Mechanisms and Implications of CDK4/6 Inhibitors for the Treatment of NSCLC

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Cyclin-dependent kinases (CDKs) are key regulators of cell cycle progression in malignant tumor cells and play an important role through complex molecular interactions. Dysregulation of CDK dependent pathways is often found in non-small cell lung cancer, which indicates its vulnerability and can be used in clinical benefit. CDK4/6 inhibitors can prevent tumor cells from entering the G1 and S phases, which have been studied in a series of explorations and brought great clinical effect to patients and encouragement to both physicians and researchers, thereby showing potential as a new therapeutic agent. A series of preclinical and clinical studies have been carried out on CDK4/6 inhibitors in NSCLC, and have been achieved some results, which may become a new potential treatment in the future. This review focuses on the research progress on CDK4/6 inhibitors in NSCLC, particularly the mechanisms of action, drugs, clinical research progress, and future application.

Keywords: cyclin D-dependent kinase 4/6 inhibitor, cell cycle, NSCLC, therapy, drugs

INTRODUCTION

Lung cancer is one of the frequently diagnosed cancer and is among the main causes of cancer death. Non-small cell cancer (NSCLC) accounts for approximately 85% of lung malignancies. Most of newly diagnosed patients are considered incurable because of the presence of metastases at the time of initial presentation (1). Despite a growing number of treatment methods for advanced NSCLC, the overall benefit is limited. Novel therapeutic targets for NSCLC have attracted considerable interest.

In normal and malignant cells, cyclin dependent kinases (CDKs) are the key regulators, which play roles in multiple points in the cell cycle to drive cellular proliferation through most complex molecular interactions (2). The expression and activation of cell cycle mediators is deranged, especially within the CDK–cyclin–RB pathways, and is involved in malignant transformation and tumor progression in lung cancer (3). In over 90% of lung cancers, the cell cycle occurs as dysregulation, which makes the derangements of cell cycle mediators in the expression and/or activation, especially within the CDK–cyclin–RB pathways, and is integrally involved in malignant transformation and tumor progression, destroying the cell proliferation mechanism controlling the growth of advanced NSCLC (3–5). Cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) form a complex with D-type cyclins, which promote the cell cycle through the G1 restriction point through phosphorylation of the Rb tumor suppressor protein (6). Inhibition of CDK4 and CDK6 can prevent cell cycle progression, prevent tumor growth and promote senescence. Through aberrant
retinoblastoma protein (RB) expression and the mutations of cyclin D (INK4) proteins (p16INK4A) (7) and K-RAS, these cyclins promote uncontrolled cellular proliferation and drive cell cycle progression in lung carcinogenesis (8). According to the analysis of UALCAN cancer database, the CDK6 gene was moderately expressed in LUAD, and the overall survival rate of patients was negatively correlated with it. Figure 1 shows frequencies of aberrations in the Cyclin D-CDK4/6-Rb pathway related genes in NSCLC from the publicly available cBiportal webpage: Pan-Lung Cancer (TCGA, Nat Genet 2016). Therefore, CDK4/6 has been a key target for the clinical development for cancer therapy (9, 10).

CDK4/6 inhibition has been tested in several clinical trials as a plausible treatment option for lung cancer (11–14). CDK4/6 inhibitors, designed to inhibit uncontrolled cellular proliferation, made tumor types with better efficacy and few adverse effects in which CDK4/6 plays a key role in G1-to-S-phase cell-cycle transition to be targeted (9). It can inhibit tumor growth by decreasing phosphorylation of retinoblastoma (RB) protein and inducing cell cycle arrest at the G1/S phase transition, inducing irreversible growth arrest or cell death when used alone or in combination with other therapies (15, 16) (Figure 2) and also promote anti-tumor immunity (17). Some drugs have been approved by the Food and Drug Administration (FDA) as treatment agents to be combined with letrozole in the treatment of hormone receptor (HR)-positive advanced-stage breast cancer (18, 19). Some clinical trials of CDK4/6 inhibitors in other tumors have achieved initial impressive results (20). CDK4/6 inhibitors are still in the early stage of other cancers, mainly confined to basic experiments and stage I or II clinical trials, such as liposarcoma, lymphoma and many other advanced cancers (21–23). A study indicated that CDK4/6 inhibitors in patients with head and neck squamous cell carcinoma have the objective response rate of 39% (n = 62) (24). Some cell cycle inhibitors also have been used in human clinical trials and achieved success in lung cancer (25, 26). Therefore, this article reviews the mechanisms of CDK4/6 inhibitors in NSCLC, monotherapy using CDK4/6 inhibitors, and the effects of combining them with other drugs in the context of NSCLC treatment.

**MONOTHERAPY OF CDK4/6 INHIBITORS IN NSCLC**

With the recent development of highly specific CDK4/6 inhibitors (Palbociclib, Ribociclib, and Abemaciclib) and the approval of their use by the FDA for advanced metastatic breast cancer, designing multiple clinical trials using these agents for lung cancer have attracted great interest (9). However, effective strategies for formulating appropriate trial designs have not been determined. Thus, proper experiments in suitable animal models and clinical trials are needed. Palbociclib was approved in 2016 in terms of structure, and ribociclib and palbociclib are extremely similar. An *in vitro* study showed that the inhibitory effects of ribociclib and abemaciclib on CDK4 are stronger than the inhibitory effect of CDK6 and palbociclib is similar (27). Current clinical studies on NSCLC mainly focus on the phases I and II clinical studies of palbociclib and abemaciclib (Table 1).

That NSCLC tumor actively targets the CDKN2a/p16 locus rather than the observed mutational enrichment in this locus due to a selection process during lung carcinogenesis and tumor progression. Hence, several clinical studies have been conducted.

**Palbociclib**

Palbociclib is a unique selective and promising inhibitor of CDK4 and CDK6 and a cell permeable pyridopyrimidine with oral

![Figure 1](https://example.com/figure1.png)

**Figure 1** Frequencies of aberrations in the Cyclin D-CDK4/6-Rb pathway related genes in NSCLC.
bioavailability (20, 28). Although CDK4/6 can bind with cyclin D1, resulting in Rb hyperphosphorylation, palbociclib can block Rb phosphorylation and prevent E2F1 release by separating CDK4/6–cyclin D1 complexes, resulting in G1 phase arrest and inhibit tumor growth (29). A phase II clinical study of palbociclib included 19 patients with advanced NSCLC previously treated with p16-null staining and immunohistochemistry, and tumor progression was documented (30). There were 16 evaluable patients who had no objective response, and eight (50%) patients were stable for 4.0–10.5 months. The median progression-free survival (PFS) was 3.2 months, and median overall survival (OS) was 7.7 months. The results showed that palbociclib alone was mainly used as a cell inhibitor inducing aging, but not apoptosis, and the median PFS was equivalent to other available second-line chemotherapeutic drugs (31) and PD-1 inhibitors (32, 33). In addition, the reduction rate of grade 3/4 cytopenia with palbociclib in the treatment of NSCLC was 16%, which was better than that of many effective chemotherapeutic drugs for second- or third-line therapy. A Lung-MAP trial (SWOG S1400) demonstrated the amplification of CDK4 or CCND1/2/3 in patients with squamous NSCLC and tumor. Of the 32 patients included in this study, only two (6%) had a partial response and 38% were stable. The median PFS was 1.7 months, and the median OS was 7.1 months. Unfortunately, in these genomically selected patients, palbociclib did not demonstrate any antitumor activity (12). A phase II pragmatic basket trial demonstrated antitumor activity of palbociclib in patients with NSCLC with CDKN2A alterations. Of the 29 patients who were enrolled, one patient had partial response, and six patients with SD were observed, for a disease control rate of 31%. The median PFS was 8.1 weeks, and the median OS was 21.6 weeks. There were 11 patients who had at least one grade 3 or 4 adverse event (AE) or serious AE (SAE) possibly related to palbociclib (most common, cytopenias) (34).

**Abemaciclib**

As an effective and selective small-molecule inhibitor of CDK4 and CDK6, abemaciclib has a wide range of antitumor activity in preclinical models and acceptable toxicity profile in animals such as mice. Preclinical data showed that the sensitivity of KRAS-mutant NSCLC xenograft models to abemaciclib was higher than that of wild-type KRAS gene expression model (13). Moreover, a JPBA phase I study showed that a single-agent abemaciclib has acceptable tolerability or safety and presented evidence of clinical activity in patients with heavily pretreated metastatic NSCLC (35). In addition, they demonstrated that the combined use of ramucirumab and abemaciclib is consistent with the safety profile of single-agent abemaciclib, with lower hematologic toxicity. The total incidence of neutropenia was 23%, and the incidence of grades 3–4 neutropenia was 10%. A phase III JUNIPER clinical trial was designed according to the result of these studies. In this trial, 453 patients who had stage IV NSCLC with KRAS mutations (codon 12 or 13) and disease progression after two lines of therapy were randomized in a ratio of 3:2 into abemaciclib and erlotinib groups (including a platinum-based regimen). The median OS was similar in both groups (7.4 vs. 7.8 months; HR, 0.97; 95% CI, 0.77–1.22; p = 0.77), and the median PFS was significantly better in the abemaciclib group (3.6 vs. 1.9 months; HR, 0.58; 95% CI, 0.47–0.72; p <0.001). The response rate (8.9% vs. 2.7%; p = 0.01) and disease control rate (54% vs. 32%; p <0.001) were significantly better in the abemaciclib group. In this study, compared with erlotinib, the OS in stage IV NSCLC patients harboring KRAS mutations did not improve. However, the additional studies of abemaciclib in other NSCLC subpopulations or in combination with other drugs are required to increases in response rates and PFS (13).
COMBINATION OF CDK4/6 INHIBITORS AND OTHER ANTI-LUNG CANCER THERAPIES

The disappointing results of palbociclib and abemaciclib in NSCLC clinical trials have prompted studies on the effect of combination of CDK4/6 inhibitions and other therapies. Owing to the unsatisfactory results of single-drug treatments, in-depth study of the pathogenesis of NSCLC, and increasing treatment methods for NSCLC, combinations of CDK4/6 inhibitors have been extensively studied.

Combination of CDK4/6 Inhibitors and Chemotherapy

CDK4/6 inhibitors and chemotherapeutic drugs may have antagonistic effects. For example, CDK4/6 inhibitors in combination with gemcitabine improved antitumor activity without G1 cell cycle arrest in calu-6 xenografts tumor-bearing mice (36). However, another study demonstrated combinations of palbociclib and taxanes at clinically available doses in multiple SqCLC models enhanced antitumor effects by destroying the pRB-E2F signaling pathway (37). Based on preclinical data, a phase Ib clinical study tested abemaciclib in combination with pemetrexed, gemcitabine, or ramucirumab in patients with metastatic NSCLC and confirmed the safety and tolerability of these combinations in previously treated unselected patients with advanced/metastatic NSCLC (38). In these patients, the all-cause high grade (3/4) fatigue occurred in 17–25%. High-grade diarrhea can be well controlled by antidiarrheal treatments and/or dose adjustments.

Combination of CDK4/6 Inhibitors and Immune Checkpoint Inhibitors

The emerge as the times require of immune checkpoint blockade immediately led to the studies of the possible interactions of these therapies with CDK4/6 inhibitors. CDK4/6-targeted therapies have a complex network of immunomodulatory effects on tumor cells and their tumor microenvironment (39). The addition of CDK4/6 inhibitor to chemotherapy/ICI regimens in murine syngeneic tumor models enhanced antitumor response and overall survival compared with chemotherapy, and ICI combinations alone and transient exposure of CDK4/6 inhibition in patients with SCLC during chemotherapy treatment enhanced immune system function by preserving peripheral lymphocyte counts and enhancing T-cell activation (17). These results showed the synergistic antitumor effect of CDK4/6 and immune checkpoint-related inhibitors. The mechanism of CDK4/6 inhibitors combined with immunotherapy may be as follows: First, CDK4/6 inhibitors decrease promoter hypomethylation and inhibit E2F release by inhibiting the proliferation of regulatory T (Treg) cells and the expression of DNA methyltransferase in Treg cells (17). Furthermore, CDK4/6 inhibitors promote tumor cell clearance by enhancing cytotoxic T cells (CTLs) to kill tumor cells (40). Finally, the cyclin D1–CDK4 complex directly phosphorylates speckle-type POZ protein (SPOP), and CDK4/6 inhibitors can enhance the immune escape of tumors by reducing the
ubiquitination of SPOP and the degradation of PD-L1 (41). Preclinical research showed that CDK4/6 inhibitors in combination with anti-PDL1 antibodies promote tumor regressions and the effect is accompanied by enhanced antigen presentation, T cell inflamed phenotype, and cytotoxic T cell-mediated clearance of lung cancer cells; moreover, this combination improves the overall survival rates in mouse tumor models (17, 40, 42). All of these mechanisms provide a theoretical basis for the combination therapy of CDK4/6 inhibitors and immune checkpoint inhibitors in NSCLC in the future and related clinical trials (NCT03601598) are ongoing at present (43).

**CDK4/6 Inhibitors as Radiosensitizers**

Multiple preclinical and small sample clinical studies showed that CDK4/6 inhibitors exhibit a collaborative effect during radiotherapy in vitro and in vivo and show well-tolerated toxicity and promising efficacy in patients (44–47). The potential mechanisms of clinical radiosensitization effects might be apoptosis enhancement, cell cycle progression blockage, and induction of cellular senescence and antitumor immunity (48). A preclinical study showed that abemaciclib and ionizing radiation (IR) had a good radiosensitization effect on tumor cells in proliferative and plateau-phase and tumor xenografts, but had little radiosensitization effect on normal cells, and improve the radiation sensitivity of NSCLC in vitro and in vivo. Abemaciclib inhibited IR-induced DNA damage repair and caused RB-dependent cell cycle arrest; furthermore, the study identified possible predictive biomarkers (p53, RB, and SDF-1) to guide the efficacy and efficacy of the combination therapy, emphasized that CDK4/6 axis is a potential radiation target for NSCLC and warranting the value of abemaciclib as a radiation modifier in clinical trials (49). Therefore, CDK4/6 inhibitors may have different radiosensitization effects in NSCLC, and its mechanisms need to be further assessed. However, most clinical trials of combination therapies are still in the recruitment stage and further work is needed to find the best combination of radiotherapy drugs.

**Combination of CDK4/6 Inhibitors and Other Anti-Lung Cancer Drugs**

Combinations of CDK4/6 inhibitors and other targeted drugs have broad prospects. PI3K-AKT-mTOR and RASRAF-MEK-ERK pathway inhibitors showed synergistic tumor inhibition in many preclinical vitro and vivo models in NSCLC with CDK4/6 inhibitors (50–52). Palbociclib sensitizes lung cancer cells to EGFR-TKI and gefitinib (25). In addition, the combination of MEK inhibitor (trametinib) and palbociclib has significant anti-CDKN2A-mutant and anti-KRAS-mutant NSCLC activities in preclinical models (53). Moreover, in view of the key role of mTOR in cell growth and proliferation, mTOR inhibitors are considered as good candidates for synergism action with CDK4/6 inhibitors. Combinations of CDK4/6 inhibitors and mTOR inhibitors can enhance growth inhibition and induction of apoptotic cell death in p16-null NSCLC cells (30). A recent study also demonstrated that combined treatment with the CDK4/6 inhibitor and a novel distinctive structure PI3Kα inhibitor through arrest enhancing G1-phase and enhancing inhibition of Rb phosphorylation to against KRAS-mutated NSCLC (54). In addition, several ongoing clinical trials are studying advanced NSCLC associated with the combination of CDK4/6 inhibitors with ERK, MEK, or mTOR inhibitors (NCT03170206, NCT02065063, NCT02857270, and NCT03454035) based on these and other promising preclinical data (3).

**PROSPECTS AND FUTURE APPLICATION**

CDK4/6 inhibitors may exert an essential role in the treatment of NSCLC. Although some phase I/II clinical trials of CDK4/6 inhibitors in patients with advanced/metastatic lung cancer have not yet achieved positive results, which may be related to the small sample size of clinical trials and the lack of effective biomarkers. Given the preclinical benefits of CDK4/6 inhibitors in molecularly selected subsets, CDK4/6 inhibitors may have another role in the treatment of NSCLC in selected populations based on reasonable biomarkers, combined with radiotherapy and other agents, including growth factor pathway inhibitors and immune checkpoint inhibitors. Besides, the mechanism of CDK4/6 inhibitor resistance and the identification of sensitive predictive markers have also been reported, including acquired RB1 mutations, loss of RB1, loss of function mutations of FAT-1, CCNE1 overexpression, CDK6 overexpression, CCNE1/RB1 ratio, interferon β expression (55), CDK4 phosphorylation and tumor cloning kinetics (2, 56, 57). Therefore, the clinical efficacy of CDK4/6 inhibitors in NSCLC depend on the development of predictive biomarkers and biologically rational combination therapy, which might include the addition of growth factor pathway inhibitors in patients with signal transduction pathway mutations or the addition of immune checkpoint inhibitors in patients with immunostimulatory tumor phenotypes. Based on these, more basic and clinical studies are needed explore the precise beneficiaries of CDK4/6 inhibitors in NSCLC treatment in the future.

**AUTHOR CONTRIBUTIONS**

JZ, DX, and YZ collected the references and wrote the manuscript. All authors contributed to the article and approved the submitted version. ZZ and XY acquired funding and supervised this study.

**FUNDING**

This work was supported by National Natural Science Foundation of China (No. 81872461).
REFERENCES

1. Cheng TY, Cramb SM, Baade PD, Youlden DR, Negassa A, Reid ME. The International Epidemiology of Lung Cancer: Latest Trends, Disparities, and Tumor Characteristics. *J Thorac Oncol* (2016) 11(10):1653–71. doi: 10.1016/j.jto.2016.05.021

2. Gong X, Litchfield LM, Webster Y, Chio LC, Wong SS, Stewart TR, et al. Genomic Aberrations That Activate D-Type Cyclins Are Associated With Enhanced Sensitivity to the CDK4 and CDK6 Inhibitor Abemaciclib. *Cancer Cell* (2017) 32(6):761–76.e6. doi: 10.1016/j.ccell.2017.11.006

3. Qin A, Reddy HG, Weinberg RA. The Retinoblastoma Protein and Cell Cycle Control. 5.

4. Milestones in Cell Division.

3. Qin A, Reddy HG, Weinberg FD, Kalemkerian GP. Cyclin-Dependent Kinase Inhibitors for the Treatment of Lung Cancer. Expert Opin Pharmacother (2020) 21(8):941–52. doi: 10.1080/14656566.2020.1738385

4. Otto T, Sicinski P. Cell Cycle Proteins as Promising Targets in Cancer Therapy. *Nat Rev Cancer* (2017) 17(2):93–115. doi: 10.1038/nrc.2016.138

5. Milestones in Cell Division. *Cell Biol* (2001) 3(12):E265. doi: 10.1038/nbcl2013e265

6. Weinberg RA. The Retinoblastoma Protein and Cell Cycle Control. 6.

5. Milestones in Cell Division.

6. Weinberg RA. The Retinoblastoma Protein and Cell Cycle Control. *Cell* (1995) 81(3):323–30. doi: 10.1016/0092-8674(95)90385-2

7. Kong T, Xue Y, Cencic R, Zhu X, Monast A, Fu Z, et al. ElA4A Inhibitors Suppress Cell-Cycle Feedback Response and Acquired Resistance to CDK4/6 Inhibition in Cancer. *Mol Cancer Ther* (2019) 18(11):2158–70. doi: 10.1158/1535-7163.MCT-19-0162

8. Fang H, Huang D, Yang F, Guan X. Potential Biomarkers of CDK4/6 Inhibitors in Hormone Receptor-Positive Advanced Breast Cancer. *Breast Cancer Res Treat* (2018) 168(2):287–97. doi: 10.1007/s10549-017-4612-y

9. O’Leary B, Finn RS, Turner NC. Treating Cancer With Selective CDK4/6 Inhibitors. *Nat Rev Clin Oncol* (2016) 13(7):417–30. doi: 10.1038/nrclinonc.2016.26

10. Sherr CJ, Beach D, Shapiro GL. Targeting CDK4 and CDK6: From Discovery to Therapy. *Cancer Discov* (2016) 6(4):533–67. doi: 10.1158/2159-8290.CD-15-0894

11. Besse B, Barlesi F, Femandes I, Fuentes Pradera J, Robinet G, Gazzah A, et al. SWOG S1400C (NCT02154490)-A Phase II Study of Palbociclib for Non-Small-Cell Lung Cancer (Lung-MAP Substudy).

12. Genomic Aberrations That Activate D-Type Cyclins Are Associated With Enhanced Sensitivity to the CDK4 and CDK6 Inhibitor Abemaciclib. *Cancer Cell* (2017) 32(6):761–76.e6. doi: 10.1016/j.ccell.2017.11.006

13. Qin A, Reddy HG, Weinberg RA. The Retinoblastoma Protein and Cell Cycle Control.

14. Milestones in Cell Division.

15. Weinberg RA. The Retinoblastoma Protein and Cell Cycle Control. 6.

16. Weinberg RA. The Retinoblastoma Protein and Cell Cycle Control. *Cell* (1995) 81(3):323–30. doi: 10.1016/0092-8674(95)90385-2

17. Goel S, DeCristo MJ, Watt AC, BrinJones H, Sceneay J, Li BB, et al. CDK4/6 Inhibitors Triggers Anti-Tumour Immunity. *Nature* (2017) 548(7668):471–5. doi: 10.1038/nature23463

18. Bilgin B, Sendur MAN, Sener Dede D, Akinci MB, Yalcin B. A Current and Comprehensive Review of Cyclin-Dependent Kinase Inhibitors for the
36. Gelbert LM, Cai S, Lin X, Sanchez-Martinez C, Del Prado M, Lallena MJ, et al. Preclinical Characterization of the CDK4/6 Inhibitor LY2835219: In-Vivo Cell Cycle-Dependent/Independent Anti-Tumor Activities Alone/in Combination With Gemcitabine. *Invest New Drugs* (2014) 32(5):825–37. doi: 10.1007/s10637-014-0120-7

37. Cao J, Zhu Z, Wang H, Nichols TC, Lui GY, Deng S, et al. Combining CDK4/6 Inhibition With Taxanes Enhances Anti-Tumor Efficacy by Sustained Impairment of pRB-E2F Pathways in Squamous Cell Lung Cancer. *Oncogene* (2019) 38(21):4125–41. doi: 10.1038/s41388-019-0708-7

38. Zhang J, Bu X, Wang H, Geng Y, Nihira NT, et al. Cyclin D-CDK4/6 Inhibition Augments Antitumor Immunity by Enhancing T-Cell Activation. *Cancer Discovery* (2018) 8(2):216–33. doi: 10.1158/2159-8290.CD-17-0915

39. Zhang J, Bu X, Wang H, Geng Y, Nihira NT, et al. Cyclin D-CDK4 Kinase Destabilizes PD-L1 via Cullin 3-SPOP to Control Cancer Immune Surveillance. *Nature* (2018) 553(7686):91–5. doi: 10.1038/nature25015

40. Schaefer DA, Beckman RP, Dempsey JA, Huber L, Fosters A, Amaladas N, et al. The CDK4/6 Inhibitor Abemaciclib Induces a T Cell Inflamed Tumor Microenvironment and Enhances the Efficacy of PD-L1 Checkpoint Blockade. *Cell Rep* (2018) 22(11):2978–94. doi: 10.1016/j.celrep.2018.02.053

41. Ameratunga M, Kipps E, Okines AFC, Lopez JS. To Cycle or Fight-CDK4/6 Inhibitors at the Crossroads of Anticancer Immunity. *Clin Cancer Res* (2019) 25(1):21–8. doi: 10.1158/1078-0432.CCR-18-1999

42. Huang CY, Hsieh FS, Wang CY, Chen LJ, Chang SS, Tsai MH, et al. Palbociclib Enhances Radiosensitivity of Hepatocellular Carcinoma and Cholangiocarcinoma via Inhibiting Ataxia Telangiectasia-Mutated Kinase-Mediated DNA Damage Response. *Eur J Cancer* (2018) 102:10–22. doi: 10.1016/j.ejca.2018.07.010

43. Li F, Yu Y, Liu B, Singh PK, Zhao W, Jin J, et al. YAP1-Mediated CDK6 Activation Confers Radiation Resistance in Esophageal Cancer - Rationale for the Combination of YAP1 and CDK4/6 Inhibitors in Esophageal Cancer. *Clin Cancer Res* (2019) 25(7):2264–77. doi: 10.1158/1078-0432.CCR-18-1029

44. Whittaker S, Madani D, Joshi S, Chung SAJ, Johns T, Day B, et al. Combination of Palbociclib and Radiotherapy for Glioblastoma. *Cell Death Discov* (2017) 3:17033. doi: 10.1038/cddiscovery.2017.33

45. Naz S, Cook JA, Mitchell JB. Abemaciclib: A Multi-Functional Radiation Modifier. *OncoTarget* (2019) 10(12):1230–2. doi: 10.18632/oncotarget.26652

46. Yang Y, Luo J, Chen X, Yang Z, Mei X, Ma J, et al. CDK4/6 Inhibitors: A Novel Strategy for Tumor Radiosensitization. *J Exp Clin Cancer Res* (2020) 39(1):188. doi: 10.1186/s13046-020-01693-w

47. Naz S, Sowers A, Choudhuri R, Wissler M, Gamsan J, Mathias A, et al. Abemaciclib, a Selective CDK4/6 Inhibitor, Enhances the Radiosensitivity of Non-Small Cell Lung Cancer *In Vitro* and *In Vivo*. *Clin Cancer Res* (2018) 24(16):3994–4005. doi: 10.1158/1078-0432.CCR-17-3575

48. Tao Z, Le Blanc JM, Wang C, Zhan T, Zhuang H, Wang P, et al. Coadministration of Trametinib and Palbociclib Radiosensitizes KRAS-Mutant Non-Small Cell Lung Cancers *In Vitro* and *In Vivo*. *Clin Cancer Res* (2016) 22(1):122–33. doi: 10.1158/1078-0432.CCR-15-0589

49. Wong CH, Ma BBY, Hui WC, Lo KW, Hui EP, Chan ATC. Preclinical Evaluation of Ribociclib and its Synergistic Effect in Combination With Alpelisib in non-Keratinizing Nasopharyngeal Carcinoma. *Sci Rep* (2018) 8:10801. doi: 10.1038/s41598-018-26201-1

50. Chen SH, Gong X, Zhang Y, Van Horn RD, Yin T, Huber L, et al. RAF Inhibitor LY3009120 Sensitizes RAS or BRAF Mutant Cancer to CDK4/6 Inhibition by Abemaciclib via Superior Inhibition of Phospho-RB and Suppression of Cyclin D1. *Oncogene* (2018) 37(6):821–32. doi: 10.1038/onc.2017.384

51. Zhou J, Zhang S, Chen X, Zheng X, Yao Y, Lu G, et al. Palbociclib, a Selective CDK4/6 Inhibitor, Enhances the Effect of Selumetinib in RAS-Driven non-Small Cell Lung Cancer. *Cancer Lett* (2017) 408:130–7. doi: 10.1016/j.canlet.2017.08.031

52. Wang Y, Li X, Liu X, Chen Y, Yang C, Tan C, et al. Simultaneous Inhibition of PI3KAlpha and CDK4/6 Synergistically Suppresses KRAS-Mutated non-Small Cell Lung Cancer. *Cancer Biol Med* (2019) 16(1):66–83. doi: 10.20892/jissn.2019-3941.2018.0361

53. Cingoz O, Golf SP. Cyclin-Dependent Kinase Activity is Required for Type I Interferon Production. *Proc Natl Acad Sci USA* (2018) 115(13):E2950–E9. doi: 10.1073/pnas.1720431115

54. Raspe E, Coulonval K, Pita JM, Paternot S, Rothe F, Twyffels L, et al. CDK4/6 Inhibition by Abemaciclib - Blockade of Cyclin D1. *Cell Rep* (2018) 23(22):5543–51. doi: 10.1016/j.celrep.2018.03.010

55. Zhang et al. CDK4/6 Inhibitors and NSCLC

56. Alvarez-Fernandez M, Malumbres M. Mechanisms of Sensitivity and Resistance to CDK4/6 Inhibition. *Cancer Cell* (2020) 37(4):514–29. doi: 10.1016/j.ccell.2020.03.010

57. Deng J, Wang ES, Jenkins RW, Li S, Dries R, Yates K, et al. CDK4/6 Inhibition Enhances the Radiosensitivity of NSCLC via Overexpression of Cyclin D1. *Cancer Cell Rep* (2018) 102:10

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