# Targeted Combos Deal Double Blow Against Chronic Lymphocytic Leukemia

Imbruvica, Calquence and Venclexta demonstrate good results in combination regimens.

December 11, 2019 By Liz Highleyman

---

Combination regimens that include approved BTK and BCL-2 inhibitors pack a potent punch against chronic lymphocytic leukemia (CLL), the most common type of leukemia in adults, according to study results presented at the American Society of Hematology (ASH) Annual Meeting in Orlando.

CLL involves overproduction of abnormal white blood cells, usually antibody-producing B cells. These cells can crowd out normal blood cells, leading to anemia, increased susceptibility to infections and other complications. Although traditional chemotherapy can put CLL into remission, relapse is common.

Rather than killing malignant and healthy cells indiscriminately, like chemotherapy does, targeted therapies work more specifically against cancer cells, often by blocking proteins that play a role in cell growth and death. Two such targets, BTK (Bruton's tyrosine kinase) and the BCL-2 protein, have been widely studied for the treatment of CLL and related B-cell malignancies including small lymphocytic lymphoma (SLL) and mantle cell lymphoma (MCL).

## Approved Therapies

The BTK inhibitor Imbruvica (ibrutinib), from AbbVie's Pharmacyclics and Janssen, is approved for the treatment of CLL, SLL, MCL and certain other B-cell lymphomas.

Phase III studies have shown that Imbruvica plus CD20-targeted monoclonal antibodies such as Rituxan (rituxumab) or Gazyva (obinutuzumab) delays disease progression more than chemotherapy combinations.

At the ASH meeting, researchers presented long-term follow-up data from the CLL14 trial (abstract 33), which enrolled people age 70 or younger with previously untreated CLL. After 45 months, those assigned to take Imbruvica plus Rituxan had improved overall survival compared with those who used Rituxan plus chemotherapy.

Last month, the Food and Drug Administration (FDA) approved another BTK inhibitor, Calquence (acalabrutinib), from AstraZeneca, for first-line or subsequent treatment of CLL and SLL. Approval

was based in part on results from the Phase III ELEVATE-TN study, which enrolled people with previously untreated CLL.

Data presented at ASH (abstract 31) showed that Calquence plus Gazyva led to a 94% overall response rate (meaning complete or partial remission), compared with 86% for Calquence alone and 79% for Gazyva plus chemotherapy. At 24 months, 93%, 87% and 47% of participants, respectively, remained free of disease progression (known as progression-free survival, or PFS). That is, Calquence plus Gazyva reduced the risk of disease progression or death by 90%.

The most common side effects included headache, diarrhea, neutropenia (low white blood cell count), fatigue, bruising, joint pain and nausea. Just under 4% experienced atrial fibrillation (a type of abnormal heart rhythm), slightly less than the rate seen in studies of Imbruvica. Presenter Jeff Sharman, MD, of Willamette Valley Cancer Institute in Eugene, Oregon, said that Calquence is a more selective BTK inhibitor with fewer off-target effects, suggesting it may have a more favorable safety profile. A head-to-head study comparing Calquence versus Imbruvica in people with previously treated CLL is now under way.

Venclexta (venetoclax), from AbbVie and Genentech, is the sole FDA-approved BCL-2 inhibitor for treatment of CLL and SLL. Approval for previously untreated patients was based on results from the CLL14 trial, which showed that first-line Venclexta plus Gazyva improved progression-free survival more than Gazyva plus chemotherapy. Overall response rates were 85% versus 71%, respectively.

New data presented at ASH (abstract 36) offered detailed findings on depth of response. Minimal residual disease (MRD) refers to remaining leukemia cells that can be detected using molecular tests but that are not apparent using standard methods. MRD was undetectable in the blood in 76% of people treated with Venclexta plus Gazyva versus just 35% of those who received Gazyva plus chemotherapy; 57% and 17%, respectively were MRD negative in their bone marrow. In the Venclexta arm, those who were MRD negative had a higher progression-free survival rate at 24 months than those with detectable MRD (89% versus 62%).

Approval of Venclexta for previously treated people with relapsed or refractory (nonresponsive) CLL was based on results from the MURANO trial, which compared Venclexta plus Rituxan versus Rituxan plus chemotherapy. Overall response rates were 92% versus 72%, respectively. After two years of treatment, the median PFS was not reached in the Venclexta plus Rituxan group because a majority of participants were still responding.

Longer-term data from this study were also presented at ASH (abstract 355). After four years of follow-up—two years past the end of the fixed-duration treatment—those who received Venclexta plus Rituxan were more likely to still be MRD negative than those who received the chemotherapy combination. What's more, they had an 81% lower risk of disease progression, and those who completed treatment had a 59% lower risk of death. Four-year PFS rates were 57% versus 5%, respectively. Overall survival rates were 85% versus 67%.

BTK Plus BCL-2 Blockers

Other research presented at the conference showed that combining BTK and BCL-2 inhibitors can lead to deeper responses. While Venclexta clears cancer cells in the blood, BTK blockers are better able to root out residual cancer cells in the lymph nodes and spleen.

Constantine Tam, MBBS, MD, of the Peter MacCallum Cancer Centre in Melbourne, Australia, presented interim findings from the Phase II CAPTIVATE study, which is evaluating Imbruvica plus Venclexta as first-line therapy for CLL and SLL (abstract 35).

The minimal residual disease cohort included 164 people age 70 or younger with previously untreated CLL or SLL. They first received Imbruvica alone for three cycles, followed by Imbruvica plus Venclexta for 12 cycles; about 90% completed all 15 cycles. They were then randomized to continue or stop treatment if they were MRD negative, or to continue Imbruvica alone or combination therapy if they were MRD-positive (randomized data not yet available).

MRD status was evaluated in the blood and in the bone marrow; undetectable MRD was defined as having less than 0.01% cancer cells according to flow cytometry. Three quarters of participants achieved undetectable MRD in their blood—with the proportion rising over time—and 72% had undetectable MRD in their bone marrow. Among those with matched blood and bone marrow samples, 93% were MRD-negative in both. After about 15 months of follow-up, there were no deaths and just three people experienced disease progression.

Treatment was generally safe. The most common adverse events included diarrhea, joint pain, headache, nausea and blood cell depletion, mostly mild or moderate. The most common severe adverse event was neutropenia. Four people developed suspected tumor lysis syndrome (TLS), a reaction that can occur when many cancer cells die suddenly, but only one case was confirmed; Tam noted that the Imbruvica-only lead in helps prevent this side effect. Three cases of atrial fibrillation were reported. Eight people (5%) stopped treatment because of adverse events.

“First-line treatment with [Imbruvica plus Venclexta] represents an all oral, once-daily, chemotherapy-free regimen that provides high rates of undetectable MRD in both peripheral blood and bone marrow in patients with CLL,” the researchers concluded. They added that the randomized portion of the study is expected to provide evidence to support a time-limited treatment option with a fixed duration of 12 cycles of combination therapy.

A smaller study (abstract 34) evaluated Imbruvica plus Venclexta taken for two years in previously untreated people classified as being at high risk for CLL progression. Among the participants with available data, none had undetectable MRD in their bone marrow after three cycles of Imbruvica alone, according to the study abstract. But after adding Venclexta, the proportion with MRD-negative bone marrow rose from 65% at one year to 79% at two years, suggesting that outcomes may improve with longer treatment.

Finally, Benjamin Lampson, MD, PhD, of Dana-Farber Cancer Institute in Boston, presented results from a Phase II trial that evaluated a triple combination of Calquence, Venclexta and Gazyva

(abstract 32). Imbruvica, Venclexta and Gazyva triple therapy is also under study, but this regimen may cause too many side effects.

This study included 37 people with previously untreated CLL. They first received Calquence alone for one monthly cycle, then added Gazyva. Venclexta was added and the dose was ramped up starting at cycle 4. After six months, Gazyva was discontinued and they continued on Calquence and Venclexta through cycle 15. Those with undetectable bone marrow MRD could then opt to stop treatment while others continued through cycle 24. At that point, disease was restaged. Again, those with complete response and undetectable bone marrow MRD could discontinue therapy while the rest continued Calquence and Venclexta until disease progression or intolerable toxicity.

An interim analysis after a median of eight months on treatment found that the overall response rate for the evaluable patients was 97% (all partial responses) after four cycles and 100% (25% complete responses) after eight cycles. At the eight-month mark, 68% were MRD-negative in their blood and 48% were MRD-negative in their bone marrow; 17% had complete responses plus undetectable bone marrow MRD. By cycle 16, the response rate remained 100% and 75% had MRD-negative bone marrow.

The most common adverse events were fatigue and headache. Nearly 50% reported bruising and 32% had severe neutropenia. Eight people experienced infusion reactions, two developed tumor lysis syndrome and there was one case of severe atrial fibrillation. Again, starting with Calquence and Gazyva appeared to reduce the likelihood of TLS after starting Venclexta. One participant stopped treated because of adverse events.

These preliminary data suggest that even after just eight cycles of therapy—including only four months of Venetoclax—this triple combination as frontline CLL therapy leads to a high proportion of patients achieving complete response and undetectable bone marrow MRD, the researchers concluded.

Click here to learn about the different types of leukemia.

---

© 2026 Smart + Strong All Rights Reserved.

http://beta.docker.cancerhealth.com/article/targeted-combos-deal-double-blow-chronic-lymphocytic-leukemia