IN THE SPOTLIGHT

CDK4/6 Inhibitors: Promising Opportunities beyond Breast Cancer

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Summary: Patnaik and colleagues report on the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of abemaciclib for the treatment of advanced solid cancers, demonstrating antitumor activity in advanced breast cancers as well as glioblastoma, melanoma, non–small cell lung cancer, colorectal cancer, and ovarian cancer. The development of abemaciclib and other CDK4/6 inhibitors should now be fully optimized through the use of novel predictive biomarkers of response and rational combinations. *Cancer Discov; 6(7); 697–9. ©2016 AACR.*

See related article by Patnaik et al., p. 740 (4).

It is now more than two decades since the critical roles of D-type cyclins (CCND) and cyclin-dependent kinases (CDK) in the cell cycle were established. Although the inhibition of these targets to halt G_1–S phase progression is a rational therapeutic strategy, a delicate balance needs to be struck between optimal target blockade to induce cell death in tumor cells and the relative sparing of CDK activity in nonmalignant cells. Early efforts to target CDK in the clinic had been largely unsuccessful due to toxicity, but next-generation CDK inhibitors have created a therapeutic window with improved selectivity for CDK4 and CDK6 (1). The three selective CDK4/6 inhibitors, abemaciclib, palbociclib, and ribociclib, all in late-stage clinical development, are structurally similar, bind within the ATP-binding pocket of CDK4 and CDK6, and have high selectivity for CDK4/6 over CDK1/2. In 2015, palbociclib was the first CDK4/6 inhibitor to obtain FDA accelerated approval for the first-line treatment of postmenopausal women with estrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer in combination with letrozole (PALOMA-1; ref. 2), before subsequently gaining full FDA approval with fulvestrant in metastatic breast cancer after progression on initial endocrine therapy (PALOMA-3; ref. 3).

In this issue, Patnaik and colleagues report data from the phase I trial of abemaciclib, which led in part to the FDA breakthrough therapy designation for refractory hormone receptor–positive (HR^+) advanced breast cancer (4). This study comprised a two-stage phase I trial design with dose escalation and expansion cohorts conducted in multiple *a priori*–determined tumor-specific groups. The authors should be commended on a comprehensive and well-conducted phase I trial where key hypothesis-testing questions involving drug pharmacology, antitumor activity, and putative predictive biomarkers of response and resistance were tested. This phase I biomarker-driven trial design, supported by robust and biologically rational preclinical data to identify the tumor and molecular subtypes likely to benefit (5), may accelerate the development of promising new agents by enabling early clinical testing of enriched tumor-selected and molecularly selected patients, so as to generate sufficient data to support expedited regulatory approval.

The authors established the recommended phase II dose (RP2D) at 200 mg twice daily of abemaciclib and, importantly, observed antitumor activity in multiple solid tumors at this dose (4). Abemaciclib demonstrated a response rate of 23%, a clinical benefit rate of 49%, and median progression-free survival of 5.8 months in heavily pretreated patients with advanced breast cancers. Encouraging early signals of clinical activity were also observed in other malignancies, including non–small cell lung cancer (NSCLC), glioblastoma (GBM), melanoma, and colorectal and ovarian cancers, suggesting a potential role for CDK4/6 inhibitors beyond breast cancer. Antitumor responses were also observed with palbociclib and ribociclib, and phase I/II studies are ongoing in NSCLC, GBM, and melanoma with all three CDK4/6 inhibitors (6). Interestingly, in the NSCLC cohort, patients achieved a disease control rate of 49%, possibly with improved outcomes in *KRAS*-mutant versus *KRAS*–wild-type NSCLC. Abemaciclib is currently being assessed in a phase II study against docetaxel in squamous cell NSCLC and in the phase III JUNIPER trial against erlotinib in *KRAS*-mutant NSCLC in the second-line setting after platinum-based chemotherapy (NCT02450539 and NCT02152631).

In the race to drug registration, abemaciclib tails palbociclib in breast cancer, although phase II/III studies of abemaciclib, assessing efficacy as monotherapy (MONARCH 1, NCT02102490) and in combination with endocrine therapy (MONARCH 2, NCT02107703; MONARCH 3, NCT02246621), have completed accrual. Although an objective clinical comparison with other CDK4/6 inhibitors will require a randomized head-to-head study, abemaciclib has demonstrated unique clinical characteristics that may set it apart from the other CDK4/6 inhibitors. A strength of abemaciclib appears

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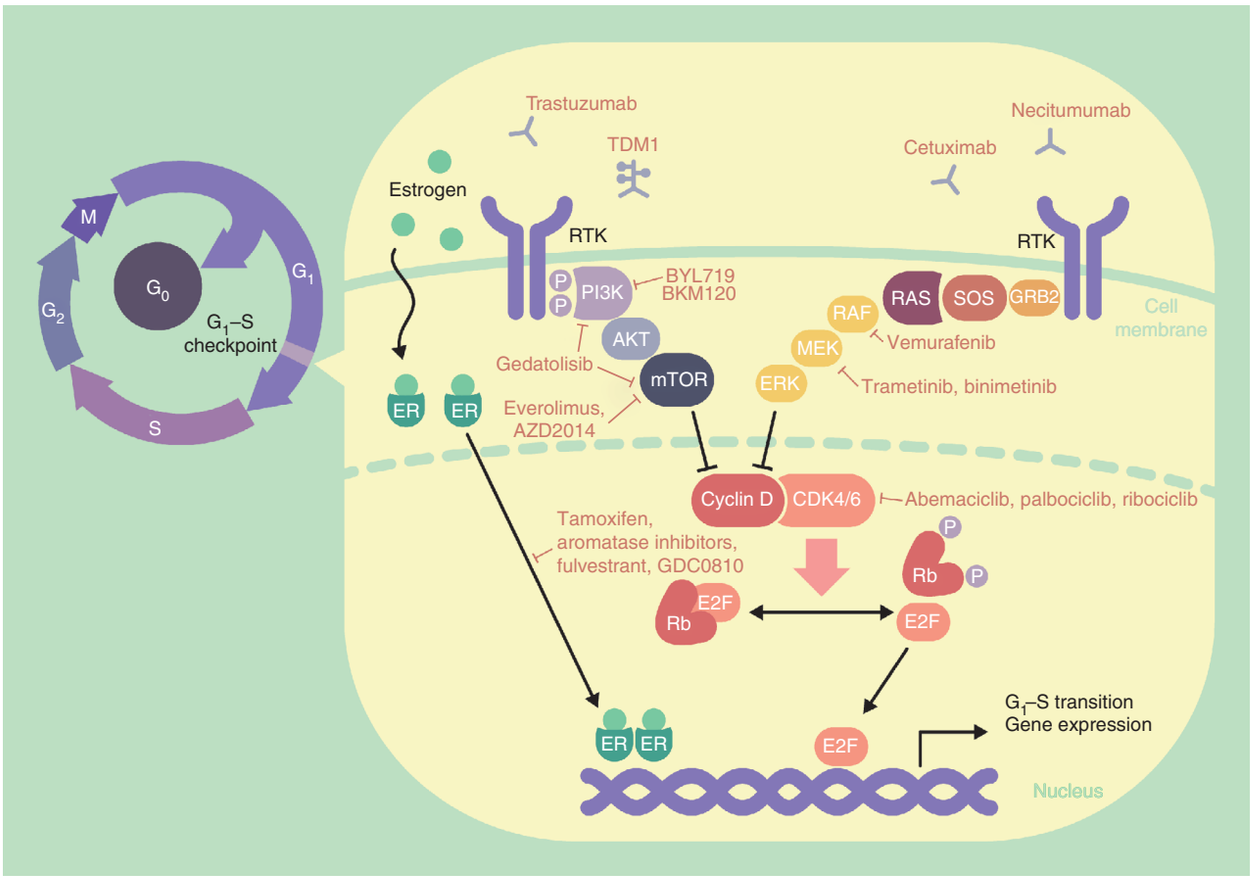

Figure 1. Potential combination strategies for CDK4/6 inhibitors. CDK4/6 inhibitors bind within the ATP-binding pocket of CDK4 and CDK6, preventing G_1–S phase transition and leading to cell-cycle arrest. ER signaling activates the cyclin D–CDK4–Rb axis to induce G_1–S phase transition, and blockade with selective estrogen receptor modulators/degraders and aromatase inhibitors is an effective combination strategy. Signaling of the MAPK–ERK and PI3K–AKT pathways leads to transcriptional induction of cyclin D1 and other cyclins, and *HER2* amplification has also been shown to increase cyclin D1 expression. Blockade of these pathways has shown additive or synergistic effects when combined with CDK4/6 inhibitors.

to be its relatively low rate of neutropenia (23% all grades; 10% grades 3–4), which has enabled it to be dosed continuously, in contrast to the intermittent dosing regimen required for both palbociclib and ribociclib (6). However, abemaciclib appears to have higher rates of fatigue (41% all grades; 3% grades 3–4) and diarrhea (63% all grades; 5% grades 3–4; ref. 4). Diarrhea prophylaxis with loperamide may reduce the rate of diarrhea, and this is being investigated in ongoing studies. This difference in toxicity profile is potentially due to the greater selectivity and relative potency of abemaciclib for CDK4 compared to CDK6, as well as activity against CDK9 (5).

In this study, drug concentrations of abemaciclib in the cerebrospinal fluid (CSF) approached those of unbound plasma concentrations in selected study subjects where both plasma and CSF samples were collected, suggesting better absorption across the blood–brain barrier, allowing for improved central nervous system penetration (7). In the subgroup of patients with GBM treated on this study, three patients achieved durable disease stabilization (4). Although this will need to be confirmed in larger late-phase clinical trials, the potential efficacy of abemaciclib for the treatment of GBM or even patients with brain metastases may possibly open up additional new drug applications.

In the era of precision medicine, identifying and validating robust predictive biomarkers will be key to establishing niche areas for this class of drugs. Currently, the ER-positive/HER2-negative breast cancer subtype is the only clinically qualified predictive biomarker of response for CDK4/6 inhibitors, although there is still considerable variability in antitumor responses observed among these patients (8). Although preclinical studies have suggested that *CCND1* amplification or *CDKN2A* loss may be predictive of response to CDK4/6 inhibitors (1), the presence of such aberrations did not predict for clinical benefit in this subgroup of patients selected in the PALOMA-1 study (2). Markers of drug resistance, such as loss of RB1 function and *CCNE1* amplification, have been observed in preclinical studies and are currently being investigated in ongoing clinical trials (9). Patnaik and colleagues found through exploratory biomarker studies that breast cancers harboring *TP53* mutations in the region encoding the p53 DNA-binding domain were less likely to respond to abemaciclib, which is a preliminary but intriguing finding.

Beyond breast cancer, the role of CDK4/6 inhibitors in other solid tumors and hematologic malignancies should also be explored in cancers where aberrations along the CCND/CDK pathway have been identified. Early-phase trials of palbociclib in patients with mantle cell lymphoma, where the pathogenic t(11;14)(q13;q32) translocation leads to increased cyclin D1 expression, have demonstrated promising antitumor activity. In addition, as part of the 12q14.15 amplicon, *CDK4* amplification has been observed in liposarcomas; a study evaluating 30 patients with RB-positive, *CDK4*-amplified well-differentiated or dedifferentiated liposarcoma demonstrated evidence of durable responses. Furthermore, large multicenter umbrella studies such as the Lung-MAP and UK National Lung Matrix trials, as well as the SIGNATURE basket study, are also treating patients with identified CDK4/6-activated tumors (e.g., *CDK4* or *CDK6* amplification or mutation, *CCND1* or *CCND3* amplification, or *CDKN2A* mutations) with CDK4/6 inhibitors, and should provide additional insights into the clinical activity associated with such molecularly selected tumors (6).

In view of the inevitable emergence of drug resistance with CDK4/6 inhibitors, the identification of rational and potentially effective combinations in molecularly selected groups of patients will also be crucial (Fig. 1). Preclinical data suggested that CDK4/6 inhibitors would be active in *HER2*-amplified breast cancer (10). In this study, Patnaik and colleagues showed that 4 of 11 patients (36%) with HER2-positive disease achieved objective antitumor responses to abemaciclib (4), supporting ongoing clinical studies of combination regimens with anti-HER2 agents (NCT02448420, NCT01976169, and NCT02657343). Proof-of-concept has also been established preclinically for the combination of palbociclib and the MEK inhibitor trametinib in melanoma mouse models, with significantly improved tumor regression observed (11), as well as for the combination of PI3K/mTOR inhibition with CDK4/6 inhibitors in breast cancer models (Fig. 1). These synergistic effects may be due to MEK inhibitors in melanoma and PI3K inhibition in breast cancer suppressing cyclin D/E, thus overcoming bypass signaling mechanisms that develop when single-agent CDK4/6 inhibitors are used. Phase I trials are currently assessing the MEK inhibitor combination in *BRAF*-mutant (NCT01777776) and *NRAS*-mutant (NCT01781572) melanoma, as well as in *KRAS*-mutant NSCLC (NCT02022982).

CDK4/6 inhibitors are now established in the therapeutic landscape of breast cancer, but will likely require the identification of novel predictive biomarkers of response and rational combinations to achieve their full potential in cancer medicine (Fig. 1; refs. 5, 6). This phase I study by Patnaik and colleagues has identified a number of promising opportunities beyond breast cancer (4), and abemaciclib and other CDK4/6 inhibitors are already at different stages of clinical trial testing in multiple molecularly selected and unselected tumor types. The inhibition of CDK4/6 in these cancers, including *KRAS*-mutant NSCLC and GBM, where effective targeted therapy has remained elusive thus far, may provide substantial benefit to such patients should these studies recapitulate early clinical trial findings.

Disclosure of Potential Conflicts of Interest

N.C. Turner reports receiving commercial research grants from Pfizer and Roche, and is a consultant/advisory board member for Pfizer, Novartis, and Lilly. T.A. Yap reports receiving commercial research grants from Pfizer, Roche, and Genetech, and is a consultant/advisory board member for Pfizer. No potential conflicts of interest were disclosed by the other author.

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