Imbruvica (Ibrutinib) Now FDA Approved as First-Line Treatment for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

By Lisa A. Raedler, PhD, RPh, Medical Writer

Chronic lymphocytic leukemia (CLL), the most common type of leukemia in adults, is a cancer of B-cell lymphocytes. More than 20,000 Americans will be diagnosed with CLL in 2017, and 4660 patients with die from the disease. In CLL, the cancer cells are located primarily in the blood and the bone marrow.

Small lymphocytic lymphoma (SLL) also affects B-cells, and is a different manifestation of the same disease, but it differs from CLL in the location of the cancer. In SLL, the cancer cells are located predominantly in the lymph nodes. SLL is the third most common subtype of non-Hodgkin lymphoma, and is estimated to affect approximately 400 people annually in the United States.

At the time of diagnosis, the majority of patients with CLL are elderly and asymptomatic. As it evolves, CLL can result in spleen and lymph node enlargement, severe fatigue, shortness of breath, and infections.

The prognosis of CLL or SLL is variable—some patients live for decades with no treatment, and others have aggressive disease. The 5-year survival rate for patients with CLL is approximately 82% (all stages combined).

The initial therapy for CLL has historically included chemoimmunotherapy regimens that contain a CD20 antibody and ≥1 cytotoxic agents. Although these combinations are effective, they can cause significant immunosuppression and second malignancies. Patients with high-risk CLL, including patients with chromosome 11q deletion, chromosome 17p deletion, and TP53 mutations, have particularly poor outcomes. To date, only allogeneic stem-cell transplantation is potentially curative in patients with relapsed CLL.

In light of these challenges, researchers are exploring the intricacies of CLL cell growth and proliferation signaling. B-cell receptors located on the cell surface and in the microenvironment contribute to cancer progression. This knowledge has prompted the development of novel agents, including Bruton’s tyrosine kinase (BTK), PI3 kinase, and BCL-2 inhibitors, all of which target the B-cell receptor pathway.

Ibrutinib Approved as First-Line Treatment for CLL and SLL, First Treatment for Marginal Zone Lymphoma

On March 4, 2016, the US Food and Drug Administration (FDA) approved ibrutinib (Imbruvica; Pharmacycics), an orally administered BTK inhibitor, for the first-line treatment of patients with CLL.

On May 9, 2016, the FDA expanded ibrutinib’s indication in the first-line setting to include patients with SLL, regardless of chromosome 17p deletion status.

“This update helps to affirm the established efficacy, safety and tolerability of this therapy for treatment of patients with CLL/SLL, both as a monotherapy or in combination with other agents. It reflects the growing body of clinical evidence supporting this therapy as a potential treatment option for people living with CLL/SLL,” said Jan Burger, MD, PhD, Associate Professor, Department of Leukemia, Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, and lead investigator of the RESONATE-2 study.

On the same day, the FDA updated ibrutinib’s label to include data from the HELIOS clinical trial, which demonstrated improved progression-free survival (PFS) and overall survival (OS) in patients with relapsed or refractory CLL or SLL who received ibrutinib plus bendamustine and rituximab versus placebo plus bendamustine and rituximab.

Ibrutinib was initially FDA approved in 2013 for patients with mantle-cell lymphoma. In 2014, ibrutinib was approved for patients with CLL who received at least 1 previous therapy, and for patients with CLL with chromosome 17p deletion. In 2015, ibrutinib was approved for Waldenström’s macroglobulinemia.

On January 19, 2017, ibrutinib became the first nonchemotherapy ever to receive FDA approval specifically for the treatment of patients with relapsed or refractory marginal zone lymphoma who require systemic therapy and who have received at least 1 previous anti-CD20–based therapy. The FDA used its accelerated review process for this approval.
Mechanism of Action
Ibrutinib inhibits BTK enzymatic activity by forming a covalent bond with a cysteine residue in the BTK active site.9

Dosing and Administration
The recommended dosage of ibrutinib for CLL or SLL is 420 mg once daily (3 capsules, 140 mg each) until disease progression or until unacceptable toxicity.9

Patients should take ibrutinib with water at approximately the same time every day. Ibrutinib capsules should be swallowed whole; they should not be chewed, crushed, or broken.9

Ibrutinib Distribution
Ibrutinib can be accessed through several specialty pharmacies, including ASD Healthcare, Avella Specialty Pharmacy, Biologics, Diplomat, McKesson Specialty Health, McKesson Plasma and Biologics, Onco360, and Oncology Supply.14

Resonate-2 Clinical Trial
RESONATE-2 was a randomized, multicenter, open-label, phase 3 clinical trial that compared the efficacy and safety of ibrutinib versus chlorambucil in 269 treatment-naive patients aged ≥65 years with CLL or SLL. Ibrutinib therapy was associated with significant improvements in PFS, overall response rate (ORR), and OS.9-11,15 The efficacy results from this study are summarized in the Table.9

Adverse Events
The safety of ibrutinib in CLL or SLL is based on data from 668 patients with CLL or SLL who received ibrutinib in clinical trials.9 The most frequently (≥20%) reported adverse reactions associated with ibrutinib included neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia, and hemorrhage.9

Overall, 4% to 10% of patients who received ibrutinib discontinued treatment because of adverse reactions, such as pneumonia (1%), hemorrhage (1%), atrial fibrillation (1%), rash (1%), and neutropenia (1%).9

Ibrutinib has no contraindications.9

Drug Interactions
Ibrutinib should not be used concomitantly with strong or moderate cytochrome (CY) P3A inhibitors or with strong CYP3A inducers; ibrutinib dose should be reduced when used with a moderate CYP3A inhibitor.9

Selected Warnings and Precautions
Severe bleeding events (grade ≥3) have been reported in up to 6% of patients who received ibrutinib. Bleeding events of any grade occur in approximately 50% of patients who receive ibrutinib.9

Infections, including progressive multifocal leukoencephalopathy, have occurred in clinical trials of ibrutinib.9

Severe cytopenias were observed with ibrutinib therapy. Monthly complete blood cell counts are recommended.9

Atrial fibrillation and atrial flutter have occurred in 6% to 9% of patients who received ibrutinib.9

Second malignancies have occurred in 3% to 16% of patients using ibrutinib, including nonskin carcinomas (1%-4%); nonmelanoma skin cancer was the most frequently reported second primary malignancy (range, 2%-13%).9

Tumor lysis syndrome has been reported in patients who received ibrutinib. Clinicians should monitor patients closely, particularly those with a high tumor burden.9

Because ibrutinib can cause fetal harm, women of reproductive potential should avoid pregnancy while taking ibrutinib and for up to 1 month after ending treatment. Men should avoid fathering a child while taking ibrutinib and for up to 1 month after ending treatment.9

Use in Specific Populations
The health benefits of breast-feeding should be considered, in addition to the mother’s clinical need for ibrutinib and potential adverse effects from ibrutinib on the breast-fed child.9

No overall differences were observed in the effectiveness of ibrutinib between patients aged ≥75 years and younger patients.9

Because ibrutinib exposure increases in patients with hepatic impairment, ibrutinib is not recommended for patients with moderate or severe hepatic impairment.9

<table>
<thead>
<tr>
<th>Efficacy end point</th>
<th>Ibrutinib (N = 136)</th>
<th>Chlorambucil (N = 133)</th>
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<tbody>
<tr>
<td>Progression-free survivala</td>
<td>Not reached</td>
<td>18.9</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.16 (95% CI, 0.09-0.28)</td>
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<tr>
<td>Overall survival</td>
<td></td>
<td></td>
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<tr>
<td>2-year overall survival, %</td>
<td>94.7</td>
<td>84.3</td>
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<tr>
<td>Hazard ratio</td>
<td>0.44 (95% CI, 0.21-0.92)</td>
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<tr>
<td>Overall response rate</td>
<td></td>
<td></td>
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<tr>
<td>Complete response and partial response, %</td>
<td>82.4</td>
<td>35.3</td>
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*Evaluated by an Independent Review Committee.

Overall 5 (3.7%) patients in the ibrutinib arm and 2 (1.5%) patients in the chlorambucil arm achieved complete response.

CI indicates confidence interval.

Source: Imbruvica (ibrutinib) capsules prescribing information; January 2017.
Conclusion

Ibrutinib, a once-daily, orally administered BTK inhibitor, is now FDA approved as first-line therapy for patients with CLL or SLL who warrant treatment, regardless of their cytogenetics and risk status. These expanded indications were based on results of the RESONATE-2 clinical trial, which demonstrated significant OS, PFS, and ORR benefits and an acceptable safety profile with ibrutinib compared with chlorambucil in treatment-naïve patients with CLL or SLL.

References