Chronic lymphocytic leukemia (CLL), a monoclonal disorder characterized by progressive accumulation and proliferation of functionally incompetent B-cells, is the most frequently diagnosed leukemia in the United States. The American Cancer Society has estimated that 4580 Americans will die from CLL in 2013, which represents approximately 19% of all leukemia deaths. Because it can have an insidious onset, CLL is often discovered incidentally after blood work is conducted for another reason. Between 25% and 50% of patients with CLL are asymptomatic at the time of presentation.

Patients with CLL are typically receiving treatment when their disease becomes symptomatic or when the signs of rapid disease progression are detected. Drug combinations for patients with CLL who warrant treatment include cytotoxic agents, such as the purine nucleoside analog fludarabine (Fludara), and therapeutic antibodies. Rituximab (Rituxan), a CD20 antibody, is widely used in patients with previously untreated symptomatic CLL and in salvage regimens. Other antibodies with clinical activity in CLL include the anti-CD20 antibody ofatumumab (Arzerra) and the anti-CD52 antibody alemtuzumab (Campath). Researchers continue to explore multiple novel strategies for the treatment of patients with CLL, including small molecules and newer-generation monoclonal antibodies, such as RG7356 and veltuzumab.

For patients with CLL who are fit enough to tolerate treatment-related toxicities, including bone marrow suppression, modern chemoimmunotherapy combinations have significantly improved clinical outcomes. None of these regimens is curative, and a significant number of patients with CLL succumb to their disease. The effective management of elderly patients with CLL represents a particular challenge, in part because older patients with multiple comorbidities have been underrepresented in clinical trials of novel agents and drug combinations.

Because the majority of patients with CLL are older than 65 years at the time of their diagnosis, reimbursement for the treatment of CLL in the United States is typically provided by Medicare. An analysis of US Medicare data (1999-2007) has demonstrated that the cost burden associated with CLL is substantial. This study, which was published in 2012, analyzed the total lifetime cost of treatment for more than 7400 patients with CLL compared with matched controls who did not have cancer. The results demonstrated that patients with CLL incurred average treatment costs of more than $87,000 compared with approximately $47,600 for the matched controls, a very significant difference.

New Treatment Option for CLL: Obinutuzumab

In November 2013, the US Food and Drug Administration (FDA) approved obinutuzumab (Gazyva; Genentech) for use in combination with chlorambucil in patients with previously untreated CLL. The approval was done under the FDA’s priority review. Obinutuzumab is the first cancer agent with the “breakthrough therapy” designation to receive FDA approval. The approval of obinutuzumab for the treatment of patients with CLL was based on the demonstration of significant improvement in progression-free survival (PFS) in a randomized, open-label, multicenter trial comparing obinutuzumab in combination with chlorambucil versus chlorambucil alone.

The study included 356 patients with previously untreated CD20-positive CLL and coexisting medical conditions or reduced renal function. In this study, known as CLL11, patients received 1 of 3 treatment regimens: chlorambucil alone for 6 cycles, chlorambucil plus obinutuzumab for 6 cycles, or chlorambucil plus rituximab for 6 cycles. All cycles were 28 days. Data from the first portion of the CLL11 study—the comparison of obinutuzumab plus chlorambucil and chlorambucil alone—were initially presented at the 2013 American Society of Clinical Oncology annual meeting and served as the basis for the FDA’s approval of the drug.

In an interview regarding the CLL11 study, lead investigator Valentin Goede, MD, of the German CLL Study Group, Department of Internal Medicine, University Hospital Cologne, Germany, stated, “This [significant PFS] finding suggests an 86% reduction in the risk for a progression, relapse, or death in the obinutuzumab arm.”
Mechanism of Action

Obinutuzumab is a humanized monoclonal antibody directed against CD20.14 On binding to CD20, obinutuzumab mediates B-cell lysis in 3 ways: (1) the engagement of immune effector cells, whose mechanisms include antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, (2) direct activation of intracellular death signaling pathways, and (3) complement cascade activation.14

Dosing and Administration

For patients with newly diagnosed CLL, the dose of obinutuzumab is 100 mg intravenously on day 1 in cycle 1, 900 mg on day 2, and 1000 mg on days 8 and 15; in cycles 2 to 6, the dose is 1000 mg, administered intravenously every 28 days.14

Premedication before infusion with obinutuzumab is recommended to reduce the risk for infusion-related adverse reactions.14

CLL11: Pivotal Phase 3 Clinical Trial

In the first portion of the multicenter CLL11 trial, 356 previously untreated patients with CLL were randomly assigned to treatment with obinutuzumab plus chlorambucil or to chlorambucil alone.12 All patients had coexisting medical conditions or reduced renal function as measured by creatinine clearance (CrCl) of <70 mL/min.12

The majority of the patients received 1000 mg of obinutuzumab on days 1, 8, and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of obinutuzumab was divided between day 1 (100 mg) and day 2 (900 mg) for 45 patients in the CLL11 trial. Chlorambucil was given orally at 0.5 mg/kg on days 1 and 15 of all treatment cycles (1-6).12

The trial’s primary end point was PFS as assessed by independent review.12 Secondary end points included response rate, complete response rate, duration of response, disease-free survival, overall survival, minimal residual disease, safety, adverse events, patient-reported outcomes, and symptom burden defined by the European Organisation for Research and Treatment of Cancer questionnaire.15

Patient Population

In the phase 3 obinutuzumab trial, the patient demographics and clinical characteristics were balanced between the treatment arms.12 The patients’ median age was 73 years, 60% were male, and 95% were Caucasian.12,14 Overall, 68% of the patients had a CrCl of <70 mL/min and 76% had multiple comorbidities.14 The median estimated CrCl was 61 mL/min.12 Of the patients who received obinutuzumab plus chlorambucil, 81% received all 6 cycles compared with 67% of patients who received chlorambucil alone.14

Efficacy

The phase 3 study demonstrated that obinutuzumab is active and safe in patients with newly diagnosed CLL and comorbidities.12 At the time of data cutoff for primary end-point analysis, patients receiving chlorambucil alone and obinutuzumab plus chlorambucil had been followed for a median of 13.6 and 14.5 months, respectively.12 On assessment by independent reviewers, the median PFS was significantly prolonged for patients receiving obinutuzumab plus chlorambucil compared with patients receiving chlorambucil alone (23 months vs 10.9 months, respectively; *P* <.001).12 This significant difference in median PFS was maintained in a subsequent analysis. After a median observation time of 23 months, the median PFS for patients receiving obinutuzumab plus chlorambucil was 23 months compared with 11.1 months in patients receiving chlorambucil alone (*P* <.001).14 The PFS and overall response findings from the CLL11 study are summarized in Table 1.14

Safety

Of the 240 patients included in the phase 3 trial, approximately 194 (81%) received all 6 cycles (28 days each) of obinutuzumab-based therapy.14 Among the patients who received obinutuzumab, the most common adverse reactions (incidence, ≥10%) were infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorder (Table 2).14

Infusion reactions were noted in 69% of patients undergoing their first infusion of obinutuzumab.14 Severe (grade 3 or 4) infusion reactions were observed in 21% of patients receiving obinutuzumab, and 8% of patients

### Table 1  Phase 3 Clinical Trial CLL11: Efficacy Results

<table>
<thead>
<tr>
<th>Efficacy end point</th>
<th>Obinutuzumab plus chlorambucil (N = 238)</th>
<th>Chlorambucil (N = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>Median PFS, months</td>
<td>23</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>Stratified log-rank test P value</td>
<td>0.16 (95% CI, 0.11-0.24)</td>
</tr>
<tr>
<td>Response rate</td>
<td>Overall, %</td>
<td>75.9</td>
</tr>
<tr>
<td></td>
<td>Complete, %</td>
<td>27.8</td>
</tr>
<tr>
<td>Median duration of response, mo</td>
<td>15.2</td>
<td>3.5</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; PFS, progression-free survival. Source: Gazyva (obinutuzumab) injection prescribing information; 2013.
The incidence of infusion reactions was significantly lower with subsequent infusions—3% with the second 1000-mg dose of obinutuzumab, and less than 1% thereafter. No severe infusion reactions were reported after the first 1000-mg infusion. After this initial experience with infusion reactions in the CLL11 trial, study protocol modifications were made to require premedication with a corticosteroid, an anti-histamine, and acetaminophen. The first dose of obinutuzumab was also divided into 2 infusions—100 mg on day 1 and 900 mg on day 2. Among the 45 patients for whom these measures were implemented, 21 (47%) had an infusion reaction with the first 1000 mg of obinutuzumab. Less than 2% of patients experienced an infusion reaction with subsequent doses of obinutuzumab.

**HBV infection reactivation.** Hepatitis B virus (HBV) reactivation can occur in patients treated with anti-CD20 antibodies, including obinutuzumab. Reactivation of HBV replication is often followed by hepatitis, manifesting as an increase in transaminase levels and, in severe cases, increases in bilirubin level, liver failure, and death.

In some recipients of obinutuzumab, the reactivation of the HBV resulted in fulminant hepatitis, hepatic failure, and death. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive, as well as in patients who are HBsAg negative but are anti–hepatitis B core antibody (HBc) positive. Reactivation was also observed in patients who appeared to have resolved HBV infection (ie, HBsAg negative, anti-HBc positive, and hepatitis B surface antibody positive).

**Warnings and Precautions**

**Boxed warning.** The approval of obinutuzumab includes a boxed warning regarding HBV infection reactivation and progressive multifocal leukoencephalopathy (PML). Clinicians should advise patients of these warnings, and should assess patients for HBV and reactivation risk.

All patients receiving obinutuzumab should be screened for HBV infection by measuring HBsAg and anti-HBc before treatment initiation. Patients who show evidence of HBV infection should consult with physicians experienced in managing patients with HBV infection to discuss the potential use of HBV antiviral therapy.

In patients who develop reactivation of the HBV while receiving obinutuzumab, obinutuzumab and any concomitant chemotherapy should be discontinued immediately. Appropriate treatment should be instituted. In patients whose HBV reactivation resolves, resumption of obinutuzumab can be discussed with physicians who are experienced in managing patients with HBV infection. There are insufficient data regarding the safety of resuming obinutuzumab in patients who develop reactivation of the HBV.

**Progressive multifocal leukoencephalopathy.** JC virus infection resulting in PML, a potentially fatal condition,
was observed in patients receiving obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations or with changes to preexisting neurologic manifestations. If PML is diagnosed, therapy with obinutuzumab should be discontinued. Hypotension may occur as part of the obinutuzumab infusion reaction. Consider withholding antihypertensive treatments for 12 hours before the obinutuzumab infusion, during the infusion, and for the first hour after administration until blood pressure is stable. For patients who are at increased risk of hypertensive crisis, the benefits and risks of withholding their hypertensive medication should be deliberated.

**Infusion reactions.** Obinutuzumab can cause severe and life-threatening infusion reactions during initial and subsequent infusions. Symptoms include hypotension, tachycardia, dyspnea, and respiratory symptoms. Other common symptoms include nausea, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

Patients should receive premedication with acetaminophen, an antihistamine, and a glucocorticoid. Patients should be closely monitored during the entire infusion; reactions within 24 hours of receiving obinutuzumab have occurred. If infusion reactions occur, institute medical management with glucocorticoids, epinephrine, bronchodilators, and/or oxygen as needed. Table 3 summarizes the recommendations for managing infusion reactions associated with obinutuzumab.

Because patients with preexisting cardiac or pulmonary conditions may be at greater risk for experiencing more severe infusion reactions, they should be monitored more frequently throughout the obinutuzumab infusion and the postinfusion time frame.

**Table 3** Recommended Management of Adverse Reactions to Obinutuzumab Infusion, by Disease Severity (Grade)

<table>
<thead>
<tr>
<th>Infusion reaction severity</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 reaction (life-threatening): includes, but not limited to, anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction</td>
<td>• Stop the obinutuzumab infusion and permanently discontinue obinutuzumab therapy • Manage symptoms</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>• Interrupt obinutuzumab infusion • Manage symptoms • On resolution of symptoms, consider restarting obinutuzumab infusion at no more than 50% of the previous rate (used at the time that the infusion reaction occurred) • If no further infusion reaction symptoms occur, infusion rate escalation may be resumed at the increments and intervals as appropriate for the treatment cycle dose (see drug labeling) • Permanently discontinue treatment if the patient has a grade 3 infusion-related symptom on rechallenge</td>
</tr>
<tr>
<td>Grade 1 or 2 infusion reactions (mild to moderate)</td>
<td>• Interrupt obinutuzumab therapy or reduce the rate of the infusion • Manage symptoms • On resolution of symptoms, continue or resume infusion • If no further infusion reaction symptoms occur, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose (see drug labeling)</td>
</tr>
</tbody>
</table>

Source: Gazyva (obinutuzumab) injection prescribing information; 2013.
Obinutuzumab is the first cancer drug with a designated breakthrough therapy to receive FDA approval. This third-generation anti-CD20 monoclonal antibody has demonstrated improved efficacy with manageable side effects compared with chlorambucil alone.

Special Populations
Obinutuzumab has not been specifically studied in pregnant or nursing women. Women of childbearing age should use an effective contraceptive when receiving this medication and for the 12 months after treatment.14 Nursing women should be carefully evaluated for the benefits of obinutuzumab for the woman versus potential risk for the infant.14

The combination of obinutuzumab and chlorambucil has resulted in serious adverse events in geriatric patients. Among 240 treatment-naïve patients who received obinutuzumab in combination with chlorambucil, 82% were aged ≥65 years and 45% were aged ≥75 years. Of those aged ≥75 years, 45% had serious adverse events and 5% died. Among those aged ≥65 years, adverse event rates were similar in the active treatment and the comparator arms. The efficacy rates were not significantly different among patients of different ages.14

Conclusion
Obinutuzumab is the first cancer drug with a designated breakthrough therapy to receive FDA approval. This third-generation anti-CD20 monoclonal antibody, which was approved for the initial treatment of patients with CLL in combination with chlorambucil, has demonstrated improved efficacy with manageable side effects compared with chlorambucil alone.11,16 For patients with CLL and coexisting medical conditions and/or reduced renal function, obinutuzumab plus chlorambucil represents an effective alternative to purine analog-based therapy and to the use of chlorambucil alone. Obinutuzumab may also confer clinical benefit in other cancers that express CD20. Clinical studies are under way to evaluate the use of obinutuzumab combined with cytotoxic agents in indolent and aggressive subtypes of non-Hodgkin lymphoma (NHL), including follicular NHL, diffuse large B-cell lymphoma, and mantle-cell lymphoma.17

References