Chronic lymphocytic leukemia (CLL) is a cancer of B-cell lymphocytes and is the most common type of leukemia in adults. More than 20,000 Americans were diagnosed with CLL in 2018.

At the time of diagnosis, many patients with CLL are elderly and asymptomatic. As CLL evolves, it can result in spleen and lymph node enlargement, severe fatigue, shortness of breath, and infections. First-line therapy regimens for CLL often contain 1 or more cytotoxic agents, such as fludarabine or cyclophosphamide, combined with a monoclonal antibody that targets CD20, such as rituximab (Rituxan).

The treatments for patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) include cytotoxic agents, monoclonal antibodies, and targeted agents. Targeted drug development is based on evolving knowledge about the effect that B-cell receptors have on the cell surface and in the tumor microenvironment. Novel agents that affect this pathway include small-molecule drugs that inhibit Bruton’s tyrosine kinase, the PI3-kinase (PI3K) pathway, and BCL-2.

Follicular lymphoma is the second most common subtype of non-Hodgkin lymphoma (NHL), and approximately 22% of all patients with NHL have follicular lymphoma. Follicular lymphoma is characterized by a translocation between chromosomes 14 and 18, which causes the overexpression of the BCL-2 gene and enhances resistance to treatment. Follicular lymphoma is generally indolent; only a minority of patients have follicular lymphoma that transforms into a more aggressive lymphoma.

For patients with advanced-stage follicular lymphoma, the initial treatment depends on the patient’s age, performance status, disease-related symptoms, and other features. Chemotherapy regimens that include rituximab (eg, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) are considered standard first-line treatment for follicular lymphoma.

Despite high response rates associated with chemotheraphy in patients with follicular lymphoma, the disease will relapse in approximately 20% of patients within 2 years of initial treatment. A retrospective data analysis showed that the 5-year overall survival rate was significantly lower in patients with follicular lymphoma whose disease progressed early than in those without early progression within 2 years after diagnosis (50% vs 90%, respectively).

The treatment of relapsed or refractory follicular lymphoma is not standardized. Two PI3K inhibitors, the oral drug idelalisib (Zydelig) and copanlisib (Aliqopa), administered by intravenous infusion, were recently approved by the US Food and Drug Administration (FDA) for patients with relapsed follicular lymphoma after at least 2 previous therapies.

Duvelisib Approved for CLL/SLL or Follicular Lymphoma

On September 24, 2018, the FDA approved duvelisib (Copiktra; Verastem), an oral small-molecule drug that targets PI3K, for the treatment of patients with relapsed or refractory CLL or SLL. On the same day, duvelisib also received accelerated approval for the treatment of relapsed or refractory follicular lymphoma in adults who have received at least 2 previous systemic therapies.

Mechanism of Action

Duvelisib, a PI3K inhibitor, is active predominantly against PI3K-delta and PI3K-gamma isoforms that are expressed in normal and malignant B-cells. Duvelisib blocks several key cell-signaling pathways, including BCR signaling and CXCR12-mediated chemotaxis of malignant B-cells. Duvelisib also blocks macrophage colony-stimulating factor–and interleukin-4–driven M2 polarization of macrophages and CXCL12-induced T-cell migration.

Dosing and Administration

The recommended dose of duvelisib is 25 mg twice daily, with or without food. Duvelisib capsules should be swallowed whole. The drug should be given until disease progression or until unacceptable toxicity.

Prophylaxis for *Pneumocystis jirovecii* is recommended during treatment with duvelisib.
Clinical Trials: DUO and DYNAMO

A total of 442 patients with previously treated hematologic malignancies, including primarily CLL or SLL (69%) and follicular lymphoma (22%), received duvelisib in clinical trials. Of these, approximately 36% of patients received at least 12 months of duvelisib treatment.\textsuperscript{11}

The 2 pivotal clinical trials with duvelisib were DUO and DYNAMO. DUO was a randomized phase 3 clinical trial that compared the efficacy and safety of duvelisib versus ofatumumab monotherapy in 319 patients with relapsed CLL or SLL after receiving at least 1 previous therapy.\textsuperscript{11,12} The FDA approval of duvelisib for CLL or SLL was based on an efficacy and safety analysis of 196 patients who received 2 or more previous lines of therapy (Table 1).\textsuperscript{11} In these more heavily pretreated patients, the benefit to risk ratio of duvelisib was greater than in other study enrollees.\textsuperscript{11}

DYNAMO was a single-arm phase 2 clinical trial that assessed the efficacy and safety of duvelisib, in combination with chemotherapy or radioimmunotherapy, in patients with relapsed follicular lymphoma refractory to rituximab (Table 2).\textsuperscript{11} Refractory disease was defined as less than a partial remission or relapse within 6 months after the last treatment dose.

Adverse Events

Serious adverse events with duvelisib were reported in 65% of patients in clinical trials. The most common serious events were infection (31%), diarrhea or colitis (18%), pneumonia (17%), rash (5%), and pneumonitis (5%). Overall, 8% of patients had a fatal adverse reaction within 30 days of receiving duvelisib.\textsuperscript{11}

The most common (≥25%) side effects with duvelisib were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, and cough.\textsuperscript{11} Dose interruptions resulting from adverse reactions occurred in 35% of patients who received duvelisib, and 24% of patients required dose reductions.\textsuperscript{11}

Duvelisib has no contraindications.\textsuperscript{11}

Drug Interactions

The concomitant use of strong or moderately strong cytochrome (CY) P3A inhibitors can increase the plasma concentration of duvelisib. The dose of duvelisib should be reduced to 15 mg twice daily in patients who receive strong or moderately strong CYP3A inhibitors.\textsuperscript{11}

The use of duvelisib together with strong or moderately strong CYP3A inducers should be avoided.\textsuperscript{11} The concomitant use of duvelisib and sensitive CYP3A substrates may increase toxicities.\textsuperscript{11}

Use in Specific Populations

No clinical studies of duvelisib were conducted in pregnant women. Pregnant women should be advised of the potential risk to a fetus.\textsuperscript{11}

Women should not breastfeed during treatment with duvelisib or for 1 month after the final dose of duvelisib.\textsuperscript{11}

Women of reproductive potential and men with female partners of reproductive potential should use effective contraception during treatment with duvelisib and for 1 month after the final dose.\textsuperscript{11}

Male fertility may be impaired by treatment with duvelisib.\textsuperscript{11}

The safety and effectiveness of duvelisib have not been established in children.\textsuperscript{11} No differences in safety or efficacy were observed between patients aged ≥65 years and younger patients who received duvelisib in clinical studies.\textsuperscript{11}

Warnings and Precautions

The prescribing information for duvelisib has 4 boxed warnings regarding serious or fatal conditions, including (1) fatal and/or serious infections, including pneumonia, cytomegalovirus reactivation, sepsis, and lower respiratory infections; (2) fatal and/or serious diarrhea or colitis; (3) fatal and/or serious cutaneous reac-
tions (ie, drug reaction with eosinophilia and systemic symptoms and toxic epidermal necrolysis); and (4) fatal and/or serious pneumonitis.11

Duvelisib is also associated with the risk for hepatic toxicity, including grade 3 or 4 alanine aminotransferase and/or aspartate aminotransferase elevations; neutropenia; and embryo-fetal toxicity.11

Conclusion

The FDA approval of duvelisib, an oral PI3K inhibitor, provides a new treatment option as monotherapy for patients with relapsed or refractory CLL or SLL and in patients with relapsed or refractory follicular lymphoma who have received at least 2 previous treatments. The clinical trial data on duvelisib demonstrate significant efficacy benefits, as well as an acceptable safety profile.11

References