2 and mTOR and overexpression of CDK6, cyclin D and cyclin E, which was driven by FGFR1 signaling in non-small cell lung cancer, indicating that FGFR1-MAP kinase-mTOR pathway contributed to palbociclib resistance through upregulation of CDK6 and cyclin D expression (109). In ER+ BC cells, FGFR1 amplification demonstrated the resistance to fulvestrant ± ribociclib/palbociclib. FGFR1/2 amplification or activating mutations were identified in 14 of 34 patients who have progressed after treatment with CDK4/6 inhibitors by next generation sequencing (NGS) of circulating tumor DNA (ctDNA) (110). Furthermore, data of MONALESSA-2 trial (ribociclib plus letrozole arm) showed that patients with FGFR1 amplification in ctDNA has a shorter PFS (10.61 months) than that (24.84 months) in patients without FGFR1 amplification (110). Taken together, amplification of FGFR1 should be considered as a useful biomarker of resistance to CDK4/6 inhibitors.

Immune regulation

The promising data and clinical success of immune checkpoint inhibition is the milestone of cancer immunotherapy. Results of KEYNOTE-522 showed that the pathological complete response rate increased to 64.8% with combination of pembrolizumab and neoadjuvant chemotherapy compared with 51.2% in the neoadjuvant chemotherapy in patients with early triple negative BC, demonstrating the potential clinical use of pembrolizumab in BC (111). CDK4/6 and cyclin D have been revealed to play a role in immune cells (112). Cyclin D3 is required for early development of B cells by integrating cytokine and is essential for maturation of T lymphocyte (113,114). Inhibition of CDK4/6 may promote the infiltration of immune cells through senescence-associated secretory phenotype (115). Inhibition of CDK4/6 by palbociclib or trilaciclib increased T cell activation but decreased T cell proliferation. Combination of CDK4/6 inhibitors and anti-PD-1 antibody showed a synergistic effects on anti-tumor immunity, which is mediated by enhancement of T cell activation (116). These preclinical studies suggest that immune regulation may influence the anti-tumor activity of CDK4/6 inhibitors. Interestingly, biomarker analysis of PALOMA-2 found that higher level of PD-1 showed less clinical benefit from the combination of palbociclib and letrozole compared with low PD-1expression (49). Taken together, immune regulation may also one of the mechanisms of resistance to CDK4/6 inhibitors.

Conclusions

In conclusion, this review summarized the mechanism of CDK4/6 inhibitors, preclinical and potential clinical biomarkers of resistance to CDK4/6 inhibitors. Resistance to CDK4/6 inhibitor was mainly caused by upregulation of downstream proteins, excessive activation of downstream signaling pathways, and activation of bypass signaling pathways. However, most of the biomarkers mentioned in this review are under preclinical research. Only few of them have been validated by clinical data. Therefore, large clinical trials and real-world evidences are warranted to figure out the resistant mechanism of CDK4/6 inhibitors, which will facilitate oncologists to maximize clinical benefits of CDK4/6 inhibitors and optimize the therapeutic regimens after disease progression.

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tbcr-20-52). The authors have no conflicts of interest to declare.

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