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# Not All Bruton's Tyrosine Kinase Inhibitors are Created Equal: Pharmacologic Insights into the Efficacy, Resistance, and Safety of Covalent and Non-covalent BTK Inhibitors

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## About the Author

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# Not All Bruton's Tyrosine Kinase Inhibitors are Created Equal: Pharmacologic Insights into the Efficacy, Resistance, and Safety of Covalent and Non-covalent BTK Inhibitors

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*As the therapeutic landscape for B-cell malignancies continues to evolve, understanding the pharmacologic nuances of Bruton's tyrosine kinase inhibition has become increasingly important. In this interview, Rohit Khanna, publisher of Canadian Hematology Today, speaks with Giorgio Minotti, Professor of Pharmacology at the Università Campus Bio-Medico in Rome about the mechanistic differences between covalent and noncovalent BTK inhibitors, and the clinical implications for BTK inhibitor efficacy, resistance, and safety.*

## You have spent much of your career studying how drugs interact with their molecular targets. What drew you to the pharmacology of BTK inhibitors specifically?

Bruton's tyrosine kinase (BTK) is crucial for B-cells, and it plays a key role in many B-cell malignancies. BTK is not only central to B-cell receptor signaling but it also regulates processes such as proliferation, migration, and homing of malignant B cells. This is why BTK inhibition has become such a dominant therapeutic strategy over the past 15 years.

I was also attracted to BTK because it belongs to an ancestral family of proteins that are involved in many different pathways. When you completely block BTK with covalent BTK inhibitors, there can be many off-target effects.

## How do covalent BTK inhibitors like ibrutinib, acalabrutinib, and zanubrutinib bind to and inactivate BTK?

The covalent BTK inhibitor enters the kinase domain and binds to the C481 cysteine residue, effectively and permanently inactivating that BTK protein. However, BTK can be resynthesized continuously. The plasma levels of covalent BTK inhibitors decline quite rapidly. For this reason, it is important to be very diligent in ensuring adherence to covalent BTK inhibitors, to restore the plasma levels necessary to inhibit the newly synthesized BTK. There is a continual confrontation between the BTK inhibitor and the resynthesized BTK protein.

If patients are not adherent to the dosing schedule, or they stop covalent BTK inhibitors for toxicity, surgery or another reason, this can create a window for BTK resynthesis and disease progression. For this reason, I recommend reducing the dosage of covalent BTK inhibitors whenever possible, rather than interrupting the medication.

## Pirtobrutinib is described as a noncovalent, reversible BTK inhibitor. How does its binding mechanism fundamentally differ from the covalent agents?

Pirtobrutinib does not bind to the cysteine residue. Instead, it engages BTK through a network of non-covalent interactions across the kinase domain. While pirtobrutinib is often labelled simply as a 'reversible' inhibitor, I find that term misleading at the clinical level. At the molecular scale individual binding events are indeed reversible, but the pharmacological consequence is the opposite of intermittent: continuous re-engagement of BTK by drug molecules in the plasma produces what I prefer to call tonic, sustained inhibition (**Figure 1**).

The clinically relevant question is not whether a single bond is covalent or non-covalent, but whether BTK occupancy is maintained across the dosing interval — and with pirtobrutinib, it is.

## There is sometimes a perception among clinicians that noncovalent inhibitors may be less potent than covalent agents. How would you address that?

I strongly disagree with that perception. The idea that noncovalent equals weaker is a misunderstanding. Pirtobrutinib achieves persistent, high-level occupancy of BTK through both its pharmacokinetics and its network of binding interactions. In practice, it works by continuous inhibition of BTK, rather than transient engagement.

Its ability to debulk lymph nodes and suppress resistant clones demonstrates that it is very effective.

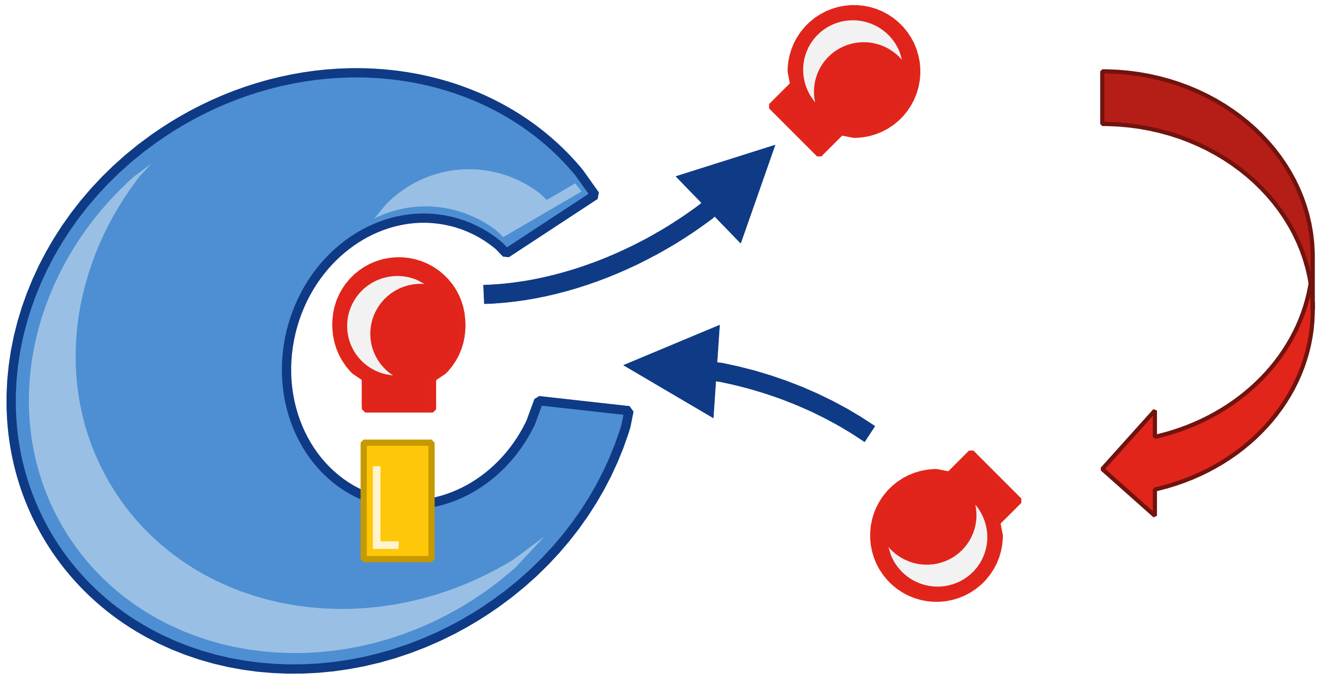



**Figure 1.** Conceptual rendering of how the high plasma levels of pirtobrutinib allow for tonic, sustained occupation and inhibition of BTK; *courtesy of Giorgio Minotti, MD.*

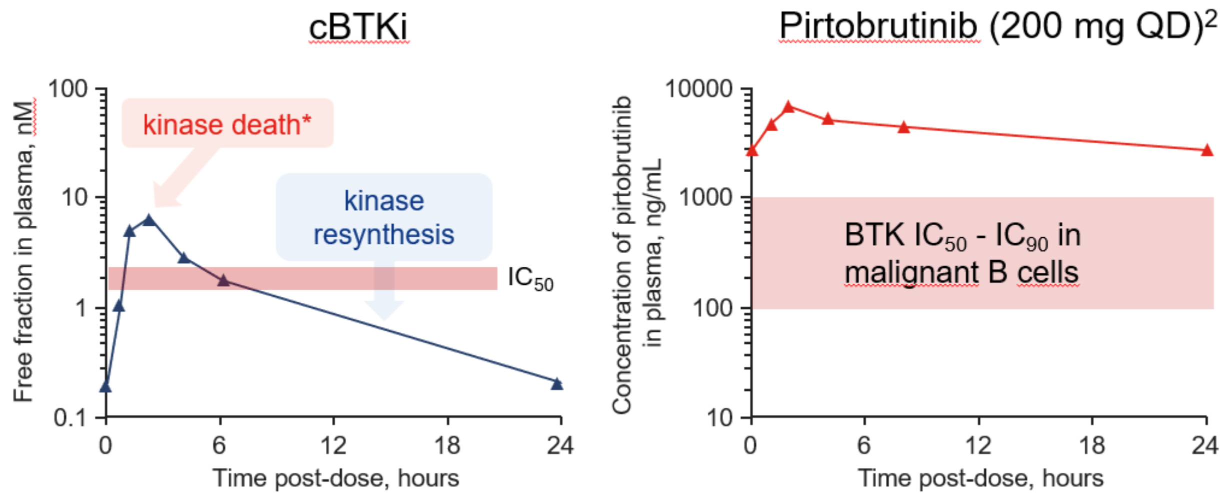



**Figure 2.** Pirtobrutinib pharmacokinetics are different and more cooperative with its mechanism of action (MOA); *author's conceptualization of 1. Tam CS, et al. Blood Cancer J. 2023;13(1):141. 2. Mato AR, et al. Lancet. 2021;397(10277):892-901.*

*Irreversibly inhibited.

**Abbreviations: cBTKi:** covalent Bruton's tyrosine kinase inhibitor; **PK:** pharmacokinetics; **QD:** once daily.

## Can you elaborate on the pharmacokinetics of pirtobrutinib and how the pharmacokinetics differ from covalent BTK inhibitors?

Pharmacokinetics describe how a drug is distributed in blood and tissues. Pirtobrutinib engages BTK through multiple noncovalent interactions within the kinase domain, while covalent BTK inhibitors bind only to the C481 residue. With pirtobrutinib, a network of binding sites ensures that it effectively occupies the kinase (**Figure 2**).

Another important difference in the pharmacokinetic profile of covalent versus non-covalent BTK inhibitors is that while covalent BTK inhibitors rapidly decline in plasma, pirtobrutinib maintains higher and more sustained plasma concentrations, with a half-life approaching 18 to 19 hours. This allows for continuous 'pressure' on BTK, as drug molecules repeatedly occupy the active site as others dissociate.

In fact, the pharmacokinetics of pirtobrutinib are such that at least 90% of patients on 200 mg pirtobrutinib QD will develop plasma concentrations sufficient to inhibit BTK activity by 90% or more across the dosing interval.

## Data suggest that pirtobrutinib achieves lymph node debulking that is comparable to first-generation covalent BTK inhibitors. How do you interpret this data from a pharmacological standpoint?

Lymph node debulking involves the redistribution of lymphocytes from the lymph node microenvironment into the peripheral blood. This is an elaborate process that involves drug-induced modulation of receptor expression and cell-cell signaling pathways that normally retain lymphocytes within the node. The fact that pirtobrutinib is as effective as ibrutinib at lymph node debulking is indicative of the efficacy of its strong, networked binding to BTK and persistence in the plasma (**Figure 3**).

## A major clinical challenge with covalent BTK inhibitors is acquired resistance, particularly through the C481S mutation. Can you explain why this mutation undermines covalent agents, but not pirtobrutinib?

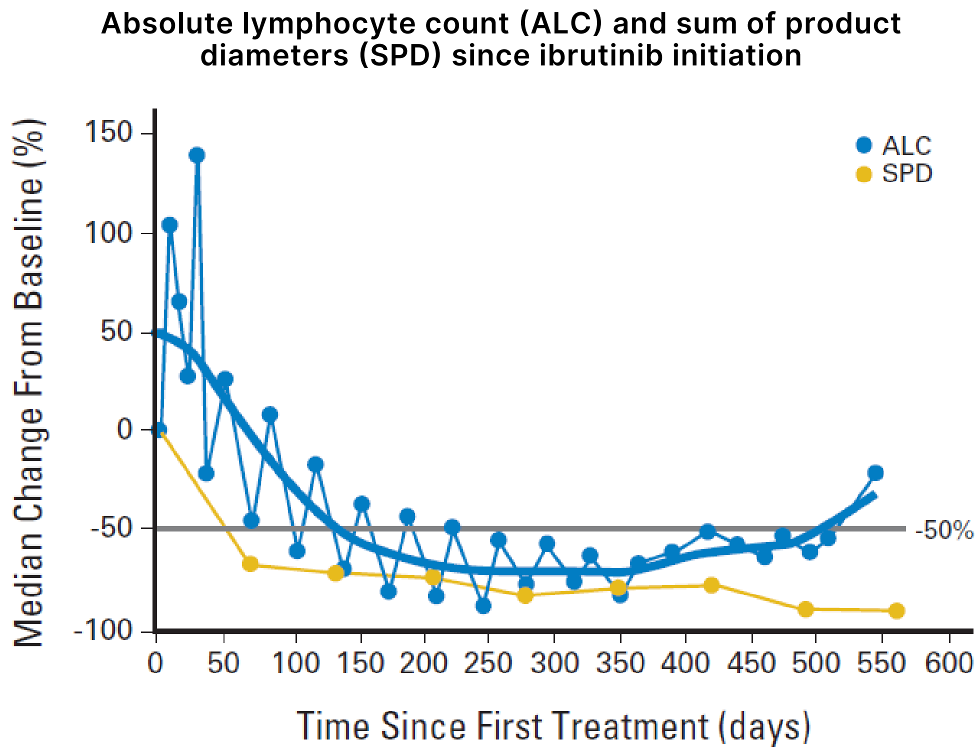
The C481S mutation arises as a resistance mechanism driven by the covalent binding mode of first-generation BTK inhibitors, which irreversibly target the cysteine residue at position 481. Under selective pressure, the C481S mutation disrupts covalent binding and abrogates drug efficacy.

Clinically, mutation at C481 arises in approximately 30% to 40% of patients progressing on ibrutinib, and the mutation occurs with other covalent BTK inhibitors as well. This is a typical example of mutation driven by the mechanism of action. On the other hand, because pirtobrutinib does not depend on this residue and instead engages BTK through a distinct, reversible interaction, it does not drive C481S mutation.

The activity of pirtobrutinib is retained in the presence of the C481S mutation. In fact, analyses show that in patients harboring C481S mutation treated with pirtobrutinib, the frequency of mutant clones declines over time.

## You have published extensively on the idea that BTK shares its cysteine residues with other kinases through a common evolutionary ancestral protein. What does this mean for the off-target effects of covalent versus noncovalent inhibitors?

BTK is a very ancient protein that arose before the development of multi-cellular organisms. The family to which BTK belongs disseminated cysteine in many other kinases, what I call "innocent kinases," that are not involved in B-cell malignancy. These innocent kinases play a role in the cardiovascular system. Covalent inhibitors like ibrutinib, acalabrutinib, and zanubrutinib will recognize cysteines homologous to C481 on these innocent kinases and will covalently bind to and inhibit them. This off-target inhibition is thought to contribute to



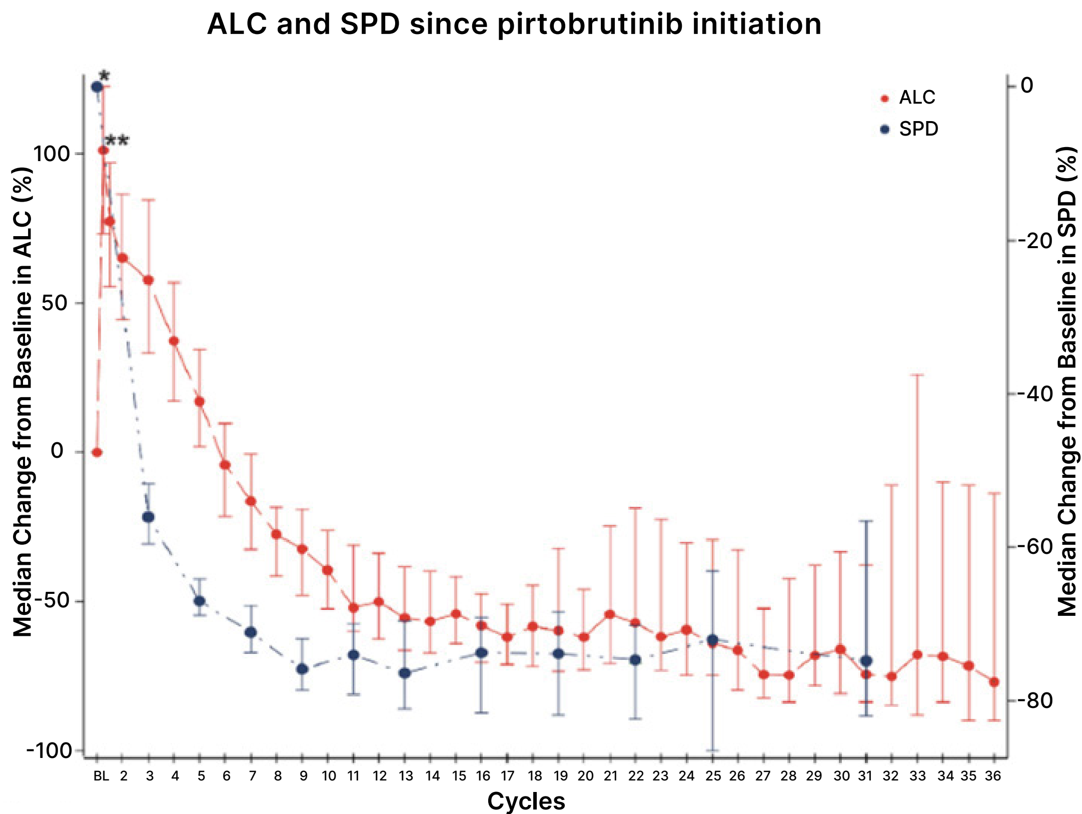




**Figure 3.** In Chronic lymphocytic leukemia (CLL), pirtobrutinib debulks lymph nodes as precisely as ibrutinib does; *adapted from Advani et al., J. Clin. Oncol., 31::88-94, 2013 and Mato et al., N Engl J Med 389:33-44, 2023.*

the atrial fibrillation, bleeding, hypertension, heart failure, and ventricular arrhythmias associated with covalent BTK inhibitors. These are class effects, occurring across covalent inhibitors, although with varying levels of incidence and time to event.

It is therefore a remarkable advantage that pirtobrutinib does not bind to the cysteine residue. This means it has less propensity to engage with kinases expressing amino acid sequences and cysteine residues homologous to C481. This is a key factor underlying the greater selectivity and improved safety profile of pirtobrutinib compared with covalent BTK inhibitors.

The unique efficacy and safety features of pirtobrutinib make it ideal for patients with comorbidities and prior cardiotoxic therapies. Prior exposure to other cardiotoxic drugs increases the risk of subsequent cardiac or vascular events. Pirtobrutinib has been shown to be safe in heavily pretreated populations, with relatively low incident rates of atrial fibrillation and hypertension.

## As we learn more from ongoing clinical trials, how do you see the approach to treating B-cell malignancies changing in the future?

If we look back 15 years ago, we only had alkylating agents. We have seen incredible pharmacological and clinical progress. The treatment of B-cell malignancies is a very evolving field.

We are also beginning to see the development of dual BTK inhibitors that combine covalent and noncovalent binding properties, potentially adapting to mutation status.

What we know today was totally unknown or unpredictable a year or two ago. I believe that the future is bright and that molecular testing will increasingly guide treatment decisions. We live in the era of precision medicine, and we should use the tests available to us to determine the best individualized treatment approach for each patient.

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