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The emerging CDK4/6 inhibitor for breast cancer treatment

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Abstract

The cyclin-dependent kinase (CDK) inhibitors have emerged as important cancer therapeutics. To date, three CDK4/6 inhibitors in combination with endocrine therapy have been approved by the U.S. Food and Drug Administration for the treatment of hormone receptor-positive, HER2-negative advanced breast cancer. These include, palbociclib, ribociclib and abemaciclib. More recently, a newer CDK4/6 inhibitor named dalpiciclib has been tested in the phase III DAWNA-1 study, which is a randomized, double-blind, placebo-controlled trial that investigates dalpiciclib in combination with fulvestrant in hormone receptor-positive, HER2-negative advanced breast cancer patients that have relapsed or progressed on prior endocrine therapy. Dalpiciclib is an oral agent and an emerging ATP-competitive CDK4/6 inhibitor. The interim results of DAWNA-1 study revealed that dalpiciclib in combination with fulvestrant significantly prolonged the progression-free survival. The clinical use and side effects of palbociclib, ribociclib and abemaciclib as well as dalpiciclib are reviewed here.

Keywords: Breast cancer; Palbociclib; Ribociclib; Abemaciclib; Dalpiciclib; Fulvestrant

It is estimated that in the United States, 281,550 new cases of breast cancer will be diagnosed in women in 2021, and 43,600 are expected to die due to breast cancer (1). Clearly, breast cancer remains a major cause of morbidity and mortality. The linear multistep model of breast cancer progression has identified a sequence of pathologically defined stages for both the ductal and lobular types. These, in the case of ductal type, include flat epithelial atypia (FEA), atypical ductal hyperplasia (ADH), ductal carcinoma in situ (DCIS) and invasive or infiltrating ductal carcinoma (IDC) (2-4). The lesions in the case of lobular type include atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS) and invasive lobular carcinoma (ILC) (4). Markers such as estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) in association with other clinicopathological features have traditionally been used for breast cancer diagnosis, prognosis and treatment decisions (5). Recent advances in molecular approaches have led to the recognition of four molecular subtypes including luminal A, luminal B, HER2 overexpression and basal-like (triple-negative) (5, 6), although the existence of the fifth subtype namely, normal-like remains debatable (6). The luminal A subtypes exhibit better prognosis, whereas the basal-like (triple-negative) subtypes have worse prognosis (5, 6).

In recent years, the cyclin-dependent kinase (CDK) inhibitors have received much attention in the management of hormone receptor-positive metastatic breast cancers. CDKs are serine-threonine kinases. The established view about the function of CDKs is that the CDK4 and CDK6 in association with D-type cyclins inhibit Rb pathway to initiate progression from the G1 to S phases of the cell cycle (Fig. 1). Cyclin E in association with CDK2 further facilitates cell cycle progression during the transition from G1 to S phase (7). CDK4/6 inhibitors interfere with the function of these kinases and induce growth arrest (Fig. 1).

Currently, three CDK4/6 inhibitors are approved by the U.S. Food and Drug Administration (FDA) for the management of advanced breast cancer in combination with endocrine therapy (7-9). These include, palbociclib, ribociclib and abemaciclib (Fig. 2). Specifically, these agents are used for the treatment of hormone receptor-positive, HER2-negative metastatic breast cancers (7-9). Palbociclib is used in combination with an aromatase inhibitor (AI) as a first line option in postmenopausal women.

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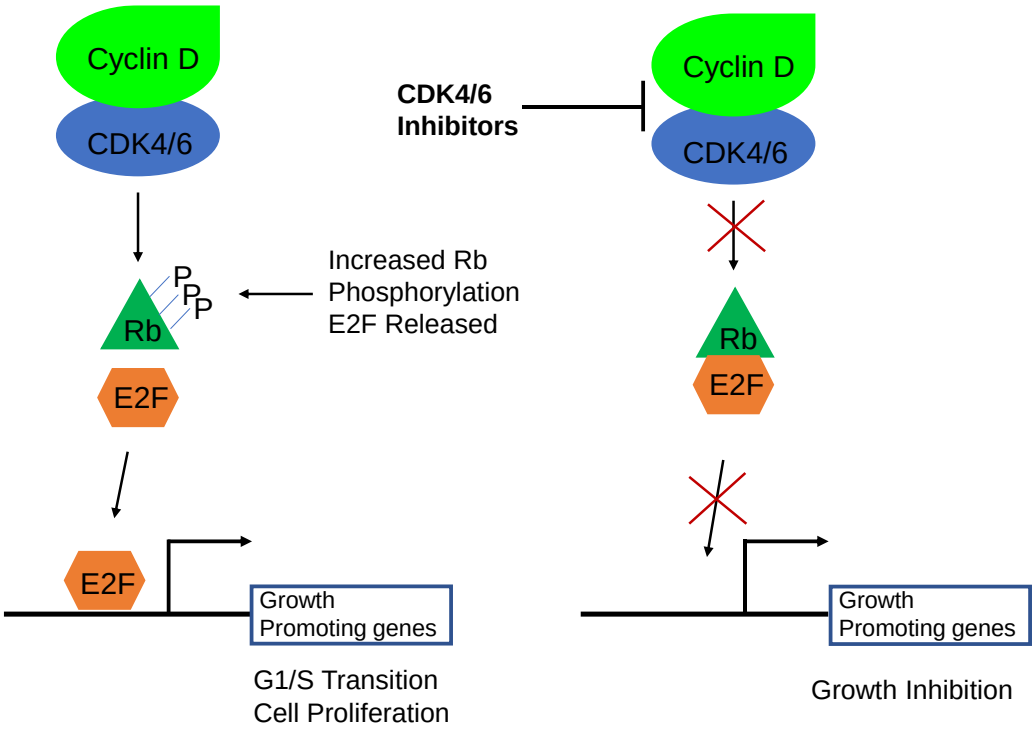

Figure 1. Schematic illustration of the effects of CDK4/6 inhibitors. CDK4 and CDK6 in association with D-type cyclins inhibit Rb pathway to initiate progression from the G1 to S phases of the cell cycle. CDK4/6 inhibitors interfere with the function of these kinases and induce growth arrest.

It is also used with fulvestrant in premenopausal and postmenopausal patients showing disease progression after endocrine therapy. Fulvestrant (Fig. 3) mediates its effect by inducing downregulation and degradation of estrogen receptor. In the case of premenopausal women, ovarian function suppression or ablation is recommended during endocrine therapy. Ribociclib is used in combination with an AI as initial endocrine treatment in premenopausal and postmenopausal patients. It is also used with fulvestrant in postmenopausal patients as initial endocrine treatment, also in postmenopausal patients showing disease progression after endocrine therapy. Abemaciclib is used in combination with an AI as initial endocrine treatment in postmenopausal patients. It is also used with fulvestrant in premenopausal and postmenopausal patients with disease progression following endocrine therapy. Abemaciclib can also be used as monotherapy if disease progresses on endocrine therapy and chemotherapy (7-9).

These CDK inhibitors are generally well-tolerated albeit with certain side effects as mentioned here (7-9). For example, fatigue, nausea, neutropenia and infection are the common side effects, and interstitial lung disease is a less frequent side effect. Ribociclib can also cause QTc prolongation and hepatotoxicity, and abemaciclib can lead to hepatotoxicity, increase in serum creatinine (SCr) and grade 3 diarrhea (7-9). Although the development and approval of these CDK inhibitors have advanced the management of metastatic breast cancer, resistance to these agents also develops. Thus, there is a need to better understand the underlying mechanism of acquired resistance to these agents and develop newer CDK inhibitors.

Dalpiciclib (Fig. 3) is a newer CDK4/6 inhibitor that is in phase III DAWNA-1 study (10). Dalpiciclib, an oral agent, has shown significant anticancer potential and selectivity towards CDK4 and CDK6 (11, 12). Just like palbociclib, ribociclib and abemaciclib, it is also an ATP-competitive CDK 4/6 inhibitor (13). Recently, interim results of DAWNA-1 study were reported (10). It is a randomized, double-blind, placebo-controlled phase 3 trial that studies dalpiciclib in combination with fulvestrant in hormone receptor-positive, HER2-negative advanced breast cancer patients that have relapsed or progressed on prior endocrine therapy (10). The study reported interim results from 361

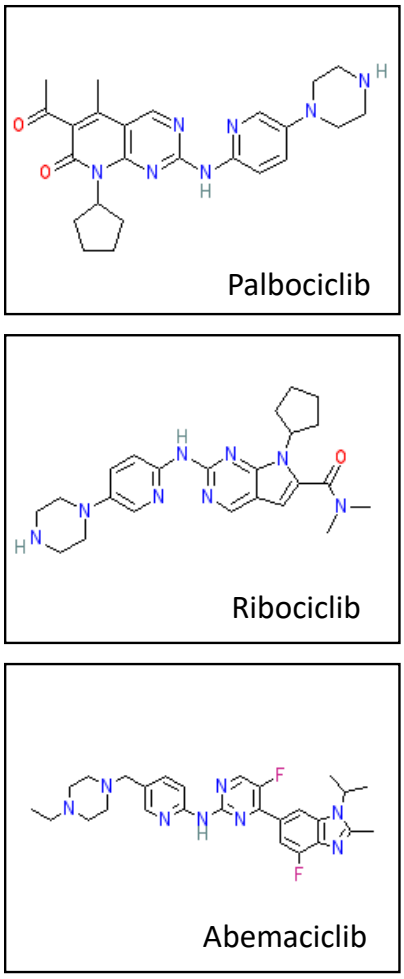

Figure 2. Structures of palbociclib, ribociclib and abemaciclib. Taken from NC-IUPHAR.

patients that had received dalpiciclib plus fulvestrant or placebo plus fulvestrant (10). The authors reported that the primary endpoint of the study was met, which was significant prolongation of progression-free survival (PFS) in the dalpiciclib and fulvestrant combination arm when compared to the placebo and fulvestrant combination (10). The data on overall survival (OS) were not ready at the time of publication of interim results. Neutropenia and leukopenia were the common grade 3/4 adverse events noted with dalpiciclib plus fulvestrant. Albeit less frequent, QT prolongation was also noted. The incidence of low-grade liver enzyme abnormalities was about similar in both arms (10).

The limitation of the study, as pointed out by the authors, include (i) assessment of patients with only secondary endocrine resistance. (ii) The study was limited to only Chinese patients. (iii) The data

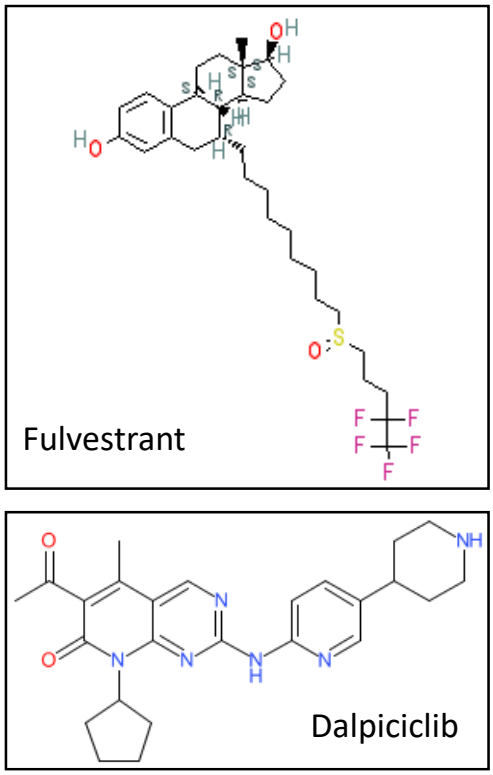

Figure 3. Structures of fulvestrant and dalpiciclib. Taken from NC-IUPHAR.

on overall survival was not ready (10). With due considerations to limitation, the study nevertheless highlights the potential of an additional CDK4/6 inhibitor for the management of advanced breast cancer (10, 14). Given that secondary endocrine resistance was assessed in the study, evaluation of patients with primary endocrine resistance will be warranted. Furthermore, because the study was limited to Chinese patients, other ethnic groups will need to be evaluated (14). Regarding the other CDK4/6 inhibitors currently in the clinical use including palbociclib, ribociclib, and abemaciclib, it is of note that the effectiveness of all three is comparable for the treatment of hormone receptor-positive HER2-negative advanced breast cancer. A head-to-head comparison of dalpiciclib with other CDK4/6 inhibitors in the clinic will also provide important information about this newer CDK4/6 inhibitor.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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