Fixed-Duration Triplet Therapy Demonstrates Efficacy for Patients with Relapsed/Refractory CLL

Adding Jaypirca to Venclexta and Rituxan for two years improves progression-free survival for patients with relapsed or non-responsive chronic lymphocytic leukemia.

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A Dana-Farber Cancer Institute investigator presented positive interim data from the BRUIN CLL-322 trial, the first randomized Phase III data to be reported about a Bruton tyrosine kinase (BTK) inhibitor as part of a fixed-duration therapy in relapsed/refractory chronic lymphocytic leukemia.

Triplet therapy with pirtobrutinib [Jaypirca], venetoclax [Venclexta], and rituximab [Rituxan] as a two-year fixed-duration therapy improves progression free survival for patients with relapsed/refractory chronic lymphocytic leukemia (CLL) compared to standard of care venetoclax plus rituximab therapy, according to interim data from the randomized, Phase III BRUIN CLL-322 clinical trial.

Matthew Davids, MD, MMSc, Chief of the Division of Lymphoma at Dana-Farber Cancer Institute, presented the results in the Late-Breaking Abstract session at the European Hematology Association 2026 Congress in Stockholm, Sweden, on June 14, 2026.

“When pirtobrutinib is added to the standard venetoclax-rituximab regimen, we see a substantial improvement in progression free survival, even better than we hypothesized,” says Davids. “That speaks to the power of the triplet-based therapy over the doublet and supports consideration of the triplet as a new standard of care option for relapsed/refractory CLL.”

In the US and in many areas of the world, patients diagnosed with CLL receive a covalent BTK inhibitor, such as ibrutinib [Imbruvica], acalabrutinib [Calquence], or zanubrutinib [Brukinsa] as standard first-line therapy. Standard second line therapy currently combines venetoclax, a BCL-2 inhibitor developed based in part on science from Dana-Farber laboratories, and rituximab, an immunotherapy targeting CD20, an antigen initially described at Dana-Farber. The combination is given over a fixed duration and has been standard of care for about eight years.

The U.S. Food and Drug Administration granted full approval for pirtobrutinib, a non-covalent BTK inhibitor, in 2025 as single-agent therapy for patients with relapsed/refractory CLL who previously received a covalent BTK inhibitor. Pirtobrutinib given continuously has been found in other studies to be effective and better tolerated than ibrutinib, likely due to its high potency and selectivity.

The randomized, Phase III BRUIN CLL-322 trial was designed to determine if a time-limited combination of a non-covalent BTK inhibitor pirtobrutinib and a BCL-2 inhibitor, venetoclax, plus immunotherapy with rituximab could deliver deeper, more durable responses in patients with relapsed/refractory CLL compared to standard therapy. The study included 639 patients with relapsed/refractory CLL, most of whom had previously received a covalent BTK inhibitor. Patients were randomized to receive either triplet or doublet therapy for a fixed duration of approximately two years.

At two years, 86.9% of patients taking the triplet therapy were still alive and had not progressed compared to 71.8% of those taking the doublet, a 45% lowered risk of worsening disease or death. Peripheral blood undetectable minimal residual disease MRD rates at end of treatment were higher with the triplet in patients with evaluable samples at 86%, compared to 61% in the doublet. Patients taking the triplet therapy experienced minimal additional side effects and tolerated the therapy well. More follow-up is needed to evaluate overall survival.

“Pirtobrutinib is one of the best tolerated targeted drugs we use in CLL, and when we add it to the standard regimen, we see only small differences in safety profile,” says Davids. “Patients are getting this added progression free survival benefit without much added toxicity, suggesting that this triplet therapy can benefit a wide range of patients, including older patients with other medical co-morbidities.”

The study reported on several planned subgroup analyses, including those with prior exposure to a covalent BTK inhibitor, those who had developed resistance to a covalent BTK inhibitor, and those who had TP53 aberration, which are all indicators of higher risk disease. Progression-free survival results were similar across subgroups.

“This study shows that pirtobrutinib can work even in the presence of covalent BTK inhibitor resistance mutations,” says Davids. “Patients with high risk TP53 mutations also did well with the triplet regimen.”

Prior to this study, the current standard second line therapy had only been evaluated in the Phase III setting in a patient population predominantly treated with first-line chemoimmunotherapy, not the covalent BTK inhibitors used commonly as first-line therapy today. This shift raises questions about how well the current standard second line therapy is working in patients today. The control arm of the BRUIN CLL-322 study provides insights, showing shorter progression free survival in patients receiving current standard therapy after a BTK inhibitor compared to data from previous trials in patients receiving the current standard therapy after chemotherapy.

“This evidence aligns with what we have been observing in the clinic, which is that the current

standard of care is not as effective in the modern patient population as it was in a more historical patient population," says Davids. "This new approach is an opportunity to add another drug to standard therapy to safely extend the duration of remission, and the time-limited nature of the regimen opens up the possibility of retreatment strategies in the future."

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