Setting the Pick: Can PI3K Inhibitors Circumvent CDK4/6 Inhibitor Resistance?

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SUMMARY

PI3K and CDK4/6 inhibitors (CDK4/6i) are targeted therapies approved to treat advanced breast cancer; CDK4/6is are more widely used. Here, we discuss trials that examine PI3K inhibitors with novel drug combinations, including a CDK4/6i, given data implicating the pathway in CDK 4/6 resistance.

See related articles by Lu et al., p. 408, and Tolaney et al., p. 418

In this issue of *Clinical Cancer Research*, Tolaney and colleagues (1) and Lu and colleagues (2) examine the PI3K inhibitors (PI3Ki), buparlisib or alpelisib, with fulvestrant/ribociclib in patients with more heavily treated metastatic breast cancer (1) or with tamoxifen/goserelin in premenopausal patients with advanced breast cancer (2). Combining buparlisib with either tamoxifen/goserelin or fulvestrant/ribociclib was determined to be too toxic for further study, putting into question the future of the drug in further development. While the combination of alpelisib with tamoxifen/goserelin demonstrated safety and preliminary efficacy, the triple combination of alpelisib/fulvestrant/ribociclib was also felt to be too toxic for further study.

Over the last several years, the outlook for patients with metastatic hormone receptor (HR)-positive, HER2-negative breast cancer has improved significantly with the advent of CDK4/6 and PI3K inhibitors. In addition to improving progression-free survival, CDK4/6i, in combination with endocrine therapy, prolong survival over endocrine therapy alone (3), and do so with a minimum of added toxicity, which is easily managed by holding the drug and/or dose reduction (4). Benefits are observed in both endocrine-sensitive and endocrine-refractory disease, but there are no predictive tumor biomarkers that identify patients who will benefit. However, the development of CDK4/6i resistance is universal, and although multiple mechanisms have been postulated, of particular interest is the cross-talk between cell-cycle regulatory pathways and the PIK3CA/AKT/mTOR signaling pathway. The PI3Ki, alpelisib, when combined with fulvestrant in patients with tumors that harbor a PIK3CA mutation, has also been shown to provide additional benefit over endocrine therapy alone. However, alpelisib comes with substantial toxicity, including hyperglycemia that requires intensive medical management (5). There has been intense interest in the potential to combine CDK4/6i, PI3ki, and endocrine therapy to overcome or forestall resistance, and further improve outcome.

The trials conducted by both Tolaney and colleagues and Lu and colleagues were designed to clinically translate preclinical observations regarding these issues. The PI3K/AKT/mTOR pathway is implicated as a common endocrine therapy escape pathway, with up to 40% of patients with HR-positive metastatic breast cancer harboring *PIK3CA* mutations. In fact, this signaling cascade exhibits significant cross-talk with the estrogen receptor (ER) and CDK/RB/E2F pathways to effect antiapoptotic, proliferative, and survival signals in breast cancer, with cyclin D1 acting as a common node (**Fig. 1**). For instance, cyclin D1 binds to and activates CDK4/6 to promote cell-cycle progression through phosphorylation of Rb, causing its uncoupling from E2F and thus, activating transcription of genes involved in G_1–S-phase transition. Feeding into this pathway, estrogen induces cyclin D1 transcription; conversely, cyclin D1 can bind directly to the ER and, in the absence of estrogen, induces ligand-independent ER-mediated transcription; S6K, a downstream kinase of mTOR, acts on the ER in this manner as well (6). Cyclin D1 is also protected from proteolytic degradation via AKT-mediated phosphorylation of glycogen synthase kinase-3β (6). This complex network of interrelated pathways converges on signals ultimately promoting cell-cycle progression and survival.

The convergence of these pathways becomes even more intriguing during investigations into mechanisms of CDK4/6i resistance. Through CDK4/6i-resistant cell lines, investigators have elaborated on various alterations in the PI3K/AKT/mTOR pathway as prominent mechanisms of resistance, including upregulation and expression of phospho-AKT, PDK1 (required for full AKT activation), p70S6K (a downstream target of mTORC1), and downregulation of PTEN (7). In particular, increased levels of phosphorylated-AKT were shown to correlate with sustained expression of CDK2/Cyclin E2, rendering the cells able to bypass CDK4/6; treatment with a PI3Ki was able to reduce E cyclins and thus, shut down the CDK2–Cyclin E resistance pathway (8). In this same study, a patient-derived xenograft breast cancer mouse model also demonstrated that first-line treatment with dual CDK4/6 and PI3K inhibition led to sustained tumor regressions and prevented acquired CDK4/6i resistance, whereas monotherapy with either agent led to acquired resistance and tumor growth (8). Further supporting PI3K as an attractive target, O'Brien and colleagues have recently published a series of mouse xenograft models showing that tumor progression on combination CDK4/6i and endocrine therapy could be reversed with the addition of a PI3Ki, regardless of *PIK3CA* mutation status, and that the same rescue effect could be achieved with addition of a CDK4/6i and endocrine therapy to mice treated with upfront PI3K inhibition (9). These data showcase the compensatory relationship between the CDK/Rb/E2F and PI3K/AKT/mTOR signaling pathways, and further support combinatorial strategies with endocrine therapy, CDK4/6i, and PI3Ki.

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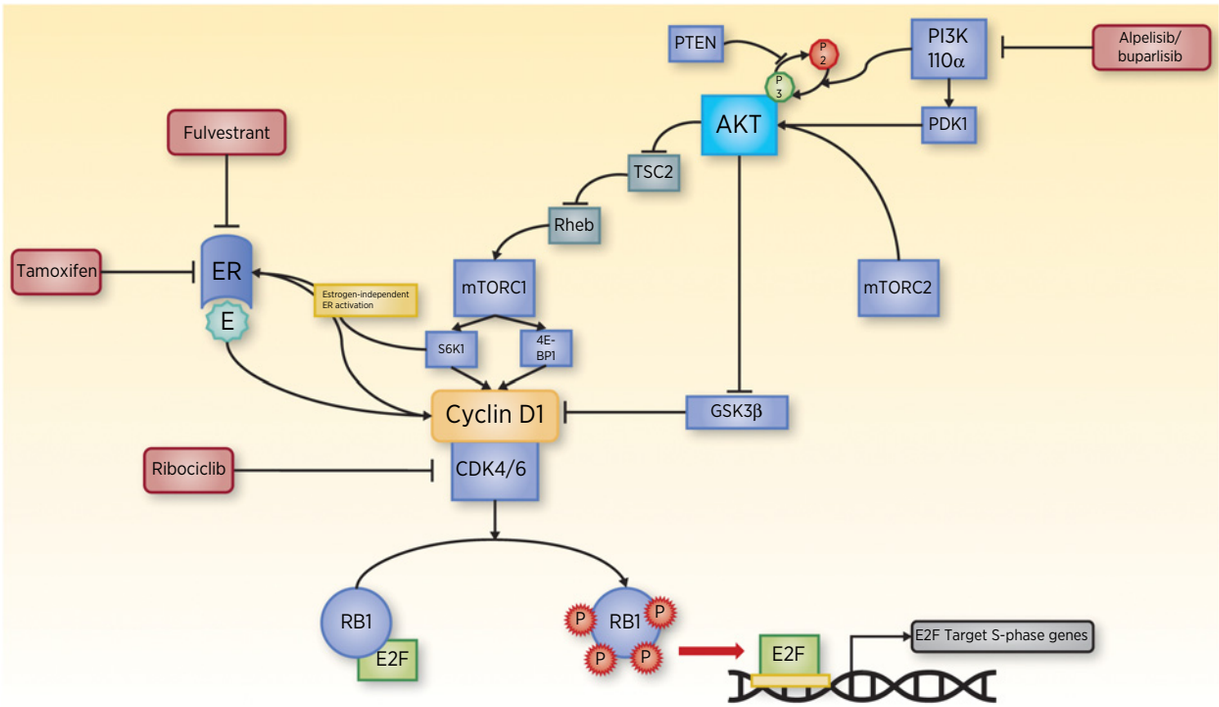

Figure 1.

The intersection among ER, PI3K/AKT/mTOR, and CDK/Rb/E2F pathways, with cyclin D1, a notable common node, along with therapeutics targeting PI3K, ER, and CDK4/6. Cyclin D1 plays a central role in regulating cell-cycle progression through binding CDK4/6, leading to a cascade of phosphorylation events on Rb tumor suppressor protein, causing its uncoupling from E2 factor (E2F) transcription factors, allowing them to traverse into the nucleus and induce transcription of genes promoting G_1–S-phase transition. Cyclin D1 can complex with ER and thereby induce ligand-independent transcriptional activity of ER; estrogen may also induce cyclin D1 expression to drive cell-cycle progression. Downstream effectors of PI3K/mTOR complex 1 (mTORC1), S6K and eukaryotic initiation factor 4-binding protein 1 (4E-BP1), induce translation of cyclin D1, while AKT stabilizes cyclin D1 via inhibition of glycogen synthase kinase-3β (GSK3β), a kinase that facilitates proteolytic turnover of cyclin D1 through phosphorylation. The ER pathway is targeted by fulvestrant (an ER degrader) or tamoxifen (an ER modulator) along with goserelin (a GnRH agonist, not shown). Inhibition of CDK4/6 is achieved with ribociclib. PIK3K 110α is inhibited by alpelisib or buparlisib. E, estrogen; P2, phosphatidylinositol (4,5)-bisphosphate, also known as PIP2; P3, phosphatidylinositol (3,4,5)-trisphosphate, also known as PIP3.

So what can we take away from these investigations? The findings of Lu and colleagues provide another potential endocrine partner for alpelisib, while the future for buparlisib seems bleak, given its more toxic profile. Importantly, the triplet combination of CDK4/6i/PI3Ki/endocrine therapy is not feasible when either alpelisib or buparlisib is partnered with ribociclib. This, however, does not rule out other possible combinations. The TRINITI trial (NCT02732119) followed a similar triplet concept, but targeted mTOR, a downstream effector of PI3K. In TRINITI, exemestane, ribociclib, and everolimus were administered specifically to patients who had HR-positive/HER2-negative metastatic breast cancer, the majority of whom had progressed on an aromatase inhibitor and CDK4/6i. In contrast to the findings of Tolaney and colleagues, TRINITI showed an acceptable toxicity profile for the combination, and preliminary efficacy showed a 1-year PFS of 33% (10). While still far from proof of concept that a triple combination can benefit patients with CDKi resistance, this should be explored further.

Given the findings from Tolaney and colleagues and Lu and colleagues, we are left with several other critically important questions. First, what is the optimal order of targeted therapy for patients with *PIK3CA* mutations: should alpelisib be prescribed first, or, given its higher toxicity profile, should it remain an option for later-line therapy? The results presented by Lu and colleagues certainly support further exploration of this question. If larger trials are able to show prolonged progression-free and overall survival for those who receive alpelisib first, a care standard would be set. Second, how can we best circumvent the resistance mechanisms that develop with CDK4/6i treatment? This begs the question of whether all patients with HR-positive/HER2-negative metastatic breast cancer, regardless of *PIK3CA* mutation status, should receive triplet therapy upfront. While Tolaney and colleagues show that neither buparlisib nor alpelisib can be safely combined with a CDK4/6i and fulvestrant, there are other proteins within the PI3K pathway, such as mTOR or Akt, that can be targeted with available drugs or drugs in development. Thus, there remain promising drug combination options to circumvent PI3K-induced CDK4/6i resistance. The bottom line: well designed, multi-armed randomized trials are needed to fully answer these questions. Tolaney and colleagues and Lu and colleagues provide evidence on where to start.

Authors' Disclosures

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