Calquence (Acalabrutinib) Approved for Relapsed or Refractory Mantle-Cell Lymphoma in Adults

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

Mantle-cell lymphoma is a rare and fast-growing type of non-Hodgkin lymphoma (NHL), comprising approximately ≥4% of NHL cases in the United States.1 Mantle-cell lymphoma most often affects men aged ≥60 years,2,3 and the key factors affecting prognosis include the patient’s age, performance status, lactate dehydrogenase levels, and white blood cell count.4

The overall survival (OS) rate is 29 months for patients with high-risk mantle-cell lymphoma compared with 51 months for patients with intermediate-risk disease.1 For patients with low-risk mantle-cell lymphoma, the 5-year OS rate is 60%.1

In clinical practice, combinations of a chemotherapy plus an anti-CD20 monoclonal antibody therapy or high-dose chemotherapy followed by autologous stem-cell transplant are the current options for patients with newly diagnosed mantle-cell lymphoma.3 The management of relapsed or refractory mantle-cell lymphoma depends on the timing of the relapse, the patient’s age and overall health, disease extent, and previous therapies used.1,2

Several treatment options are currently available for patients with relapsed or refractory mantle-cell lymphoma. In 2013, ibrutinib (Imbruvica) became the first Bruton’s tyrosine kinase (BTK) inhibitor to receive US Food and Drug Administration (FDA) approval for the treatment of patients with relapsed or refractory mantle-cell lymphoma.5 Other treatment options include combination chemotherapy; targeted agents; proteasome inhibitors, such as bortezomib (Velcade); immunomodulatory drugs, such as lenalidomide (Revlimid); and anti-CD20 monoclonal antibodies.2,5

Although significant progress has been made in understanding the molecular biology and key prognostic factors of mantle-cell lymphoma, and the available treatment options, more treatment options are needed for patients whose disease relapses after initial treatment with current therapies.1,5

Calquence Second Bruton’s Tyrosine Kinase Inhibitor Approved for Mantle-Cell Lymphoma

On October 31, 2017, the FDA granted an accelerated approval for acalabrutinib (Calquence; AstraZeneca), an oral BTK inhibitor, for the treatment of adults with mantle-cell lymphoma who have received at least 1 therapy.6 Acalabrutinib became the second BTK inhibitor to receive FDA approval for this indication.6

“Mantle cell lymphoma is a particularly aggressive cancer,” said Richard Pazdur, MD, Director of the FDA’s Oncology Center of Excellence. “For patients who have not responded to treatment or have relapsed, Calquence provides a new treatment option that has shown high rates of response for some patients in initial studies.”6

The FDA granted priority review and breakthrough therapy designations to acalabrutinib for this indication. The FDA requires additional clinical trials to confirm the efficacy of acalabrutinib.6

Mechanism of Action

Acalabrutinib is a small molecule that inhibits BTK, a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. BTK signaling activates pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Acalabrutinib and its active metabolite, ACP-5862, inhibit BTK enzymatic activity.7

Dosing and Administration

The recommended dose of acalabrutinib is 100 mg administered orally twice daily until disease progression or until unacceptable toxicity. Patients should swallow the acalabrutinib capsule whole with water and should not open, break, or chew the capsules. Acalabrutinib can be taken with or without food.7

Pivotal Clinical Trial

The FDA approval of acalabrutinib for mantle-cell lymphoma was based on results from ACE-LY-004, a phase 2 single-arm clinical trial.7 A total of 124 patients with relapsed or refractory mantle-cell lymphoma received acalabrutinib (100 mg orally twice daily) until disease progression or unacceptable toxicity. Patients who had previously received a BTK inhibitor were excluded from the study.8

The primary end point was overall response rate (ORR) assessed by the Lugano classification. After a median follow-up of approximately 15 months, the ORR with acalabrutinib based on independent review was 80%, with 40% of patients achieving a complete response.8

Using Kaplan-Meier estimates, the median duration of response, progression-free survival (PFS), and OS were not reached. The 12-month duration of response was 72% (95% confidence interval [CI], 62%-80%), the
PFS rate was 67% (95% CI, 58%-75%), and the OS rate was 87% (95% CI, 79%-92%).

Most patients (median age, 68 years) were male (80%) and Caucasian (74%). The median time since the diagnosis of mantle-cell lymphoma was approximately 46 months. Patients who received acalabrutinib had received a median of 2 previous therapies for mantle-cell lymphoma (range, 1-5), most often chemotherapy-based treatment with cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone, or with cytoseine arabinoside.

The Table outlines key efficacy parameters with acalabrutinib.7

<table>
<thead>
<tr>
<th>Table Acalabrutinib Efficacy in Patients with Mantle-Cell Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy parameter</strong></td>
</tr>
<tr>
<td>Overall response rate, %</td>
</tr>
<tr>
<td>Complete response rate, %</td>
</tr>
<tr>
<td>Partial response rate, %</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
</tr>
</tbody>
</table>

*Based on assessment by an independent review committee. CI indicates confidence interval.

**Use in Specific Populations**

The safety and efficacy of acalabrutinib have not been established in children. No overall differences in the safety or efficacy of acalabrutinib were observed between patients aged ≥65 years and younger patients.7

**Warnings and Precautions**

Serious hemorrhagic events, including fatal events, have occurred with acalabrutinib monotherapy. Severe bleeding events, including GI, intracranial, and epistaxis, were reported in 2% of patients. Bleeding events of any grade occurred in approximately 50% of patients with hematologic malignancies who received acalabrutinib.7

In patients who use antiplatelet or anticoagulant agents, acalabrutinib may increase the risk for bleeding. Holding treatment with acalabrutinib for 3 to 7 days before and after surgery may be appropriate.7

Atrial fibrillation and atrial flutter have been reported with acalabrutinib (3%, all grades); monitoring is recommended.7

Cytopenias have been reported with acalabrutinib.7

Second primary malignancies, including skin cancers (7%), have been reported with acalabrutinib. Protection from sun exposure is recommended.7

**Conclusion**

Acalabrutinib is a new oral BTK inhibitor approved by the FDA for the treatment of patients with relapsed or refractory mantle-cell lymphoma. Acalabrutinib demonstrated a high rate of durable responses in this patient population and a favorable safety profile; this new therapy may have an important role in the treatment of patients with this rapidly growing type of NHL whose disease continues to progress after initial treatment with current therapies. ■

**References**