

Targeting treatment resistance in chronic lymphocytic leukemia with a compound that goes beyond current BTK inhibitors

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New research from Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine and collaborating



organizations has identified a next-generation BTK degrader that could help overcome treatment resistance in chronic lymphocytic leukemia (CLL) and related blood cancers.

Their <u>findings</u>, published Feb. 2 in the journal *Science*, could offer a therapeutic option for CLL patients whose tumors become <u>drug-resistant</u> or are unresponsive to frontline treatment.

"This new compound not only inhibits the cellular molecule BTK, but goes further by taking aim at the target and destroying it," explained Justin Taylor, M.D., Sylvester hematologist-researcher and the study's senior author. "It's a new and exciting drug class called BTK degraders."

CLL is an incurable cancer of the blood and <u>bone marrow</u> that affects about 20,000 people yearly in the U.S. and accounts for roughly onefourth of new leukemia cases, according to the American Cancer Society. It mainly affects older adults, with the average age at diagnosis being 70.

Patients diagnosed with CLL are often prescribed targeted drugs known as BTK inhibitors that can shrink tumors, ease symptoms and extend lifespans. But some patients develop drug resistance, thereby limiting their therapeutic options.

Currently-approved drugs like ibrutinib work by inactivating the cellular molecule called BTK (Bruton's tyrosine kinase). Ibrutinib and other approved inhibitors don't destroy their targets. Instead, they bind to them and modulate activity.

For example, ibrutinib and other inhibitors bind to the BTK enzyme that acts to keep B cells alive in leukemia. The drugs quell BTK activity, leading to B-cell death in CLL and other blood malignancies.



For this study, Taylor and colleagues, including first author Skye Montoya, a graduate student in his research lab, Omar Abdel-Wahab, M.D., from Memorial Sloan Kettering Cancer Center, and other collaborators assessed the new compound in laboratory studies and a Phase I clinical trial involving patients with tumors that had become drugresistant or were unresponsive to therapy.

Developed by Nurix Therapeutics, the compound, called NX-2127, is constructed with two modules—one that binds to BTK and another that degrades and eliminates it. Thus, the term BTK degrader.

The researchers reported that NX-2127 efficiently destroyed its cellular targets in both petri dishes and patient cells. "More specifically, this compound destroyed BTK cells in tumors resistant to currently used BTK inhibitors, while shrinking tumors in 11 of 14 CLL patients participating in our study," said Abdel-Wahab, who was co-corresponding author with Taylor.

One patient, in particular, had an impressive response to this BTK degrader, Taylor and Abdel-Wahab noted. The elderly man had been on pirtobrutinib for two years, but became resistant to it as well as other therapies, leaving him with no other conventional options.

However, while taking NX-2127 during the trial, his symptoms and quality of life improved to where he no longer needed transfusions for anemia, they said.

Further study analysis

Although this study had a September 2022 data cutoff for the *Science* publication, the researchers provided an update this past December at the American Society of Hematology meeting. Overall, 41% of CLL patients responded to NX-2127 and the elderly man was still responding



favorably to the drug.

Additionally, the research showed that drug resistance can occur when BTK acquires mutations that give it an entirely new function. These mutations cause BTK to operate as a "scaffold" that recruits other cellular molecules to keep B cells alive.

Most importantly, NX-2127 appears to overcome resistance caused by virtually all of the BTK mutations identified to cause resistance to available BTK inhibitors.

Taylor believes that BTK degraders have the potential to treat other Bcell malignancies or even autoimmune conditions such as multiple sclerosis. He and his colleagues, including Alvaro Alencar, M.D., Sylvester hematologist-researcher and contributing study author, are now enrolling patients in another study testing a more potent and selective BTK degrader, NX-5948, also from Nurix.

"CLL is an <u>incurable disease</u>, but with treatments like BTK inhibitors and these promising new BTK degraders, we have more ways to alleviate symptoms and get patients back to their normal everyday routines," Montoya said. "The future looks brighter for them."

More information: Skye Montoya et al, Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127, *Science* (2024). DOI: 10.1126/science.adi5798. www.science.org/doi/10.1126/science.adi5798

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