

Imbruvica-Venclexta Combo Shows Benefits for Leukemia and Lymphoma

The targeted therapies led to an 87% reduction in disease progression or death for newly diagnosed chronic lymphocytic leukemia patients.

February 6, 2024 By [Liz Highleyman](#)

Combining two targeted therapies, Imbruvica (ibrutinib) and Venclexta (venetoclax), led to better outcomes than standard-of-care treatment for people with chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL), according to studies presented at the [American Society of Hematology \(ASH\) annual meeting](#).

“These results appear better than those seen in any previous Phase III trial in CLL,” Peter Hillmen, MD, PhD, of the University of Leeds, said in an [ASH press release](#). “They show that targeted therapy, with high-sensitivity testing used to individualize the duration of treatment, is a more effective approach than current standard therapy and represents a new gold standard for previously untreated CLL.”

Imbruvica is a covalent Bruton’s tyrosine kinase (BTK) inhibitor that blocks an enzyme involved in cell signaling that promotes malignant B-cell proliferation. It is approved for adults with CLL, the related blood cancer small lymphocytic lymphoma (SLL) and Waldenström’s macroglobulinemia. Late last year, the Food and Drug Administration [withdrew its accelerated approval](#) of Imbruvica for MCL and marginal zone lymphoma after additional studies failed to confirm a survival benefit.

Venclexta is a selective inhibitor of BCL-2, a protein that promotes tumor cell survival by interfering with apoptosis, the normal process of cell death. It is approved for the treatment of adults with CLL or SLL and, in combination with chemotherapy, for patients with acute myeloid leukemia who cannot tolerate more intensive treatment.

The two drugs target different key pathways involved in blood cancer proliferation and have the potential to be synergistic, meaning their combined benefit is greater than the sum of their individual effects.

Chronic Lymphocytic Leukemia

Hillmen presented results from the Phase III FLAIR trial ([ISRCTN01844152](#)), which compared Imbruvica plus Venclexta versus a standard chemoimmunotherapy regimen of [fludarabine, cyclophosphamide and rituximab \(FCR\)](#) for people with untreated CLL. The findings were also

published in [The New England Journal of Medicine](#).

CLL, the most common blood cancer in adults, involves overproduction of abnormal white blood cells, usually antibody-producing B cells. These cells can crowd out normal cells, leading to low blood cell counts, increased susceptibility to infections and other complications. Although traditional chemotherapy can sometimes put CLL into remission, relapse is common.

The FLAIR analysis included 523 people with newly diagnosed CLL at nearly 100 centers in the United Kingdom. A majority (71%) were men, and the median age was 62 years. They were deemed to require treatment according to international guidelines. (People with asymptomatic early CLL often opt for a “watch and wait” approach, and many never need treatment.) A limitation of the study is that only patients considered fit enough to undergo intensive chemotherapy were eligible.

The participants were evenly randomized to receive Imbruvica plus Venclexta or FCR. (The study also included an Imbruvica monotherapy arm that was not included in this planned analysis.)

Previously, the Phase III [GLOW trial](#) showed that Imbruvica plus Venclexta taken for a fixed duration was more effective than a chemoimmunotherapy regimen of chlorambucil and Gazyva (obinutuzumab). But treating everyone for the same length of time means some people stop therapy too soon, thus compromising effectiveness, while others are treated too long, adding to side effects and cost.

In FLAIR, the duration of treatment was personalized according to measurable residual disease (MRD), meaning remaining malignant cells in the peripheral blood or bone marrow as detected with highly sensitive tests (usually defined as less than one CLL cell per 10,000 white blood cells).

In the first group, Imbruvica was used alone for two months, then Venclexta was added for up to six years; both are once-daily pills. Treatment duration was guided by MRD status; patients stayed on the combination for double the length of time it took to achieve undetectable MRD. FCR was administered every month for six cycles or until patients experienced disease progression or unacceptable side effects.

Over a median of about four years of follow-up, 12 people (5%) in the Imbruvica plus Venclexta group experienced disease progression or died, compared with 75 (29%) in the FCR group—an 87% reduction in the risk of progression or death. Three-year progression-free survival (PFS) rates were 97% and 77%, respectively. Nine people in the Imbruvica plus Venclexta group and 25 in the FCR group died, yielding a 69% reduction in mortality; three-year overall survival rates were 98% and 93%, respectively. Results were consistent regardless of sex, age or disease stage, but patients with an IGHV gene mutation—a subgroup with less aggressive CLL—did not appear to benefit from Imbruvica plus Venclexta.

At nine months—three months after finishing FCR—48% of patients in that group had undetectable MRD in their bone marrow, compared with 42% in the Imbruvica plus Venclexta group. But with

continued treatment, the latter group fared better. At two years, outcomes were similar, with about half in each group becoming MRD negative. By three years, 58% of participants in the Imbruvica plus Venclexta group stopped treatment because they were MRD negative. At five years, 66% of people receiving Imbruvica plus Venclexta had undetectable bone marrow MRD, and 93% had undetectable peripheral blood MRD, compared with 50% and 68%, respectively, in the FRC group. The researchers determined that simple blood tests were as useful as more invasive bone marrow assays for monitoring MRD status to guide treatment.

Treatment was generally safe, though side effects were common in both groups. Overall, the likelihood of serious or severe adverse events was similar in the two groups, but patients taking FCR were more likely to have low blood cell counts and develop other cancers, while those on Imbruvica plus Venclexta were more likely to experience tumor lysis syndrome and cardiac adverse events (likely attributable to Imbruvica). People who received Imbruvica plus Venclexta had a “better quality of life during their treatment,” [according to Hillmen](#).

“In this trial, MRD-guided [Imbruvica plus Venclexta], including individualized treatment duration beyond undetectable MRD, resulted in significant improvement in progression-free survival and an apparent benefit with respect to overall survival among patients with previously untreated CLL,” the researchers concluded.

Hillmen noted that patients with features linked to more aggressive disease, such as unmutated IGHV or chromosome 11q deletion, had even better outcomes than those with more favorable prognosis. “This indicates that the combination of [Imbruvica plus Venclexta] overcomes previously reported risk factors for a poor outcome in patients with CLL,” he said.

The FLAIR trial “unequivocally shows the superiority of targeted therapy over traditional cytotoxic chemotherapy,” Mikkael Sekeres, MD, of the Sylvester Comprehensive Cancer Center at the University of Miami, said at an ASH media briefing.

But that’s a low bar now that FRC has fallen out of favor. Comparing Imbruvica plus Venclexta to other targeted therapy combinations—say, Venclexta plus Gazyva or Venclexta plus Calquence (acalabrutinib)—would be a more relevant matchup.

Mantle Cell Lymphoma

Imbruvica plus Venclexta also showed promise for treatment of mantle cell lymphoma in the Phase III SYMPATICO trial ([NCT03112174](#)). MCL is an uncommon type of non-Hodgkin lymphoma characterized by overgrowth of abnormal B cells in lymph nodes. By the time it is diagnosed, it has often spread to the bone marrow, and it frequently is refractory (unresponsive) to existing treatments or relapses after a period of remission.

“We are very encouraged by the data from this trial and for our patients to have achieved remissions using this targeted therapy,” Michael Wang, MD, of the University of Texas MD Anderson Cancer Center, said in a [news release](#). “This combination allowed us to attack the cancer cells in two ways, which made it harder for the tumor to find resistance.”

SYMPATICO enrolled 267 adults with relapsed or refractory MCL who had tried one to five prior therapies. The median age was 68 years. Most were considered to have intermediate-risk or high-risk disease, and more than 40% had bone marrow involvement. The participants were randomly assigned to receive once-daily Imbruvica with either Venclexta or a placebo for two years, followed by Imbruvica alone until patients experienced disease progression or unacceptable side effects.

After a follow-up period of about two years, progression-free survival was significantly longer with Imbruvica plus Venclexta compared with Imbruvica plus placebo, Wang reported at the ASH meeting. Median PFS time was 31.9 months versus 22.1 months, reflecting a 35% reduction in the risk of disease progression or death. At two years, the PFS rates were 57% and 45%, respectively. Benefits were consistent for the subgroup of patients with high-risk disease.

The median overall survival time was 44.9 months with Imbruvica plus Venclexta versus 38.6 months with Imbruvica plus placebo. This difference was not statistically significant, but overall survival data are not yet mature, and follow-up is ongoing. The complete response rate was also higher with Imbruvica plus Venclexta (54% versus 32%, respectively). The median duration of response was 42.1 months with the combination regimen versus 27.6 months with the placebo.

Here, too, side effects were common, with 84% of patients in the Imbruvica plus Venclexta group and 76% in the Imbruvica plus placebo group experiencing Grade 3 or higher adverse events. The serious adverse event rate was the same (60%). About a third of patients in both groups discontinued treatment due to adverse events (31% and 36%, respectively). Nausea, diarrhea and low blood cell counts were more common with the combination regimen. Heart rhythm disturbances occurred at the same rate.

“The combination was synergistic, with a complete response rate that is higher than the additive complete response rates of the two drugs,” [Wang said](#). “This is a clinical benefit for the patient and a landmark achievement for the treatment of MCL.” He suggested that this combination should be a new standard of care for patients with relapsed or refractory MCL in countries where Imbruvica is approved for MCL.

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