

RB1 gene mutations underlie clinical resistance to CDK 4/6 inhibitor breast cancer therapy

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A multi-institutional research team has identified what may be a novel mechanism underlying acquired resistance to CDK 4/6 inhibitor treatment for breast cancer. In their report published in the *Annals of Oncology*, the team—led by investigators at Massachusetts General Hospital (MGH), Institute Gustave Roussy in Paris, and Texas Oncology-Baylor Sammons Cancer Center/U.S. Oncology in Dallas—reports their discovery of new mutations in the RB1 gene, a key part of the pathway targeted by CDK 4/6 inhibitors, in women with hormone-receptor (HR)-positive breast cancer whose tumors had progressed on CDK 4/6 inhibitor treatment. Proofs of this study were made available online in December 2017, ahead of print publication in March 2018.

"CDK 4/6 inhibitors have changed the treatment landscape for HR-positive [breast cancer](#), and it is estimated that more than 70,000 patients in the U.S. have been treated with palbociclib, the first of three such drugs to receive FDA approval," says Aditya Bardia, MD, MPH, of the MGH Cancer Center, co-senior author of the study. "However, after months of responding to treatment, patients' tumors eventually progress. The mechanisms governing the development of resistance have been unknown, and this first report of the emergence of RB1 mutations by our collaborative team will hopefully lead to additional research and development of therapeutic strategies to target and perhaps even prevent clinical resistance."

The tumor suppressor RB1 (retinoblastoma) gene regulates the cell cycle—the process leading to cellular division—and the CDK4 and CDK6 enzymes block RB1 activity, which can lead to uncontrolled cellular proliferation and growth. CDK 4/6 inhibitors target this process, but as with many targeted therapy drugs, resistance develops after several months of treatment response. Bardia and

his colleagues report on three patients who received CDK 4/6 inhibitor treatment for invasive HR-positive, HER2 negative breast [cancer](#) at the MGH Cancer Center, Institute Gustave Roussy or at U.S. Oncology.

All three had developed metastases after several types of previous treatment, and their tumors had been genotyped before CDK 4/6 inhibitor treatment—either palbociclib (Ibrance) or ribociclib (Kisqali) - was initiated. When their tumors progressed after treatment with a CDK 4/6 inhibitor, repeat genotyping identified several new RB1 mutations that had led to loss of RB1 function and consequently resistance to CDK 4/6 inhibitors. The authors note that, while their findings do not prove the mutations caused resistance, the detection of these mutations by investigators at three different institutions supports their potential role in clinical resistance and validates observations from other centers' studies in cell lines and animal models that reported the loss of RB1 function in CDK 4/6-inhibitor-resistant cells or tumors.

Addressing whether resistance to CDK 4/6 inhibitor can be prevented or delayed, Bardia says, "Preclinical studies have shown that adding a PI3K inhibitor to combined CDK 4/6 inhibitor and hormone treatment could prevent or delay CDK 4/6 inhibitor [resistance](#); however, that needs validation in clinical studies. While combination therapy can enhance efficacy, it can also enhance toxicity. We are eagerly awaiting results from ongoing clinical trials evaluating triple combination [treatment](#) with endocrine therapy, a CDK 4/6 inhibitor and a PI3K inhibitor—or downstream mTOR inhibitor—in [metastatic breast cancer](#)." He is the director of Precision Medicine at the Center for Breast Cancer of the MGH Cancer Center and an assistant professor of Medicine at Harvard Medical School

More information: R Condorelli et al, Polyclonal RB1 mutations and acquired resistance to CDK 4/6 inhibitors in patients with metastatic breast cancer, *Annals of Oncology* (2017). [DOI: 10.1093/annonc/mdx784](#)

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