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# Potential biomarkers of CDK4/6 inhibitors in HR-positive advanced breast cancer

Thanks to the development of endocrine therapy, the mortality rate of estrogen receptor (ER)-positive breast cancer patients has been decreased drastically. In spite of the improvement, however, relapse and progression that are driven by different mechanisms are still inevitable. Cyclin D/cyclin-dependent kinase 4/6 (CDK4/6) complex, the pivotal regulator of cell cycle, has been verified as one of the crucial underlying mechanisms. It also indicates that targeting at CDK4/6 may be a viable way to improve clinical benefits. Therefore, many clinical trials have been carried out to investigate the combination therapy of CDK4/6 inhibitor with antiestrogen therapy, with some encouraging results yielded.

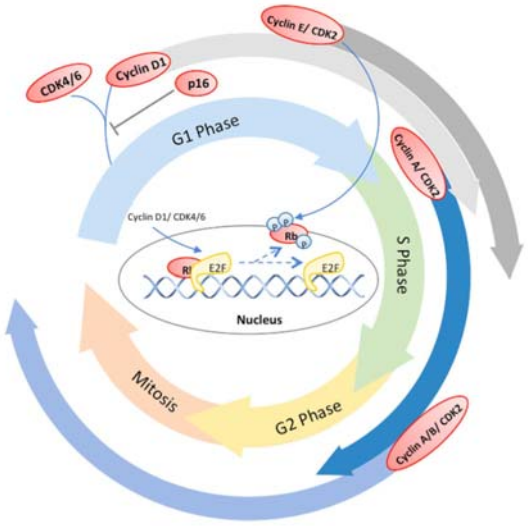


Fig. 1. CDK 4/6 pathway and cell cycle. With the progress of phase gap (G1), the Cyclin D1/CDK4/6 complex inactivates Rb, releasing E2F from sequestration which subsequently promotes the transition from G1 phase to S phase. Meanwhile, Cyclin E/CDK2 complex further phosphorylates Rb to continue the cell cycle. In S phase, Cyclin A, associated with CDK2, results in the S-G2 transition in cells. To enable the onset of M phase, Cyclin A/B/ CDK1 complex is formed to aid the completion of mitosis.

Currently, there are mainly three CDK4/6 inhibitors in clinical use, Palbociclib, Ribociclib and Abemaciclib respectively. Most clinical trials have confirmed the improved efficacy of combining CDK4/6 inhibitor with antiestrogen therapy. Nonetheless, it is observed that along with the benefit from CDK 4/6 inhibitors, the toxicity and financial burden also increase. Besides, while Fulvestrant alone has been proved as a potent first-line treatment for those with advanced ER-positive breast cancer, the addition of CDK4/6 inhibitors might be unnecessary. To optimize the clinical application of CDK4/6 inhibitors, selecting patients who do and do not need such a combination therapy is urgent. Herein, several potential predictors for population selection are being discussed.

Multiple evidence has shown that compared with most non-luminal breast cancer subtypes, luminal subtypes were more sensitive to CDK4/6 inhibitors. Given the role CDK4/6 plays in inducing resistance in ER-positive breast cancer, ER status should be taken into account before using such inhibitors.

Based on previous laboratory results, it was found that the amplification of Cyclin D1 and/or the loss of p16, another two cell cycle-associated proteins, might also be potential predictors. Nevertheless, in clinical setting, it failed to confirm what *in vitro* results have showed. It was speculated that it might be the inaccurate laboratory tests that led to the inconsistency. Since both Cyclin D1 and p16 are key factors in cell cycle progression, more clinical studies about them are needed to identify their values in patient selection.

As the main targets of CDK4/6 inhibitors, CDK4/6 and Rb are regarded as candidates for biomarkers as well. Largely, results from both preclinical and clinical settings suggested the promising roles of CDK4/6 as predictors. However, for Rb, there exists controversy and awaits more research to be carried out to demonstrate its significance.

Aside from CDK4/6, CDK2 is also known to be capable of phosphorylating Rb. In other words, when CDK4/6 is suppressed, CDK2 may substitute CDK4/6 to activate Rb, thus promoting cell cycle progression. Consistent with that, it is well recognized Cyclin E-CDK2 axis plays a crucial part in driving G1-to-S phase transition. Thus, it was hypothesized that amplification of CCNE1 might predict the insensitivity to CDK4/6 inhibitors and targeting CDK2 could reverse such unresponsiveness.

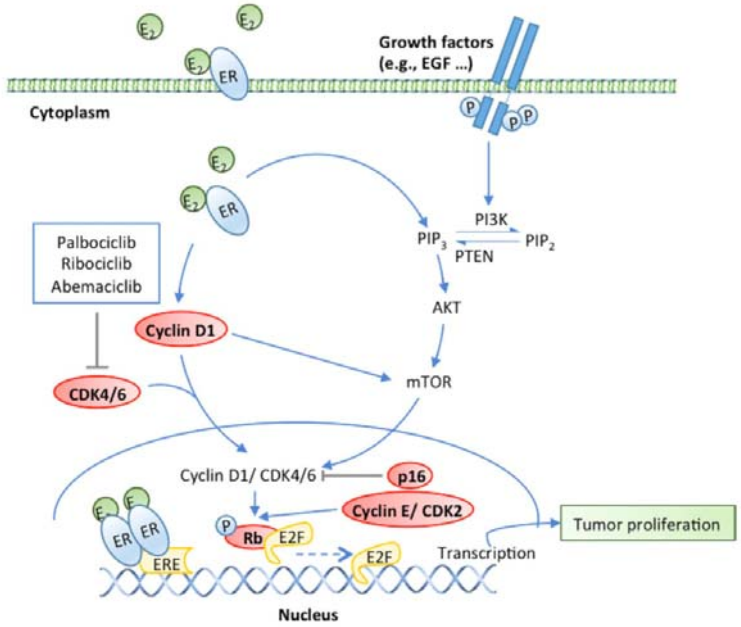


Fig. 2. Potential biomarkers for CDK 4/6 inhibitors. Growth factor receptor binding activates downstream PI3K pathway to converge on Cyclin D1/CDK4/6 complex. E 2 –ER complex, which also induces the activation of

PI3K pathway, drives cell proliferation via Cyclin D1/ CDK4/6 and results in Rb phosphorylation and inactivation, eventually releasing E2F and promoting cell cycle. Similarly, Cyclin E/ CDK2 contributes to the release of E2F from sequestration. CDK4/6 can be inhibited by pharmacologic CDK4/6 inhibitors (e.g., Palbociclib, Ribociclib, and Abemaciclib) and Cyclin D1/CDK4/6 complex is physically suppressed by p16. E2, estradiol.

Ki67 is an effective indicator of cell proliferation and serial Ki67 monitoring before surgery might be a predictor of efficacy of CDK4/6 inhibitors. Although some studies had different views, the role of Ki67 is still worth further exploration due to the wide use of Ki67 in clinic. Though several biomarkers have been introduced to predict the efficacy of CDK4/6 inhibitors, the disagreements among studies exist and currently, no single biomarker has been identified highly reliable in clinical use. As a consequence, combined biomarker strategy was proposed and has been demonstrated feasible. In summary, to find out the best predictors of CDK4/6 inhibitors, more studies are expected to be carried out.

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## Publication

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