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REVIEW ARTICLE

Emerging immunomodulatory effects of CDK4/6 inhibitors in breast cancer therapy: A comprehensive review

Yuling Zhang[1], Bingfeng Chen[2], Siyue Lin[3], Rendong Zhang[2], Jundong Wu[2,4]*, and Chunfa Chen[2,4]*

[1]Department of Medical Quality Management, Cancer Hospital of Shantou University Medical College, Shantou, Guangdong, China

[2]The Breast Center, Cancer Hospital of Shantou University Medical College, Shantou, Guangdong, China

[3]First Clinical Medical College of Guangdong Medical University, Zhanjiang, Guangdong, China

[4]The Research Laboratory for Breast Cancer Diagnosis and Treatment, Cancer Hospital of Shantou University Medical College, Shantou, Guangdong, China

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Abstract

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, initially developed to regulate cell cycle progression, have recently been recognized as potent immunomodulatory agents in cancer therapy. Accumulating evidence indicates that these inhibitors can modulate key immune cells, including T cells, natural killer cells, and macrophages, thereby enhancing their antitumor functions. By arresting cell cycle progression in both tumor and immune cells, CDK4/6 inhibitors create an immune-permissive microenvironment that facilitates more effective immune-mediated tumor eradication. In addition, these inhibitors may help overcome immune resistance mechanisms, providing a strong rationale for their combination with immune checkpoint inhibitors to amplify antitumor responses. Despite these promising findings, the specific mechanisms through which CDK4/6 inhibitors enhance immune responses, as well as their potential applications in breast cancer, remain areas of active investigation. A deeper understanding of their immunomodulatory effects is essential for developing novel combination therapies that could significantly improve the efficacy of cancer immunotherapy. This review synthesizes the latest evidence on the immunomodulatory effects of CDK4/6 inhibitors, highlighting their potential to augment antitumor immunity and exploring future directions for their clinical application.

Keywords: CDK4/6 inhibitors; Immunomodulation; Antitumor immunity; Combination therapy; Cancer treatment

***Corresponding authors:**
Jundong Wu
(wujun-dong@163.com)
Chunfa Chen
(chenchunfa@stu.edu.cn)

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1. Introduction

The field of cancer therapy has undergone remarkable advancements, transitioning from conventional cytotoxic chemotherapy to more precise strategies targeting specific

molecular vulnerabilities within cancer cells. A pivotal breakthrough in this evolution has been the development of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, which have revolutionized the treatment of hormone receptor-positive (HR^+), human epidermal growth factor receptor 2-negative ($HER2^-$) metastatic breast cancer (MBC).[1] These agents exert their therapeutic effects by inducing cell cycle arrest, thereby inhibiting tumor cell proliferation.[2] CDK4/6 inhibitors, including palbociclib, ribociclib, and abemaciclib, have demonstrated impressive efficacy in combination with endocrine therapy, significantly prolonging progression-free survival (PFS) and, in some cases, overall survival (OS).[1,3] Emerging evidence, however, suggests that the biological impact of these inhibitors extends beyond their canonical role in cell cycle regulation, revealing complex and multifaceted effects on tumor biology. Notably, these inhibitors exhibit immunomodulatory properties that are capable of reprogramming the tumor microenvironment (TME).

Immune checkpoint inhibitors (ICIs) have also revolutionized cancer therapy by targeting regulatory proteins on immune cells, such as T cells, which normally act as natural "brakes" to limit immune responses. By releasing these immune "brakes," ICIs enhance the body's ability to recognize and eliminate cancer cells.[4] Key immune checkpoint proteins targeted by ICIs include programmed cell death protein 1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[5] While ICIs have demonstrated remarkable success in treating various cancer, including melanoma, lung cancer, and Hodgkin lymphoma, their efficacy as monotherapy in $HR^+/HER2^-$ breast cancer remains limited.[6] This reduced activity may stem from the relatively low tumor-infiltrating lymphocyte (TIL) density and low tumor mutational burden characteristic of this breast cancer subtype, suggesting a less immunogenic TME. The modest success of ICIs as single agents in $HR^+/HER2^-$ breast cancer underscores the need to explore combination strategies that may enhance tumor immunogenicity and improve immune response efficacy.

Emerging evidence supports the therapeutic rationale for combining CDK4/6 inhibitors with immunotherapy in $HR^+/HER2^-$ breast cancer. These inhibitors exhibit distinct immunomodulatory properties, including enhanced tumor antigen presentation and reduced immunosuppressive regulatory T cells (Tregs), which may potentiate the efficacy of immune-based therapies.[7] The intersection of cell cycle regulation and immune response represents an exciting and evolving area of oncological research, challenging traditional paradigms of cancer treatment.[8]

Given these intriguing and evolving mechanisms, a thorough investigation into combining CDK4/6 inhibitors with ICIs is warranted to elucidate their biological interactions and therapeutic potential. This review examines the promise of such combination strategies, examining the scientific rationale, present clinical evidence, and challenges associated with this approach.

2. The effects of CDK4/6 inhibitors

2.1. Primary mechanisms of CDK4/6 inhibitors

In HR^+ breast cancer, estrogen signaling upregulates cyclin D expression, activating CDK4/6 to drive cell cycle progression.[9] The subsequent molecular cascade is highly coordinated across distinct cell cycle phases: G1 (growth), S (DNA synthesis), G2 (pre-mitotic expansion), and M (mitosis).[10] CDKs are key orchestrators, with cyclin D-CDK4/6 complexes serving as master regulators of the G1/S checkpoint.[1] These complexes initiate retinoblastoma (Rb) protein phosphorylation, inactivating this tumor suppressor and liberating E2F transcription factors to activate genes required for S-phase progression.[11] The estrogen-CDK4/6 signaling axis, therefore, represents a unique therapeutic vulnerability in HR^+ breast cancers, explaining their exceptional sensitivity to CDK4/6 inhibitors, particularly when combined with endocrine therapy.

Building upon this molecular framework, CDK4/6 inhibitors exert their therapeutic effects by blocking Rb phosphorylation, thereby maintaining its growth-suppressive hypophosphorylated state. This inhibition prevents E2F-mediated transcriptional activation of S-phase genes, resulting in potent G1 cell cycle arrest.[12,13] While sharing this core mechanism, CDK4/6 inhibitors display distinct pharmacological characteristics. For instance, abemaciclib demonstrates greater selectivity for CDK4 over CDK6 and exhibits enhanced blood–brain barrier penetration, potentially offering advantages in specific clinical scenarios.[14] It also exhibits off-target effects by inhibiting additional cyclin-dependent kinases, such as CDK2/Cyclin A/E and CDK1/Cyclin B complexes.[15] These differential properties translate to varied biological outcomes, including G2 phase arrest, cell death in Rb phosphorylation-deficient cells, and characteristic transcriptional signatures observed across experimental systems.

2.2. Modulating other cellular processes

Beyond their well-characterized roles in cell cycle control, CDK4/6 inhibitors exert profound impacts on diverse cellular processes through intricate molecular interactions. Depending on specific cellular microenvironments, these inhibitors can induce either cellular quiescence or trigger senescence. This dual regulatory capability provides a

refined strategy for managing cellular behavior.[12] For instance, the induction of quiescence in normal tissue cells preserves cellular function and prevents aberrant proliferation, while the promotion of senescence in cancer cells effectively suppresses their growth and division.

CDK4/6 inhibitors regulate autophagy in a manner dependent on cell type and pathophysiological context, thereby introducing cellular response intricacies and profoundly impacting survival and functionality.[12] Notably, their suppression of autophagy in specific cancer models may enhance the efficacy of chemotherapy or radiotherapy.

A particularly notable impact of these inhibitors is their capacity to reprogram tumor cell metabolism by disrupting the balance between anabolism and catabolism. This alteration modifies the synthesis and utilization of key metabolites, potentially impairing energy supply mechanisms and survival strategies in cancer cells.[12] Consequently, malignant cells may become more responsive to other anticancer therapies.

2. Mechanism of ICIs

The immune system maintains self-tolerance and prevents excessive immune responses through a sophisticated regulatory network known as immune checkpoints.[16] These checkpoints involve interactions between specific proteins expressed on immune cells, such as T cells, and their corresponding ligands on other cells, including tumor cells. PD-1 is an inhibitory receptor expressed on activated T-cells, while its ligand, PD-L1, is frequently overexpressed on tumor cells and antigen-presenting cells. Upon PD-1/PD-L1 binding, inhibitory signals are transmitted to T-cells, leading to T-cell exhaustion and diminished antitumor activity.[17] CTLA-4 is another critical inhibitory receptor on T cells. CTLA-4 primarily functions during early T-cell activation by outcompeting the costimulatory receptor CD28 for binding to B7 proteins on antigen-presenting cells, thereby suppressing T-cell responses.[18] ICIs, typically monoclonal antibodies, are designed to disrupt these protein-ligand interactions.[5] For example, anti-PD-1 antibodies, such as nivolumab and pembrolizumab, block PD-1 on T-cells, preventing PD-L1 engagement and restoring T-cell cytotoxic activity. Anti-PD-L1 antibodies, such as atezolizumab and durvalumab, achieve similar effects by directly targeting PD-L1 on tumor cells. Anti-CTLA-4 antibodies, such as ipilimumab, enhance early T-cell activation by inhibiting CTLA-4-mediated suppression.[19]

3. Research on the immunomodulatory effects of CDK4/6 inhibitors

Recent studies have illuminated the multifaceted immunomodulatory effects of CDK4/6 inhibitors both *in vitro* and *in vivo* (Table 1). *In vitro* research has demonstrated that CDK4/6 inhibition can significantly enhance antitumor immunity through various mechanisms. For instance, it promotes T-cell activation and triggers antitumor responses by inducing the expression of endogenous retroviral elements in tumor cells, thereby increasing antigen presentation and inhibiting the proliferation of Tregs.[8,20] In addition, CDK4/6 inhibition has been shown to inhibit p73 phosphorylation and activate death receptor 5 (DR5), potentially enhancing the efficacy of chemotherapy and immune checkpoint blockade, while also promoting immunogenic cell death in cancer cells.[21] Notably, the CDK4/6 inhibitor abemaciclib, when combined with low-dose radiotherapy, creates an inflammatory TME in Rb-deficient small cell lung cancer, thereby enhancing antitumor immune responses to PD-1 blockade.[22] Other findings have highlighted alterations in TBK1 phosphorylation that inhibit the stimulator of interferon (IFN) genes (STING) signaling pathway in prostate cancer,[23] the use of mesoporous polydopamine for targeted delivery of CDK4/6 inhibitors to improve synergistic immunotherapy in breast cancer,[24] and the promotion of chemokine-mediated T-cell recruitment to breast tumors through metabolic regulation.[25] Furthermore, single-cell profiling has been highlighted as a tool to guide combination immunotherapy for CDK4/6 inhibitor-resistant $HER2^{+}$ breast cancer, overcoming resistance and enhancing treatment efficacy.[26]

Furthermore, CDK4/6 inhibitors have been found to induce T-cell-inflamed TME, enhancing the efficacy of PD-L1 checkpoint blockade and leading to delayed tumor growth and complete regression when combined with anti-PD-L1.[27] These inhibitors also boost the efficacy of oncolytic viruses by increasing tumor-selective cell killing and T-cell activation in refractory glioblastoma, significantly inhibiting tumor growth and prolonging survival.[28] Pharmacological inhibition of CDK4/6 and mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK) has been shown to induce robust cell cycle arrest and interferon (IFN)-related genes, leading to separable cell cycle arrest and immune responses in RAS-mutant disease models.[29] Innovative approaches, such as the use of self-assembled natural triterpenoid compounds for delivering CDK4/6 inhibitors, have also been explored to improve cancer chemotherapeutic immunotherapy.[30]

In vivo studies in animal models have further corroborated the antitumor potential of CDK4/6 inhibition. These studies have shown that CDK4/6 inhibition promotes antitumor immunity by inducing T-cell memory, thereby

Table 1. Summary of research on CDK4/6 inhibition and antitumor immunity

Author	Type	Year	*In vivo/In vitro*	Key finding	Ref.
Deng *et al.*	Article	2018	*In vitro*	CDK4/6 inhibition enhances antitumor immunity by promoting T cell activation.	20
Goel *et al.*	Article	2017	*In vitro*	CDK4/6 inhibition triggers antitumor immunity by activating endogenous retroviral elements in tumor cells, enhancing antigen presentation, and suppressing regulatory T cell proliferation.	8
Tong *et al.*	Article	2022	*In vitro*	CDK4/6 inhibition suppresses p73 phosphorylation and activates DR5, potentially enhancing the efficacy of chemotherapy and immune checkpoint blockade by promoting immunogenic cell death in cancer cells.	21
Wang *et al.*	Article	2024	*In vitro*	The CDK4/6 inhibitor abemaciclib synergizes with low-dose radiotherapy to enhance anti-PD-1 immune responses by remodeling the inflammatory TME in Rb-deficient small cell lung cancer.	22
Li *et al.*	Article	2024	*In vitro*	CDK4/6 inhibitors stimulate the STING pathway and enhance the antitumor effect of STING agonists in prostate cancer, potentially overcoming immunosuppression.	23
Zhou *et al.*	Article	2024	*In vitro*	Mesoporous polydopamine enables targeted delivery of CDK4/6 inhibitors to enhance combinatorial immunotherapy in breast cancer, eliciting robust systemic antitumor immunity.	24
Uzhachenko *et al.*	Article	2021	*In vitro*	Metabolic modulation by CDK4/6 inhibitors promotes chemokine-mediated T cell recruitment into breast tumors, associated with metabolic stress.	25
Wang *et al.*	Article	2019	*In vitro*	Single-cell profiling guides combinatorial immunotherapy for rapidly evolving CDK4/6 inhibitor-resistant HER2+breast cancer to overcome drug resistance.	26
Schaer *et al.*	Article	2018	*In vitro*	The CDK4/6 inhibitor abemaciclib induces a T-cell-inflamed TME and enhances the efficacy of PD-L1 checkpoint blockade, resulting in delayed tumor growth. Combination with anti-PD-L1 leads to complete regression.	27
Xiao *et al.*	Article	2022	*In vitro*	CDK4/6 inhibition enhances oncolytic virotherapy efficacy in refractory glioblastoma by augmenting tumor-selective cytotoxicity and T-cell activation, significantly suppressing tumor growth and prolonging survival.	28
Wu *et al.*	Article	2024	*In vitro*	Pharmacological CDK4/6 and MEK co-inhibition induces dissociable cell cycle arrest and immune responses in RAS-mutant disease models, driving potent cytostatic and IFN-associated genes.	29
Zhang *et al.*	Article	2025	*In vitro*	Self-assembling natural triterpenoids enable targeted delivery of CDK4/6 inhibitors to enhance cancer chemoimmunotherapy.	30
Lelliott *et al.*	Article	2021	*In vivo*	CDK4/6 inhibition promotes antitumor immunity by inducing T cell memory, thereby fostering long-term endogenous antitumor T cell immunity.	31
Yang *et al.*	Article	2024	*In vivo*	CDK4/6 inhibitors and radiotherapy demonstrate synergistic potential with anti-PD-L1 immunotherapy in triple-negative breast cancer, warranting exploration of combination strategies.	32
Zhang *et al.*	Article	2020	*In vivo*	CDK4/6 inhibition promotes immune infiltration in ovarian cancer and synergizes with PD-1 blockade in a B cell-dependent manner, enhancing immunocyte recruitment and inducing pro-inflammatory responses, ultimately generating synergistic antitumor effects when combined with PD-1 inhibitors.	33

Abbreviations: CDK4/6: Cyclin-dependent kinase 4 and 6; DR5: Death receptor 5; HER2: Human epidermal growth factor receptor 2; IFN: Interferon; MEK: Mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; STING: Stimulator of interferon genes; Rb: Retinoblastoma; TME: Tumor microenvironment.

facilitating long-term endogenous antitumor T-cell immunity.[31] Combination therapies involving CDK4/6 inhibitors, radiotherapy, and anti-PD-L1 immunotherapy have demonstrated synergistic potential in triple-negative breast cancer, highlighting the importance of exploring such strategies.[32] In addition, CDK4/6 inhibition has been found to promote immune infiltration in ovarian cancer and synergize with PD-1 blockers in a B cell-dependent manner, enhancing immune infiltration, inducing pro-inflammatory immune responses, and producing synergistic antitumor effects when combined with PD-1 blockers.[33] These findings collectively underscore the diverse and potent immunomodulatory roles of CDK4/6 inhibitors, positioning them as promising candidates for advancing cancer immunotherapy.

5. Mechanisms of immunomodulatory effects of CDK4/6 inhibitors

5.1. Enhancement of immune cell responses

5.1.1. T-cell responses

CDK4/6 inhibitors potentiate T-cell activation and function by counteracting immunosuppressive signals, such as PD-1. This effect primarily stems from their ability to relieve suppression of the nuclear factor of activated T cells (NFAT) protein family and its downstream targets, which are critical regulators of T-cell functionality.[20] As shown in Figure 1, by inhibiting NFAT phosphorylation, these inhibitors promote the nuclear translocation of non-phosphorylated NFAT, thereby activating the transcription of effector genes. This cascade upregulates the mRNA expression of interleukins (ILs), such as IL-2, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF), and enhances IL-2 secretion, as demonstrated in PD-1-expressing Jurkat cells and primary human $CD4^+$ T cells.[34,35]

Notably, CDK4/6 inhibitors further amplify antitumor responses by elevating interferon-gamma (IFN-γ) production in T-cells.[34,35] Preclinical and clinical studies reveal that these inhibitors foster memory T-cell differentiation through upregulation of max dimerization protein 4 (MXD4), a negative regulator of myelocytomatosis viral oncogene homolog (MYC) in $CD8^+$ T cells, thereby sustaining durable antitumor immunity.[31,34] In breast cancer patients, palbociclib or abemaciclib treatment increases the proportion of $CD8^+$ T memory precursor cells while suppressing MYC target gene expression.[34] *In vivo* analyses of patient-derived organotypic tumor spheroids demonstrate enhanced infiltration of $CD4^+$ and $CD8^+$ T cells, accompanied by elevated Th1-type cytokines, such as C-X-C motif chemokine ligand (CXCL) 9, CXCL10, and IFN-γ.[20]

Further investigations show that tumor-specific $CD8^+$ T cells pretreated with CDK4/6 inhibitors exhibit superior persistence *in vivo*, markedly improving antitumor immunity.[34] Short-term CDK4/6 inhibition before chimeric antigen receptor T cell therapy further augments cellular longevity and therapeutic efficacy.[31] These synergistic effects not only optimize T-cell performance but also provide a rationale for combining CDK4/6 inhibitors with immunotherapies.

5.1.2. Natural killer (NK) cell interactions

The interaction between CDK4/6 inhibitors and NK cells represents an emerging area of investigation. While

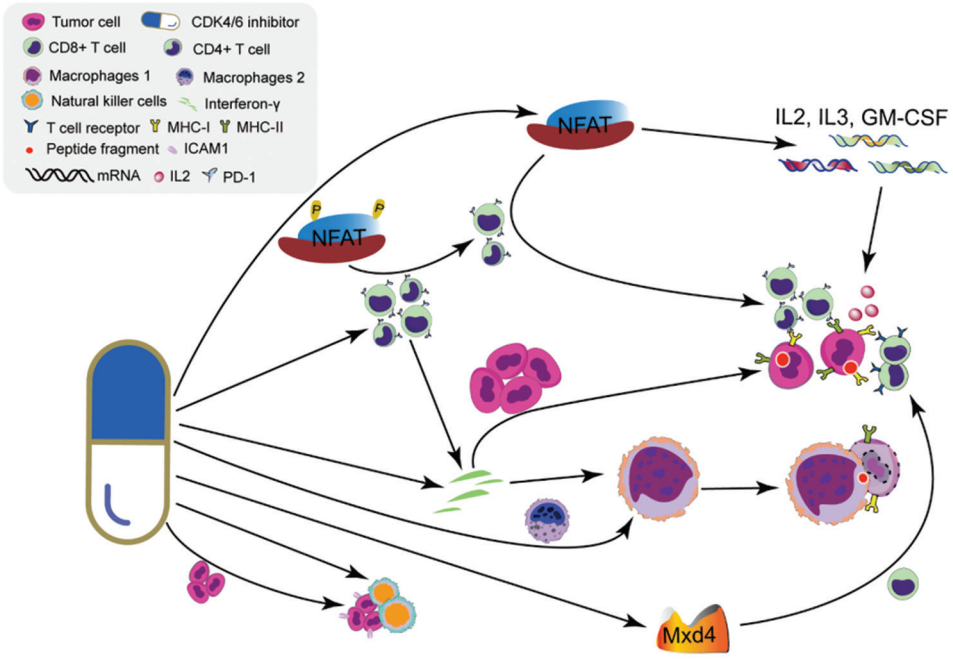


Figure 1. CDK4/6 inhibitors enhance immune cells response. CDK4/6 inhibitors potentiate adaptive immunity by enhancing T-cell activation and augment natural killer cells cytotoxicity. They also reprogram tumor-associated macrophages, shifting their phenotype from the immunosuppressive M2 state to the pro-inflammatory, tumoricidal M1 state. Image created by the authors.

Abbreviations: CDK4/6: Cyclin-dependent kinase 4 and 6; GM-CSF: Granulocyte-macrophage colony-stimulating factor; ICAM1: Intercellular adhesion molecule 1; IL: Interleukin; MHC: Major histocompatibility complex; MXD4: Max dimerization protein 4; NFAT: Nuclear factor of activated T cells; PD-1: Programmed cell death protein 1.

the exact mechanisms are not fully elucidated, available data suggest that these inhibitors can enhance NK cell activation and increase their cytotoxic capabilities (Figure 1). For instance, CDK4/6 inhibitors have been shown to elevate the expression of intercellular adhesion molecule 1, which facilitates the recognition of tumor cells by NK cells.[36] There is a growing consensus that the combination of CDK4/6 inhibitors with other agents, such as MEK inhibitors, may enhance NK cell-mediated tumor elimination through senescence-associated secretory phenotype (SASP) factors.[37] In addition, these inhibitors might influence the formation of the immune synapse between NK cells and tumor cells, potentially amplifying NK cell-mediated cytotoxicity against tumor cells.[38,39]

5.1.3. Modulation of macrophage polarization

CDK4/6 inhibitors have been shown to influence macrophage polarization within the TME. Recent findings suggest that these inhibitors can induce a transition in macrophage phenotype from the immunosuppressive macrophage M2 state to the tumoricidal macrophage M1 phenotype (Figure 1).[40] Specifically, treatment with abemaciclib has been associated with elevated levels of CSF-2, a cytokine that is pivotal for fostering macrophage M1 polarization and enhancing major histocompatibility complex (MHC) II expression in dendritic cells.[41] In addition, ribociclib has been observed to decrease the expression of immunosuppressive chemokines, including C-C motif chemokine ligand (CCL)2, CCL7, and CCL22, which play a role in the chemotaxis and differentiation of immunosuppressive cells, such as macrophage M2.[41] This modulation of macrophage polarization is believed to enhance antitumor immune responses. However, the specific molecular pathways through which CDK4/6 inhibitors reprogram macrophages are not yet fully understood.[42]

5.2. Enhancing tumor cell immunogenicity

CDK4/6 inhibitors enhance the visibility of tumor cells to the immune system by modulating immunogenic signaling pathways (Figure 2). They activate the IFN response, promote the secretion of IFN-γ, and enhance the activity of IFN-stimulated genes, thereby improving the immune system's ability to recognize cancer cells.[43] CDK4/6 inhibition induces the production of IFN-I in tumor cells, which in turn stimulates the secretion of T-cell chemokines, facilitating the recruitment of T-cells to the tumor site and strengthening antitumor immunity.[44,45] Furthermore, CDK4/6 inhibitors trigger epigenetic remodeling by suppressing DNA methyltransferases, leading to the upregulation of endogenous retroviruses. This cascade increases the production of IFN-III and

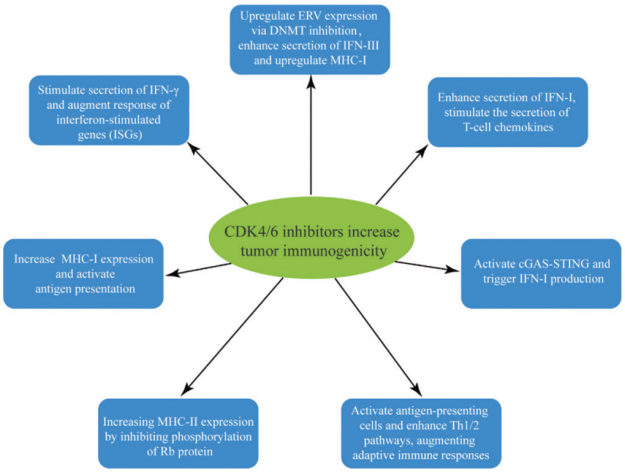


Figure 2. The specific roles of CDK4/6 inhibitors in augmenting tumor cell immunogenicity. Image created by the authors.
Abbreviations: CDK4/6: Cyclin-dependent kinase 4 and 6; cGAS-STING: Cyclic GMP-AMP synthase-stimulator of interferon genes; DNMT: DNA methyltransferase; ERV: Endogenous retroviruses; IFN: Interferon; MHC: Major histocompatibility complex; Rb: Retinoblastoma.

enhances the presentation of MHC-I molecules, making tumors more immunogenic.[46] In addition, these inhibitors activate the cyclic GMP-AMP synthase-STING pathway, driving IFN-I production and amplifying innate immune responses.[47] Finally, CDK4/6 inhibitors prime antigen-presenting cells, such as dendritic cells and macrophages, promoting the activation of Th1/Th2 pathways and playing crucial roles in adaptive immunity.[48]

CDK4/6 inhibitors enhance tumor immunogenicity by upregulating the surface expression of MHC-I molecules, which are essential for antigen presentation to $CD8^+$ T cells that recognize and eliminate tumor cells.[44,49] Research has shown that palbociclib treatment increases MHC-I expression in melanoma cell lines and alters the MHC-I peptide repertoire, thereby enhancing immunogenicity.[50] This effect is mediated through the transcriptional activation of the antigen processing and presentation machinery, including genes encoding proteasomes, transporter-associated antigen processing complexes, and MHC-I subunits. Notably, CDK4/6 inhibitors also increase MHC-II expression in tumor cells.[44,49] Mechanistically, they restore IFN-γ-induced MHC-II transcription by inhibiting the phosphorylation of the Rb protein.[36,41] In breast cancer and lymphoma models, abemaciclib and palbociclib have been shown to increase MHC-II levels, thereby augmenting T-cell activation.[41]

5.3. Remodeling the TME

CDK4/6 inhibitors have emerged as pivotal modulators of the TME, a complex ecosystem comprising immune cells, vasculature, and stromal components. As illustrated

in Figure 3, the inhibition of CDK4/6 diminishes the presence of tumor-infiltrating Tregs,[44,49] thereby reducing immunosuppressive cellular networks and promoting an immuno-permissive TME. However, this therapeutic approach might also deplete dendritic cells within the TME, potentially hindering immune activation. The adoptive transfer of dendritic cells has been demonstrated to circumvent this issue, facilitating effective tumor control when used in conjunction with CDK4/6 inhibitors and immune checkpoint blockade.[51]

Unlike DNA-damaging agents, senescence induced by CDK4/6 inhibitors is marked by minimal expression of pro-tumorigenic factors, such as IL-6 and CXCL8, resulting in a TME with augmented antitumor properties. Numerous studies have shown that CDK4/6 inhibition encourages the infiltration of cytotoxic T-cells into tumors, a critical factor for effective antitumor immunity.[27,49,52] In some cases, CDK4/6 inhibition also alters tumor-associated macrophage populations, potentially steering their polarization toward antitumor phenotypes.[52] These coordinated alterations collectively create an immunologically "hot" TME with diminished immunosuppression, offering a compelling basis for combining CDK4/6 inhibitors with cancer immunotherapy.

Beyond their immunomodulatory effects, emerging evidence suggests that CDK4/6 inhibitors may also impact tumor angiogenesis, the process of new blood vessel formation essential for tumor growth and metastasis. Although CDK6 has been associated with angiogenic regulation, its pharmacological inhibition could simultaneously target both tumor proliferation and vascularization.[53] Given the dual inhibition of CDK4/6, these agents might indirectly influence angiogenesis, even though their mechanisms are less clear compared to their immunological effects. A study on CDK4/vascular endothelial growth factor receptor 2 (VEGFR2) dual-targeting inhibitors showed synergistic suppression of cancer progression and angiogenesis,[54] yet the direct angiogenic effects of standard CDK4/6 inhibitors require further exploration.

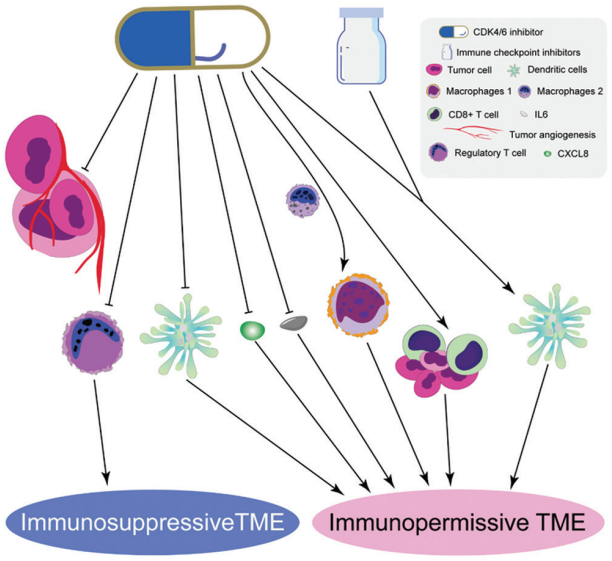


Figure 3. Mechanisms of CDK4/6 inhibitors in TME reprogramming. CDK4/6 inhibitors modulate the TME by acting on a complex ecosystem comprising immune cells, vasculature, and stromal components. Image created by the authors.
Abbreviations: CDK4/6: Cyclin-dependent kinase 4 and 6; CXCL8: C-X-C motif chemokine ligand 8; IL6: Interleukin 6; TME: Tumor microenvironment.

5.4. Regulation of PD-L1 expression

PD-L1, a critical immune checkpoint protein expressed on tumor cell surfaces, suppresses T-cell-mediated immune responses through binding to the PD-1 receptor.[55] This interaction facilitates tumor immune evasion by inhibiting cytotoxic T-cell activity and promoting T-cell exhaustion. To enhance the therapeutic efficacy of combining CDK4/6 inhibitors with ICIs, comprehending the effect of CDK4/6 inhibitors on PD-L1 expression is crucial, as depicted in Figure 4. Studies suggest that CDK4/6 inhibitors can upregulate PD-L1 expression by activating the nuclear factor kappa B signaling pathway.[49] Typically, the CDK4/6-cyclin D complex facilitates the degradation of PD-L1 through the speckle-type POZ protein-cullin 3 (CUL3) ubiquitination pathway. However, CDK4/6 inhibition interferes with this degradation process, leading to the stabilization of PD-L1 protein levels.[56] This stabilization can potentially make tumors more susceptible to

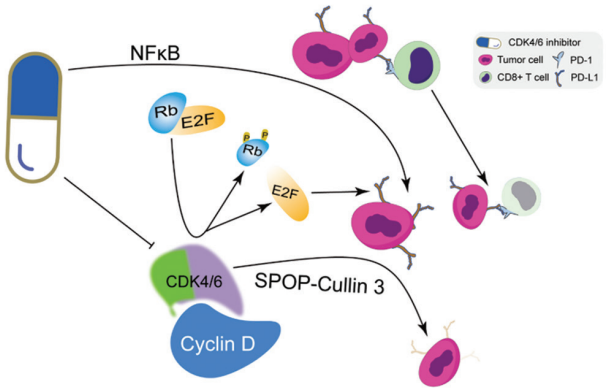


Figure 4. Modulatory effects of CDK4/6 inhibitors on PD-L1 expression. CDK4/6 inhibitors upregulate PD-L1 expression and stabilize PD-L1 protein levels, thereby sensitizing tumors to PD-1/PD-L1 blockade therapies. Image created by the authors.
Abbreviations: CDK4/6: Cyclin-dependent kinase 4 and 6; NFκB: Nuclear factor kappa B; PD-1: Programmed cell death protein 1; PD-L1: Programmed death ligand-1; Rb: Retinoblastoma; SPOP: Speckle-type POZ protein.

PD-1/PD-L1 blockade therapies. Conversely, in certain contexts, such as triple-negative breast cancer, CDK4/6 inhibitors may reduce PD-L1 levels through the RB-E2F signaling axis.[57] The overall impact of CDK4/6 inhibition on PD-L1 expression is context-dependent, varying with tumor type and microenvironment, highlighting the complex interaction that must be taken into account when formulating combination treatment strategies.[58]

6. Clinical evidence and trial assessment of CDK4/6 inhibitors in combination with ICIs in HR$^+$/HER2$^-$ breast cancer

Ongoing clinical trials are actively exploring the therapeutic potential of combining CDK4/6 inhibitors with ICIs for patients with HR$^+$/HER2$^-$ breast cancer. As summarized in Table 2, the CheckMate 7A8 trial, which assessed the

Table 2. Summary of the clinical trial assessment of CDK4/6 inhibitors in combination with immunotherapy in HR$^+$/HER2$^-$ breast cancer

Trial name/ Identifier	Phase	Tumor type	CDK4/6 inhibitor	Immunomodulator agent	Key findings	Ref.
CheckMate 7A8 (NCT04075604)	Phase II	HR$^+$/HER2$^-$early breast cancer	Palbociclib	Nivolumab (anti-PD-1)	Objective response rate of 71.4%.	59
ImmunoADAPT (NCT03820063)	Phase II	Early-stage ER$^+$/HER2$^-$ breast cancer	Palbociclib	Avelumab (anti-PD-L1)	The combination of fulvestrant, palbociclib, and avelumab showed a trend toward improved PFS, with a median PFS of 8.1 months. However, this improvement was not statistically significant compared to fulvestrant alone.	62,63
KEYNOTE-146 (NCT02779751)	Phase I/II	HR$^+$/HER2$^-$MBC	Abemaciclib	Pembrolizumab (anti-PD-1)	Overall response rate of 23.1% and disease control rate of 84.6%.	60
NCT02778685	Phase I/II	HR$^+$/HER2$^-$MBC	Palbociclib	Pembrolizumab (anti-PD-1)	Complete response rate of 31% and PFS of 25.2 months.	61
NCT03294694	Phase I	HR$^+$/HER2$^-$MBC or advanced ovarian cancer	Ribociclib	Spartalizumab (anti-PD-1)	Limited added benefit over ribociclib$^+$fulvestrant alone in HR$^+$MBC. Triplet (with fulvestrant): Objective response rates: ~30% in CDK4/6i-naïve patients. Clinical benefit rate: ~50%. Doublet (without fulvestrant): Limited activity, with objective response rates<15%, suggesting endocrine therapy is critical for synergy.	64
WJOG11418B (NEWFLAME) (NCT04075604)	Phase II	HR$^+$/HER2$^-$MBC	Abemaciclib	Nivolumab (anti-PD-1)	Objective response rates of 54.5% and 40% in the fulvestrant and letrozole cohorts, respectively.	65
PACE (NCT03147287)	Phase II	HR$^+$/HER2$^-$MBC	Palbociclib	Avelumab (anti-PD-L1)	No significant improvement in median PFS was observed with the addition of avelumab to fulvestrant plus palbociclib (8.1 months) compared with fulvestrant plus palbociclib (4.6 months) or fulvestrant alone (4.8 months; *P*=NS). Subgroup analysis showed no benefit in PD-L1$^+$or high-TIL tumors.	66

Abbreviations: CDK4/6i: Cyclin-dependent kinase 4 and 6 inhibitor; ER$^+$: Estrogen receptor-positive; HER2$^-$: Human epidermal growth factor receptor 2-negative; HR$^+$: Hormone receptor-positive; MBC: Metastatic breast cancer; NS: Not significant; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; TIL: Tumor-infiltrating lymphocytes.

neoadjuvant regimen of nivolumab in combination with palbociclib and anastrozole, reported an impressive objective response rate of 71.4%.[59] In addition, a phase II study (NCT02779751) that incorporated pembrolizumab with abemaciclib yielded an overall response rate of 23.1% and a disease control rate as high as 84.6%.[60] Furthermore, another trial (NCT02778685) that employed the combination of pembrolizumab, palbociclib, and letrozole achieved a notable 31% complete response rate, with a PFS extending to 25.2 months.[61]

It is important to highlight that a phase I trial evaluating ribociclib in conjunction with spartalizumab (an anti-PD-1 antibody), with or without fulvestrant, in patients with $HR^+/HER2^-$ MBC did not show significant additional benefit over ribociclib combined with fulvestrant alone.[64] Conversely, the phase II WJOG11418B NEWFLAME trial, which investigated the combination of nivolumab with abemaciclib in $HR^+/HER2^-$ MBC, reported objective response rates of 54.5% and 40% in the fulvestrant and letrozole treatment groups, respectively.[65] Collectively, these results suggest that the combination of CDK4/6 inhibitors with immunotherapy holds promise as a viable treatment strategy for individuals with $HR^+/HER2^-$ breast cancer.

The criteria for identifying the most suitable patients for combinations of CDK4/6 inhibitors with immunotherapy are still being explored.[67] Numerous clinical trials are underway to assess this approach, such as the ImmunoADAPT trial, which is investigating the use of palbociclib in conjunction with avelumab for early-stage estrogen receptor-positive breast cancer.[62,63] Preliminary findings from this trial suggest a trend toward better PFS with the combination of fulvestrant, palbociclib, and avelumab, achieving a median PFS of 8.1 months. However, this enhancement did not reach statistical significance when compared to fulvestrant monotherapy (hazard ratio = 0.75, 90% confidence interval: 0.50–1.12, p=0.23). In addition, the phase II PACE study (NCT03147287), which evaluated palbociclib combined with avelumab in $HR^+/HER2^-$ MBC patients who had progressed on prior CDK4/6 inhibitor treatment, concluded that PD-1/PD-L1 inhibitors offer limited efficacy in this context without a more refined patient selection process.[66]

7. Discussion

7.1. Synergistic mechanisms underlying the combination approach

The scientific rationale for combining CDK4/6 inhibitors with ICIs stems from accumulating evidence demonstrating that these drug classes act through complementary and potentially synergistic mechanisms. This combination strategy simultaneously targets multiple hallmarks of cancer, addressing both aberrant cellular proliferation and enhancing antitumor immunity, while also potentially overcoming resistance mechanisms that limit the efficacy of monotherapies.[39,68,69] The interaction between these agents occurs at multiple levels, creating a comprehensive antitumor approach with the potential for broader therapeutic efficacy.

At the cellular level, CDK4/6 inhibition fundamentally alters cancer cell biology, rendering malignant cells more susceptible to immune-mediated killing. The drug-induced G1 cell cycle arrest correlates with increased expression of endogenous retroviral elements, stimulating viral mimicry responses and subsequent IFN-I/III production.[70] This process enhances tumor immunogenicity through multiple mechanisms, including increased neoantigen presentation, upregulation of MHC-I molecules, and chemokine-mediated recruitment of cytotoxic T lymphocytes. Concurrently, CDK4/6 inhibitors suppress the expression of DNA methyltransferase 1, leading to DNA hypomethylation and further activation of immunostimulatory pathways.[71]

Moreover, CDK4/6 inhibitors remodel the TME to promote enhanced immune cell infiltration, particularly $CD8^+$ T cells and B cells. This augmented immune infiltration may potentiate the efficacy of PD-1/PD-L1 blockade therapies.[33] In certain preclinical models, the combination of CDK4/6 inhibitors with PD-L1 blockade induced complete tumor regression in a significant proportion of mice, even in cases where PD-L1 monotherapy showed limited or no efficacy.[27] Notably, mice that achieved complete responses to either combination therapy or CDK4/6 inhibitor monotherapy demonstrated resistance to tumor rechallenge, indicating the establishment of durable immune memory.[27] These findings suggest that combining CDK4/6 inhibitors with ICIs may represent a promising strategy to enhance antitumor immunity and improve therapeutic outcomes.

7.2. CDK4/6 inhibitors with ICIs tackle resistance

The PALOMA, MONALEESA, and MONARCH trial series have firmly established CDK4/6 inhibitors as a fundamental therapeutic for $HR^+/HER2^-$ advanced breast cancer.[72-79] These pivotal studies evaluated three distinct CDK4/6 inhibitors, including palbociclib, ribociclib, and abemaciclib, in combination with endocrine therapy. Across these studies, these agents consistently demonstrated significant improvements in median PFS, ranging from 16 to 28 months in the first-line setting,[72,73,75,77,78] and 5 to 20 months in later line therapies.[74,76,77,79] Despite these advancements, therapeutic resistance typically

develops after 1–2 years of treatment, posing a significant challenge for long-term disease management. ICIs have emerged as a potential strategy to overcome or delay resistance to CDK4/6 inhibitors.[80] Pre-clinical evidence suggests that CDK4/6 inhibition can modulate immune responses, potentially enhancing the efficacy of ICIs.[61] This combination approach offers two potential mechanisms: Either delaying resistance development when used concomitantly or restoring treatment sensitivity when ICIs are introduced after CDK4/6 inhibitor failure. Early clinical trials evaluating palbociclib combined with pembrolizumab and endocrine therapy have shown encouraging response rates and PFS benefits, particularly in treatment-naïve patients and those with stable disease on prior CDK4/6 inhibition.[61] Introducing ICIs after CDK4/6 inhibitor failure may be an effective strategy to restore treatment sensitivity. By reactivating the immune response against tumor cells, ICIs can overcome resistance mechanisms, transforming immunologically "cold" tumors into "hot" ones. In addition, studies have shown that CDK4/6 inhibitors can enhance the immunogenicity of tumor cells by modulating the expression of genes related to antigen presentation, thereby improving the effectiveness of immunotherapy. This combined treatment strategy offers new possibilities for addressing resistance issues in tumor immunotherapy.[42,81] While these preliminary results suggest ICIs may help address resistance mechanisms, further investigation is required to validate these findings and elucidate the underlying biological interactions.

7.3. Challenges and potential limitations

Despite their proven efficacy, the clinical use of CDK4/6 inhibitors, particularly in HR^+ breast cancer, encounters several challenges. First, clinical observations have highlighted potential adverse effects, including hepatitis and pneumonitis, which may be linked to increased secretion of pro-inflammatory cytokines and impaired Treg function.[41] Second, combination therapies often require dose reductions due to overlapping toxicities, resulting in suboptimal drug exposure and potentially compromised efficacy.[82] A significant issue with these combination regimens is the increased toxicity, particularly immune-related adverse events and hematological toxicities,[61] which must be carefully monitored and managed. Determining the optimal sequence and dosage of these drugs is essential. Third, approximately 30% of breast cancer patients exhibit intrinsic resistance to CDK4/6 inhibitors.[83] Notably, while these drugs enhance antitumor immunity, resistance mechanisms frequently involve dysregulated IFN signaling and SASP. For instance, De Angelis *et al.*[84] demonstrated that high IFN-response gene signatures, characterized by upregulation of signal transducer and activator of transcription 1, interferon regulatory factor 9, and SP100, along with suppression of immunostimulatory genes, such as inducible T-cell costimulatory (ICOS) and CD70, are strongly associated with treatment resistance. The precise mechanisms driving resistance to CDK4/6 inhibitor-immunotherapy combinations remain poorly characterized, hindering the clinical optimization of these treatments.

7.4. Future prospective

CDK4/6 inhibitors have shown significant potential in breast cancer immunotherapy, with ongoing research targeting several key areas. In early-stage breast cancer, abemaciclib has demonstrated the capacity to reduce the risk of recurrence.[85] In addition, numerous studies are investigating the synergistic effects of combining CDK4/6 inhibitors with ICIs to enhance immune responses and improve clinical outcomes.[86] Importantly, the therapeutic applications of these agents have expanded to include $HER2^+$ and triple-negative breast cancer subtypes, where they have shown clinical benefits.[87]

While research on CDK4/6 inhibitors has predominantly focused on breast cancer, there is growing interest in their application to other cancer types. In ovarian cancer, both preclinical and clinical studies are exploring the potential of CDK4/6 inhibitors as monotherapy or in combination treatments.[88] Preliminary evidence indicates that, while BRAF and MEK inhibitors have inherent antitumor effects, their combination with CDK4/6 inhibitors could further enhance immune activation.[89] Many clinical trials are currently assessing the safety and efficacy of these combined strategies, aiming to identify predictive biomarkers for treatment response and resistance. This would optimize therapeutic outcomes across various cancers through synergistic CDK4/6 inhibition.[41]

Recent studies have drawn attention to the potential of metal ions, such as selenium, zinc, and copper, as critical immunomodulatory trace elements that may enhance the efficacy of CDK4/6 inhibitors.[90,91] This enhancement is achieved by reprogramming immunometabolic pathways within the TME. Specifically, selenium bolsters T-cell resilience against oxidative stress through nuclear factor erythroid 2-related factor 2-mediated antioxidant responses.[92] Meanwhile, zinc aids T-cell proliferation through zeta-chain of T-cell receptor-associated protein kinase 70 signaling and modulates PD-L1 expression on dendritic cells.[93,94] These mechanisms indicate promising opportunities for synergistic combination therapies that target both cell cycle regulation and immunometabolic checkpoints.

It is crucial to note that present evidence largely stems from early-phase clinical trials and pre-clinical models.

Large-scale, randomized, placebo-controlled phase III trials are necessary to confirm both the efficacy and safety profiles of these treatments. Patients whose tumors develop resistance through immune evasion mechanisms may benefit more from the addition of ICIs. The gut microbiome may also play a role in predicting responses to ICI combination therapies.[95] Further research is needed to identify specific biomarkers that can predict which patients will benefit most from this approach.

8. Conclusion

CDK4/6 inhibitors modulate antitumor immunity through multifaceted mechanisms, including direct regulation of T-cell activity, remodeling of the immunosuppressive TME, and regulation of immune checkpoint expression. These immunomodulatory effects provide a mechanistic rationale for combining CDK4/6 inhibitors with ICIs, which may overcome resistance and amplify therapeutic efficacy in cancer treatment. Future studies should focus on elucidating the differential impacts of CDK4/6 inhibition across diverse immune cell populations, refining combinatorial strategies with immunotherapy, and validating these observations across a broader spectrum of tumor malignancies.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Jundong Wu, Chunfa Chen
Visualization: Bingfeng Chen, Chunfa Chen, Siyue Lin
Writing – original draft: Yuling Zhang, Chunfa Chen, Rendong Zhang
Writing – review & editing: Jundong Wu, Chunfa Chen

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