

Rational drug combinations that may overcome mantle cell lymphoma resistance to ibrutinib

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Genomic analyses of tumor and healthy tissue from patients with mantle cell lymphomas that fail to respond to treatment with the anticancer drug ibrutinib (Imbruvica) or initially respond but then stop responding and progress, provided explanations for these two types of drug resistance and suggested ways to overcome them in the clinic, according to data published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Ibrutinib, a [drug](#) that targets a protein called BTK, shows unprecedented clinical activity against mantle cell lymphoma," said Selina Chen-Kiang, PhD, professor of pathology and laboratory medicine and professor of microbiology and immunology at Weill Cornell Medical College, New York. "However, the drug doesn't work for about 32 percent of patients, and their lymphomas are said to have primary resistance to ibrutinib. We are also learning that most patients whose lymphomas respond to ibrutinib eventually relapse because their tumors acquire resistance to the drug.

"The knowledge that we gained from longitudinal RNA and genomic sequencing of mantle cell lymphomas with primary and acquired resistance to ibrutinib allowed us to identify rational drug combinations that may overcome resistance in these two settings," continued Chen-Kiang. "We recently opened a clinical trial to test one of these combinations, the selective CDK4/6 inhibitor palbociclib and ibrutinib

[NCT02159755]."

"Unfortunately, only a subset of mantle cell lymphoma patients respond to ibrutinib and those who do respond eventually relapse," said Lewis C. Cantley, PhD, who directs the Sandra and Edward Meyer Cancer Center at Weill Cornell. "In this paper, the authors conducted a longitudinal study to investigate molecular events that occur during treatment with ibrutinib and identified a mutation in the target of ibrutinib, BTK, that confers resistance to the drug. They also discovered that high levels of PI3K-AKT and CDK4 signaling could explain innate resistance to ibrutinib and showed in ex-vivo studies that a combination of a CDK4 inhibitor and a PI3K inhibitor might be effective for treating patients who do not respond to ibrutinib.

"This study not only suggests new approaches for treating mantle cell lymphoma but also has implications for treatment of other B cell lymphomas, such as CLL, and a diverse group of non-Hodgkin lymphomas," continued Cantley, who is also co-editor-in-chief of Cancer Discovery. Cantley recused himself from the peer review of the study.

Chen-Kiang and colleagues used whole-exome and whole-transcriptome analysis of five serial biopsies from a patient who had mantle cell lymphoma that initially responded to ibrutinib before progressing to identify reasons why mantle cell lymphomas acquire resistance to ibrutinib. After comparing these data with results from analysis of healthy tissues from the same patient, the researchers found that a mutation in BTK, the C481S mutation, appeared at relapse. The same mutation was detected at relapse in a second patient who had mantle [cell lymphoma](#) with acquired resistance to ibrutinib but not in any patients with primary [resistance](#) to the drug.

Further analyses revealed the consequences of the relapse-specific BTK

C481S mutation, including activation of the PI3K and CDK4 signaling pathways, which promote cell survival and proliferation. Blocking CDK4 with the investigational anticancer drug palbociclib made ibrutinib-resistant lymphoma cells carrying the BTK C481S mutation sensitive to investigational drugs that inhibit PI3K. In addition, palbociclib made ibrutinib-resistant lymphoma cells harboring normal BTK sensitive to both ibrutinib and investigational drugs that inhibit PI3K.

"We are very excited to have generated data that we have been able to put together in a way that may be meaningful for patients," said Chen-Kiang. "It is also exciting because CDK4 is a new kind of drug target; it controls the cell cycle, which is a central cancer pathway. As such, it is not just important for [mantle cell lymphoma](#) but for many forms of cancer."

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