

Behind the Study That Led to FDA Approval of Brukinsa for Leukemia and Lymphoma

The Dana-Farber led ALPINE trial looked at the drug in relapsed chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

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On Thursday, January 19, 2023, the FDA approved zanubrutinib (brand name Brukinsa), a next-generation BTK inhibitor for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The approval was based, in part, on findings from the ALPINE trial, led by [Jennifer R. Brown, MD, PhD](#), of [Dana-Farber Cancer Institute](#).

"I am encouraged that zanubrutinib has been approved for adults with CLL and SLL and optimistic that many patients across the country will benefit from this approval," said Dr. Brown, director of the CLL Center at Dana-Farber Cancer Institute, following the FDA's approval.

A head-to-head clinical trial in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) found that zanubrutinib was more effective at preventing disease progression and better tolerated than ibrutinib, the first-generation BTK inhibitor that is the current standard treatment in that setting.

The phase 3 ALPINE randomized trial had previously shown that zanubrutinib achieved a better overall response rate (ORR) than ibrutinib. Dr. Brown first presented the ALPINE results in a late-breaking oral session at the 64th American Society of Hematology (ASH) Annual Meeting and Exposition, which showed that zanubrutinib-treated patients had a longer progression-free survival (PFS) at 29.6 months follow-up. The two-year landmark PFS for zanubrutinib was 79.5%, compared to 67.3% for ibrutinib. Median PFS for zanubrutinib had not been reached at that point, while for ibrutinib the median PFS was 35.0 months.

ALPINE is the first head-to-head comparison of BTK inhibitors to demonstrate superiority of zanubrutinib in both response rate and progression-free survival, and the drug had a lower rate of treatment discontinuation — 26.3% vs 41.2% with ibrutinib — according to Brown, who is director of the CLL Center of the division of Hematologic Malignancies at Dana-Farber. Discontinuation rates caused by heart disorders were lower in patients treated with zanubrutinib, including fewer cardiac events leading to death.

“Our findings also found that zanubrutinib led to fewer side effects and adverse events than ibrutinib, leading to a better quality of life for patients,” said Brown.

CLL and SLL are essentially the same disease — an indolent, low-grade non-Hodgkin lymphoma that originates in white blood cells called lymphocytes. When the cancer cells are in the bone marrow and bloodstream, it is termed CLL, and when predominantly in the lymph nodes, the disease is called SLL. About 20,160 new cases are expected in 2022, with about 4,410 deaths. The average age of diagnosis is around 70.

The management of CLL in patients with few or no symptoms may be watchful waiting until symptoms of disease progression appear. If needed, initial treatment may be a regimen of targeted therapy with or without immunotherapy.

A standard treatment for patients in first line, or for those who have relapsed or have resistant disease but have not yet had a BTK inhibitor, is ibrutinib, a first-generation Bruton Tyrosine Kinase (BTK) inhibitor. BTK inhibitors are targeted drugs that block the enzyme BTK, a part of the B-cell receptor signaling pathway, which is used by certain leukemias and lymphomas to grow and survive. Ibrutinib has some limitations on its use because in addition to targeting the BTK enzyme, the drug also has a number of “off-target” effects. Significant side effects of ibrutinib include cardiac events like atrial fibrillation, which can lead to discontinuations and interruptions in treatment; bleeding; decreased platelets, and severe skin toxicities.

Second-generation BTK inhibitors like zanubrutinib are more selective and are associated with a lower incidence of numerous adverse effects, including cardiac events. This may make it possible for patients to stay on treatment longer.

The results of the ALPINE trial presented at ASH showed that the rate of atrial fibrillation or atrial flutter was lower with zanubrutinib (5.2%) compared with ibrutinib (13.3%), and there were zero grade 5 adverse events due to cardiac disorders with zanubrutinib versus six in patients treated with ibrutinib.

Zanubrutinib, which is manufactured by the biotechnology company BeiGene, was previously approved by the FDA for Waldenstrom macroglobulinemia, relapsed or refractory mantle cell lymphoma, and marginal zone lymphoma.

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