Fixed-Duration Imbruvica-Venclexta Combo Benefits People With Chronic Lymphocytic Leukemia

For those with undetectable minimal residual disease, treatment discontinuation was as effective as staying on Imbruvica.

December 21, 2020 By Sukanya Charuchandra

People with chronic lymphocytic leukemia (CLL) who had undetectable disease after 12 cycles of Imbruvica (ibrutinib) plus Venclexta (venetoclax) and then stopped treatment had a one-year disease-free survival rate similar to that of patients who continued on Imbruvica. This indicates that a fixed duration of first-line combination therapy may maintain remission without ongoing treatment. These data were presented at the American Society of Hematology (ASH) virtual annual meeting.

CLL, the most common type of adult leukemia, involves the 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.

The Phase II CAPTIVATE study evaluated Imbruvica plus Venclexta for people with CLL or small lymphocytic lymphoma (SLL) who were starting treatment for the first time. The deep responses seen with this combination suggest that ongoing therapy might not be needed.

“Ibrutinib and venetoclax have synergistic and complementary antitumor activity via mobilization and clearance of CLL cells from protective niches and disease compartments beyond blood and bone marrow,” William G. Wierda, MD, PhD, of the University of Texas MD Anderson Cancer Center, said during the presentation at the virtual meeting.

Imbruvica inhibits Bruton’s tyrosine kinase, which plays a role in the maturation of B cells, which grow out of control in people with leukemia. It was approved as first-line therapy for CLL in 2016.

Venclexta is a BCL-2 inhibitor approved for the treatment of CLL and SLL. It blocks the BCL-2 (B-cell lymphoma 2) regulatory protein, which interferes with the normal cell death cycle and allows uncontrolled cell growth. This protein is often present on cells that grow out of control in people with leukemia and lymphoma.

In the study, Wierda and colleagues included 164 individuals with previously untreated CLL or SLL. They received first-line treatment consisting of three cycles of daily Imbruvica alone, followed by 12 cycles of Imbruvica plus Venclexta.

As reported at last year's ASH meeting, at the end of this phase of treatment, 72% of participants had undetectable minimal residual disease (MRD) in the peripheral blood and 75% had undetectable MRD in the bone marrow.

Of the 164 participants, 86 with confirmed undetectable MRD were then randomized to continue on Imbruvica alone or a placebo (essentially, no treatment). Another 63 people with unconfirmed undetectable MRD were randomized to continue treatment with either Imbruvica alone or the combination regimen. The remaining 15 individuals were ineligible for randomization.

After a median follow-up of 16.6 months, disease-free survival (DFS) rates, defined as the proportion of people who continued to be MRD negative and did not experience clinical disease progression, were not significantly different between those receiving Imbruvica (100%) or the placebo (95%).

The one-year DFS rate of 95% in patients randomized to placebo was similar to that of patients randomized to Imbruvica, "which supports a fixed-duration treatment after 12 cycles of the combination regimen and treatment discontinuation for patients who achieve confirmed undetectable minimal residual disease," Wierda said during the presentation.

Among individuals who did not achieve confirmed undetectable MRD even after 12 cycles of the combination regimen, MRD status greatly improved with continued administration of the combination versus Imbruvica alone. MRD rates reached 45% in the blood and 42% in the bone marrow among those who continued on Imbruvica alone compared with 69% and 66%, respectively, among those who continued on combination therapy.

Nearly 30 months after initial treatment, progression-free survival (PFS) rates were greater than 95% for all treatment groups. For those in the confirmed undetectable MRD group, PFS was 100% with continued Imbruvica and 95% with the placebo. In the unconfirmed undetectable MRD group, PFS was 96% with continued Imbruvica alone and 97% with continued combination therapy.

No safety concerns were noted with the combination treatment, and few participants required dose adjustment or treatment discontinuation, Wierda said. Adverse events were mostly mild or moderate and generally decreased over time. The most common severe adverse events included neutropenia, hypertension, thrombocytopenia and diarrhea.

Wierda said that although these data clearly show that Imbruvica plus Venclexta can lead to deep and durable responses, it is too early to recommend a specific treatment duration and further data from Phase III studies are needed.

Click here to read the study abstract.