FDA Approves Venetoclax Plus Acalabrutinib for Previously Untreated Adults With CLL

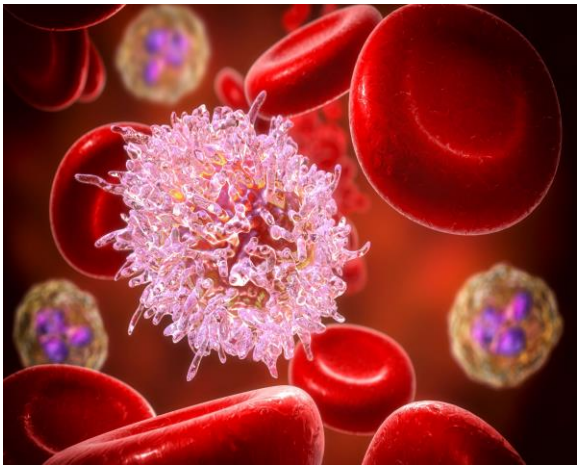
Key Takeaways

- FDA approval adds an all-oral, time-limited venetoclax-acalabrutinib option for adults with previously untreated CLL, enabling individualized first-line selection beyond indefinite BTK inhibition or chemoimmunotherapy.
- AMPLIFY randomly assigned 724 patients to acalabrutinib-venetoclax, acalabrutinib-venetoclax-obinutuzumab, or investigator's-choice FCR/BR, with PFS by blinded independent central review as the primary end point.
- At 36 months, PFS favored targeted therapy (76.5% doublet; 83.1% triplet) over chemoimmunotherapy (66.5%), with an HR of 0.65 for the doublet vs chemoimmunotherapy (P = .004).
- Overall survival at 36 months was higher with the doublet (94.1%) than the triplet (87.7%) and chemoimmunotherapy (85.9%), though cross-arm comparisons are descriptive.
- Grade 3 or greater neutropenia was frequent (32.3% doublet; 46.1% triplet; 43.2% chemoimmunotherapy), and serious COVID-19 events and COVID-19 deaths occurred across all arms.

The approval for the oral, fixed-duration chronic lymphocytic leukemia (CLL) regimen was based on results from the phase 3 AMPLIFY trial.

The FDA has approved the combination of venetoclax (Venclexta; AbbVie Inc/Genentech USA, Inc) and acalabrutinib (Calquence; AstraZeneca Pharmaceuticals LP) for the treatment of previously untreated adult patients with chronic lymphocytic leukemia (CLL). The approval was based on results from the phase 3 clinical trial AMPLIFY (NCT05197192), according to a news release from Genentech.[1,2]

"Today's approval represents an important step forward for people newly diagnosed with chronic lymphocytic leukemia," Levi Garraway, MD, PhD, chief medical officer and head of global product development, said in the news release. "As the first and only all-oral, fixed-duration regimen, this approval gives patients the opportunity to spend more time off therapy. This milestone underscores the ongoing evolution of [venetoclax]-based approaches, offering clinicians another way to individualize first-line care."[1]



Venetoclax is a first-in-class targeted medicine that binds selectively to and inhibits the BCL-2 protein. In some blood cancers and other tumors, BCL-2 accumulates and prevents cancer cells from dying or undergoing apoptosis. By blocking BCL-2, venetoclax helps restore the apoptotic process.[1]

The drug has indications in CLL and small lymphocytic lymphoma and can be used in combination with other agents to treat adults with newly diagnosed acute myeloid leukemia who are 75 years or older or have other medical conditions that prevent them from receiving standard chemotherapy.[1]

AMPLIFY is a multicenter, prospective, open-label, randomized, superiority trial that enrolled patients 18 years or older (median age, 61; range, 26-86) with CLL. Patients were randomly assigned to receive acalabrutinib plus venetoclax (n = 291; acalabrutinib, cycles 1-14; venetoclax, cycles 3-14); a combination of acalabrutinib, venetoclax, and obinutuzumab (n = 286; same dosing regimen as acalabrutinib plus venetoclax, plus obinutuzumab, cycles 2-7); or chemoimmunotherapy with investigator's choice of fludarabine, cyclophosphamide, and rituximab (n = 143) or bendamustine and rituximab (n = 147; cycles 1-6).[2,3]

The trial's primary end point was progression-free survival (PFS) in the intention-to-treat population, assessed by blinded independent central review. Results were published in the New England Journal of Medicine.[2,3]

The findings demonstrated that the estimated 36-month PFS at a median follow-up of 40.8 months was approximately 76.5% with venetoclax plus acalabrutinib, 83.1% with the triple venetoclax regimen, and 66.5% with chemoimmunotherapy (HR for disease progression or death with venetoclax + acalabrutinib vs chemoimmunotherapy, 0.65 [95% CI, 0.49-0.87]; P = .004). Additionally, the estimated 36-month overall survival was highest with venetoclax plus acalabrutinib (94.1%), followed by the triple venetoclax regimen (87.7%), and chemoimmunotherapy (85.9%).[3]

During the trial, the most common serious adverse events (AEs) in patients receiving venetoclax plus acalabrutinib were COVID-19, including COVID-19 pneumonia (9%); second primary malignancies (2.7%); and neutropenia (2.1%). Neutropenia, the most common AE at grade 3 or higher, was reported in 32.3%, 46.1%, and 43.2% in the 3 groups. Death from COVID-19 infection was reported in 10, 25, and 21 patients, respectively, in the 3 groups.[3]

"Fixed-duration regimens are a critical component of today's CLL management," John M. Burke, MD, hematology and oncology, Rocky Mountain Cancer Centers, said in the news release. "Having an all-oral option with a defined end date can provide patients with a clear and predictable treatment timeline. This approval provides an important new option for eligible patients to achieve durable responses in the first line."[1]

REFERENCES

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