RESEARCH SUMMARY

Mechanisms of Resistance to Noncovalent Bruton's Tyrosine Kinase Inhibitors

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CLINICAL PROBLEM

Noncovalent inhibitors of Bruton's tyrosine kinase (BTK) are treatment options for several B-cell cancers, including chronic lymphocytic leukemia (CLL), and may be useful in patients in whom resistance to covalent BTK inhibitors (e.g., ibrutinib and acalabrutinib) develops, often as a result of mutations in BTK residue C481. Resistance to a noncovalent BTK inhibitor has now been identified in a phase 1–2 trial of the investigational drug pirtobrutinib.

GENOMIC ANALYSIS STUDY

Among 55 patients who had previously received treatment for CLL that included a covalent BTK inhibitor, 9 had disease progression during pirtobrutinib treatment after an initial response during the study. Peripheral-blood specimens were obtained from these 9 patients before treatment with pirtobrutinib and at the time of progression. To determine the genetic mechanisms of treatment resistance, the specimens underwent genomic analysis. The identified mutations were assessed with structural modeling, BTK-binding assays, and cell-based assays.

RESULTS

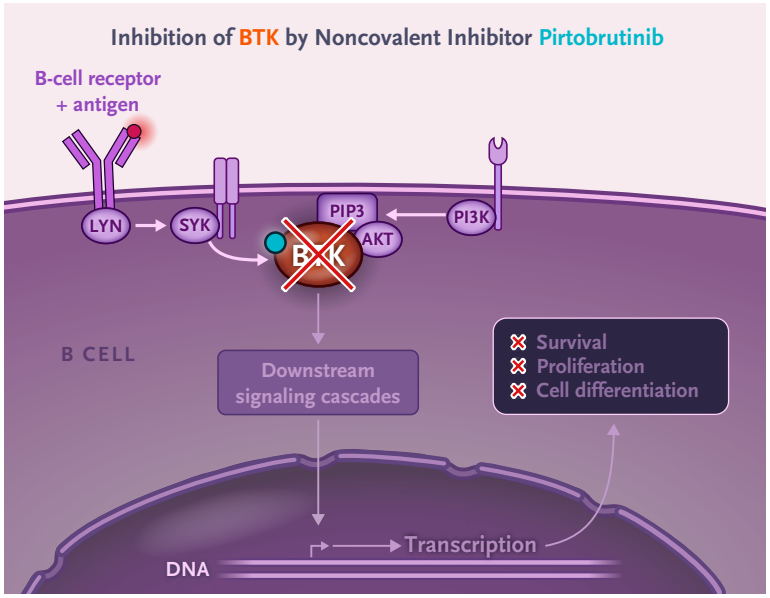
In seven patients, specimens at disease progression had new non-C481 mutations (V416L, A428D, M437R, T474I, or L528W) in the kinase domain of BTK. The other two patients had mutations in phospholipase C gamma 2, a BTK substrate, at both time points. Some of these mutations also conferred resistance to covalent BTK inhibitors. In cell-based assays, the BTK mutations resulted in persistent B-cell–receptor signaling despite BTK inhibition with pirtobrutinib.

LIMITATIONS AND REMAINING QUESTIONS

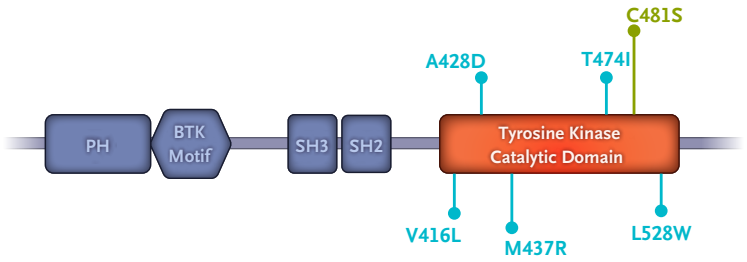
Further study is required to understand the following:

- How mutations in BTK that inactivate its kinase activity can allow ongoing B-cell–receptor signaling.
- Whether similar resistance mechanisms occur in patients who receive noncovalent BTK inhibitors without previous use of covalent BTK inhibitors.
- How frequently these mutations occur in larger groups of patients.

Links: Full Article | NEJM Quick Take



Mutations Conferring Resistance to BTK Inhibitors



Binding Affinities of BTK Inhibitors

	Noncovalent				Covalent
	Pirtobrutinib	ARQ-531	Vecabrutinib	Fenebrutinib	Ibrutinib
Wild type	Normal	Normal	Normal	Normal	Normal
A428D	None	Decreased	None	None	None
M437R	Decreased	Normal	Decreased	Decreased	Normal
T474I	Decreased	Decreased	Decreased	Normal	Normal
L528W	None	None	Decreased	Normal	None
C481S	Normal	Normal	Normal	Normal	Decreased

CONCLUSIONS

These findings show new mechanisms of acquired resistance to noncovalent and covalent BTK inhibitors in patients with CLL.