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# New Mechanisms of Genomic Escape From Noncovalent BTK Inhibitors

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In physiological conditions, B-cell receptor (BCR) signaling promotes B-cell development and maintenance by activating proliferative and survival pathways. In pathological conditions, these pathways are co-opted by malignant B-cells to promote their own survival and growth. Among the downstream signaling molecules engaged upon BCR activation is the Bruton's tyrosine kinase (BTK). The aberrant activation of this kinase elicits proliferative and pro-survival signals in multiple B-cell malignancies, such as chronic lymphocytic leukemia (CLL), mantle cell lymphoma, and marginal zone B-cell lymphoma. The development of drugs targeting BTK has led to the development of covalent BTK inhibitors, which irreversibly bind to the C481 residue within the ATP-binding pocket thereby blocking its catalytic activity. The development of these drugs holds the promises for transforming the management of B-cell malignancies as a chemotherapy-free treatment. Nevertheless, multiple mechanisms of resistance, including mutations at the C481 residue, have been observed in patients treated with these drugs. The noncovalent BTK inhibitors, which were subsequently developed, showed promising results in phase 1 and 2 clinical trials. Owning to key differences in their structure

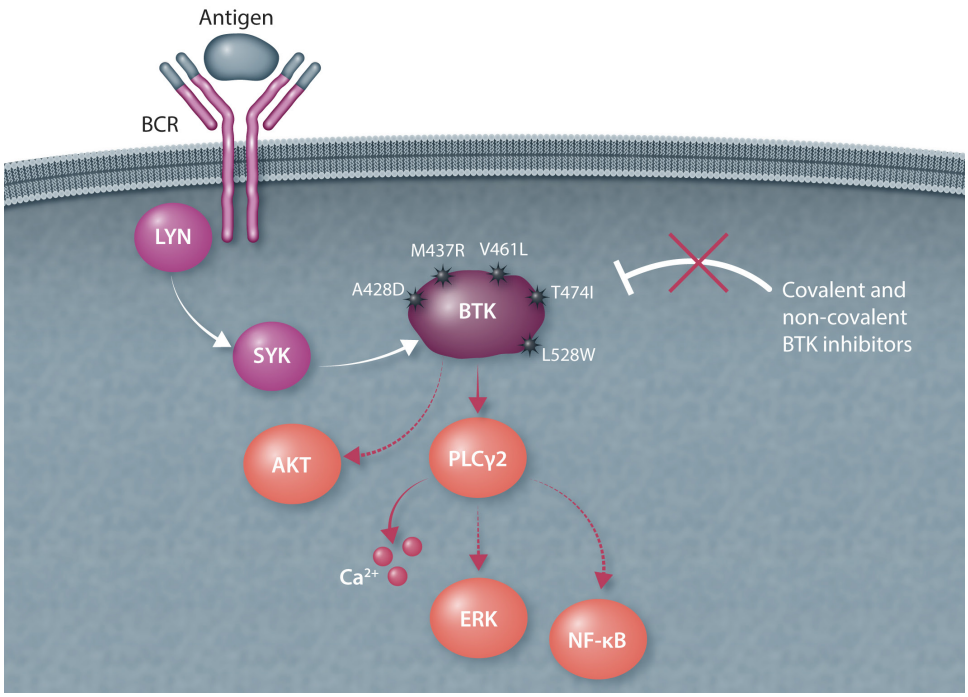


**Figure 1. In CLL cells, 5 non-C481 mutations identified in BTK kinase domain by Wang et al[2] prevent BTK binding to covalent and noncovalent BTK inhibitors.** By doing so, even if they paradoxically hinder the catalytic activity, they promote the activation of BCR downstream signaling pathways such as AKT, NF-kB, and ERK. AKT = protein Kinase B; BCR = B-cell receptor; BTK = Bruton's tyrosine kinase; CLL = chronic lymphocytic leukemia; ERK = extracellular signal-regulated kinase 1; NF-kB = nuclear factor kappa B.

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and mechanism of action, these compounds showed efficacy in patients suffering from B-cell malignancies, including those previously treated with covalent BTK inhibitors and patients presenting BTK C418 mutations.[1]

Yet, a recent report in *The New England Journal of Medicine* identified and characterized mechanisms of resistance against noncovalent BTK inhibitors.[2] Among a cohort of 55 CLL patients treated with the noncovalent BTK inhibitor pirtobrutinib, Wang et al[2] identified 9 patients with relapsed or refractory CLL. As evidenced by serial targeted sequencing, 7 out of the 9 relapsing patients presented 5 new points mutations which clustered within the BTK kinase domain outside the C481 residue (V416L, A428D, M437R, T474I, and L528W). In the remaining 2 patients, mutations in phospholipase C gamma 2 (PLCγ2), a BTK downstream substrate, were identified before treatment and persisted after therapy (PLCγ2 E1139del). As demonstrated by functional studies, the newly identified BTK mutations impaired BTK binding to a wide variety of noncovalent BRK inhibitors which are under clinical development (ie, fenebrutinib, vecabrutinib) as well as to covalent inhibitors already clinically approved (ie, ibrutinib). As such, following exposure to BTK inhibitors, these mutations allowed a persistent activation of the BCR signaling even if they paradoxically disrupted the kinase activity. Despite preventing BTK activation by autophosphorylation, in fact, the mutations were still able to activate the protein Kinase B (AKT) nuclear factor kappa B (NF-kB), and extracellular signal-regulated kinase 1 (ERK) signaling pathways (Figure 1). In line with this, reduced expression of the BCR signaling gene set was observed in relapsed patients.

Despite the small number of patients analyzed in this study, data provided by Wang et al[2] are important as they suggest novel therapeutic approaches to overcome BTK inhibitors resistance. This includes exploring synergistic effects of a combined AKT and BTK inhibition. On the molecular level, the fact that catalytic inactive BTK mutants still retain the ability to activate AKT, NF-kB, and ERK is intriguing and it suggests exploring whether BTK non catalytic functions[3] are involved in mediating drug resistance. Furthermore, given that B-cell lymphomas and CLL cells epigenetically rewire the BCR signaling to promote resistance against covalent BTK inhibitors,[4] it will be important to investigate whether similar epigenetic mechanisms intervene also against noncovalent BTK inhibitors. Investigating these points will likely be crucial in improving the treatment of multiple B-cell malignancies where the BTK kinase plays an essential role.

## DISCLOSURES

The author has no conflicts of interest to disclose.

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