# Combining BCL-2 and BTK Inhibitors Shows Promise for Chronic Lymphocytic Leukemia

All-oral, fixed-duration targeted therapy regimen was well-tolerated and improved survival in a large trial.

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A novel, fixed-duration drug combination — consisting of a second-generation BTK inhibitor, called acalabrutinib [Calquence], plus a BCL-2 inhibitor (venetoclax [Veclexta]), with or without a third blood cancer drug — shows deep and durable responses in patients with chronic lymphocytic leukemia (CLL), Dana-Farber Cancer Institute investigator Jennifer Brown, MD, PhD, reports at the 66th American Society for Hematology (ASH) Annual Meeting and Exposition, on behalf of the trial investigators.

The findings stem from a planned interim analysis of a Phase 3 international registration trial known as AMPLIFY, which included patients from 27 countries across North America, South America, Asia, Europe, and Oceania.

“This is the first combination of a BTK inhibitor plus a BCL-2 inhibitor that we expect will receive FDA approval in the U.S,” said Brown, who led the trial and [presented] the findings at ASH. “We’re very encouraged by the efficacy we’re seeing in these interim results and by the potential impact for CLL patients."

She added, “An all oral fixed-duration treatment that is effective and well-tolerated would be a very meaningful step forward as it is easy for patients and allows patients to take breaks from treatment — and that means less toxicity, a lower chance of resistance, and a better quality of life.”

CLL is a chronic disease that is typically difficult to cure, but it often can be treated and controlled for many years. The current slate of therapeutic options includes a handful of molecularly targeted therapies, which are often quite effective but there are some significant downsides.

For example, treatment with a single agent BTK inhibitor is given continuously, which means patients must take it for the rest of their lives or until their disease progresses — at which point, they have developed resistance, and the drug is no longer effective. Another targeted drug,

venetoclax, which inhibits the activity of BCL-2, is combined with obinutuzumab [Gazyva], an antibody against the CD20 protein.  Although this treatment is time-limited, obinutuzumab is given as an infusion in the clinic, so patients must make visits regularly to receive treatment.

The AMPLIFY trial, which was launched in 2019, evaluates the efficacy and safety of two first-line treatment regimens in CLL patients administered over 14 months: the second-generation BTK inhibitor acalabrutinib combined with venetoclax (AV), and the same drug pair combined with a third drug, obinutuzumab (AVO). These two treatments, AV and AVO, are compared to standard chemoimmunotherapy (either fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab).

A total of 867 patients were studied, with a median age of 61 years. Patients were randomized to the three treatment groups and followed for over 40 months. Patients with the highest risk genetic mutations, such as a chromosome 17 deletion or a TP53 gene mutation, were specifically excluded from the trial because the control arm, consisting of standard chemoimmunotherapy, is not an effective treatment option for this group.

From this interim analysis, the AMPLIFY trial met its primary endpoint, which is a higher rate of progression-free survival (PFS) in patients treated with AV compared to those receiving standard chemoimmunotherapy. The estimated 36-month PFS for the three groups are: 76.5% for AV, 83.1% for AVO, and 66.5% for the standard treatment group.

Moreover, the overall response rates for both experimental groups — AV and AVO — were over 92%; the overall response rate for the standard treatment group was 75%.  The AV regimen was very well-tolerated and also led to improved overall survival compared to the control arm.

“We’re really quite excited about these results and the effectiveness so far of these novel drug combinations,” said Brown. “Although there was no planned comparison of AV versus AVO, the progression-free survival data do look more favorable for AVO, but that has to be balanced with more toxicity and the inconvenience of regular infusions.”

In addition, the researchers also examined the rate of undetectable measurable residual disease (MRD), a parameter that reflects how well a therapy has eradicated “leftover” disease — cancer cells that cannot be detected microscopically but can be measured using more sensitive detection methods. Such MRD is important because these remaining cancer cells, while few in number, are thought to help drive cancer recurrence.

In the AMPLIFY study data, the rate of undetectable MRD is about 40% in trial patients who received the AV drug pairing — on par with what is seen following treatment with other similar drug combinations. However, in patients who received AVO, the rate of undetectable MRD was very high, roughly 95%.

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