Brukinsa's Approval Improves Targeted Treatment for Leukemia

Approved for CLL and SLL—types of leukemia and lymphoma—Brukinsa caused fewer heart-related side effects in trials.

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People with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) now have a more effective treatment option that has fewer side effects than a common CLL therapy, with the Food and Drug Administration's recent approval of the drug zanubrutinib (Brukinsa).

The approval, announced on January 19, is based on two large clinical trials of zanubrutinib.

In the first trial, called SEQUOIA, people with CLL who received zanubrutinib as their initial, or first-line, treatment lived a longer time without their cancer worsening than patients in the study who received rituximab (Rituxan) plus the chemotherapy drug bendamustine.

In the second trial, known as ALPINE, researchers compared zanubrutinib to a common CLL treatment of the same type, called ibrutinib (Imbruvica), that is known to have several challenging side effects. Both drugs inhibit a protein called BTK that fuels the growth and survival of CLL cells.

The ALPINE trial tested the two drugs as a second-line treatment, meaning in patients whose cancer had returned following at least one course of therapy for CLL.

At 2 years after starting treatment, more than 78% of patients receiving zanubrutinib were alive with no growth of their cancer, compared with 66% of patients taking ibrutinib. Zanubrutinib was particularly effective in people whose cancer had genetic mutations that typically signal a poorer prognosis.

And not only did zanubrutinib work better at stemming the return of CLL, but it did so with fewer side effects than ibrutinib.

Results of the ALPINE trial—which was funded by BeiGene, the manufacturer of zanubrutinib—were published in the New England Journal of Medicine and presented at the American Society of Hematology (ASH) annual meeting on December 13, 2022.

Zanubrutinib is also approved to treat several other cancers, including mantle cell lymphoma.

With its initial approval for CLL nearly 10 years ago, ibrutinib was a “breakthrough” for people with this disease, said Adrian Wiestner, MD, PhD, a senior investigator in the National Heart, Lung, and Blood Institute’s Laboratory of Lymphoid Malignancies, who was not involved in either trial.

The emergence of newer drugs for CLL like zanubrutinib is “making a good thing even better,” Dr. Wiestner continued.

A Better BTK Inhibitor?

CLL, a slow-growing cancer of the blood and bone marrow that is also known as SLL when found mostly in lymph nodes, is one of the most common forms of leukemia in adults in the United States.

BTK plays a critical role in supporting the growth and survival of some normal white blood cells as well as the cancerous white blood cells found in CLL. Ibrutinib, zanubrutinib, and another drug called acalabrutinib (Calquence)—which is also used to treat CLL—work by disrupting BTK’s activity.

These inhibitors turn off the active flow of communication through the cancer cells, Dr. Wiestner explained. He added that BTK inhibitors are typically prescribed to be taken indefinitely, with a goal to turn off as much BTK protein activity for as long as possible.

Like acalabrutinib, zanubrutinib is a newer type of BTK inhibitor, specifically designed to address ibrutinib’s shortcomings. For example, zanubrutinib binds BTK proteins with greater precision, remains bound to more BTK proteins for longer, and persists at high concentrations in the body during treatment, the study authors noted.

Its persistent concentration in the body makes zanubrutinib distinct from both ibrutinib and acalabrutinib. As cancer cells make more BTK protein, “zanubrutinib is still around to potentially re-inhibit it,” said Jennifer R. Brown, MD, PhD, director of the CLL Center at the Dana-Farber Cancer Institute and the ALPINE study’s lead investigator, during an education session at the December ASH meeting.

In ALPINE, 652 adults with relapsed or refractory CLL or SLL were randomly assigned to receive zanubrutinib or ibrutinib, which are both taken as a pill. All participants had previously tried at least one non-BTK-inhibitor treatment for CLL.

About 86% of participants who received zanubrutinib had at least some regression of their cancer, compared with 76% of participants who received ibrutinib.

The median time that patients receiving ibrutinib lived without their cancer getting worse (known as progression-free survival) was just short of 3 years. In the zanubrutinib group, not enough people had experienced a worsening of their cancer, so the median progression-free survival could not be determined.

Unexpectedly, zanubrutinib worked particularly well in patients whose cancer harbored specific genetic changes—either mutations in a gene called TP53 or a chromosomal alteration known as a 17p deletion—that render it more difficult to treat.

At 2 years after starting zanubrutinib treatment, 78% of patients with one or both of these mutations were still alive without their cancer getting worse, compared with 56% of patients taking ibrutinib.

The difference in progression-free survival with zanubrutinib in these high-risk patients "is really quite remarkable," Dr. Brown said at the ASH meeting.

Fewer Side Effects, but Risks Still Remain

Because BTK inhibitors for CLL are taken indefinitely, side effects are a major concern. Previous reports have shown that nearly a quarter of patients taking ibrutinib stop treatment because of side effects.

In the ALPINE trial, after a median of about 2 years since starting treatment, 22% of patients in the ibrutinib group ended treatment because of side effects, compared with 15% of those in the zanubrutinib group.

The most common side effects from ibrutinib and zanubrutinib were similar and included a decrease in white blood cells, upper respiratory tract infection, anemia, and joint stiffness.

Rates of severe high blood pressure were similar in the two treatment groups, but other heart-related side effects were less frequent in people treated with zanubrutinib. Atrial fibrillation, a condition marked by irregular heartbeats, was less common with zanubrutinib than ibrutinib.

None of the patients in the zanubrutinib group died from a heart-related issue, whereas six patients in the ibrutinib group had a fatal cardiac event.

Optimizing Treatment Approaches for Patients With CLL

The preference for zanubrutinib over ibrutinib for CLL is already reflected in the National Comprehensive Cancer Network guidelines for treating the disease, noted Dr. Wiestner, who has received research funding from AbbVie, one of the manufacturers of ibrutinib.

For patients taking ibrutinib but planning to stop because of side effects, "that person could be switched to zanubrutinib with potentially significant benefit," Dr. Brown said, which is supported by results from an ongoing trial.

Zanubrutinib is one of several options recommended for the first-line treatment of CLL. So a big question for researchers to address is how to best use it along with the other available treatments

for CLL, including the targeted therapy venetoclax (Venclexta), Dr. Wiestner said.

An area of particularly intense interest, he continued, is developing treatment strategies "that condense treatments into 1 or 2 years, typically using combination therapies that may include BTK inhibitors with other classes of drugs … to achieve deep and lasting remissions without the need for [continued] treatment."

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