Approximately 22% of all non-Hodgkin lymphoma (NHL) cases are classified as follicular lymphoma, making it the second most common NHL subtype.\(^1,2\) Follicular lymphoma is characterized by a translocation between chromosomes 14 and 18, which causes the overexpression of the BCL-2 gene and increases the potential for treatment resistance.\(^1,2\) Follicular lymphoma is generally indolent; only in a minority of patients the disease will transform into a more aggressive lymphoma.\(^1\)

Standard initial treatment for patients with advanced stages of follicular lymphoma comprises chemoimmunotherapy regimens that include cytotoxic chemotherapy and an anti-CD20 monoclonal antibody, typically rituximab (Rituxan).\(^1,2\)

Although these multiagent regimens result in high response rates, approximately 20% of patients with follicular lymphoma have disease that relapses within 2 years of initial treatment.\(^3\) Retrospective data analysis shows that the 5-year overall survival rate for this subset of patients is significantly lower than for patients with follicular lymphoma that does not progress within the first 2 years of treatment—50% versus 90%, respectively.\(^3\) Researchers continue to explore novel combination regimens to enhance complete response rates and overall survival for patients with untreated follicular lymphoma.

### Gazyva Approved for Untreated Follicular Lymphoma

On November 16, 2017, the US Food and Drug Administration (FDA) approved obinutuzumab (Gazyva; Genentech), an anti-CD20 monoclonal antibody, for the treatment of adults with untreated, stage II bulky, stage III, or stage IV follicular lymphoma, in combination with chemotherapy, followed by obinutuzumab monotherapy in patients achieving at least partial remission.\(^4\) The FDA used its priority review process for this approval.\(^4\)

Obinutuzumab was first approved in 2013, in combination with chlorambucil (Leukeran), for the treatment of patients with previously untreated chronic lymphocytic leukemia.\(^5,6\)

In February 2016, the FDA approved obinutuzumab, in combination with bendamustine, followed by obinutuzumab monotherapy, for the treatment of patients with follicular lymphoma that relapsed after or was refractory to a rituximab-containing regimen.\(^7\)

### Mechanism of Action

Obinutuzumab is a humanized monoclonal antibody directed against CD20. Upon 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.\(^5\)

### Dosing and Administration

For patients with untreated follicular lymphoma, the recommended dose and schedule of obinutuzumab is 1000 mg given intravenously on days 1, 8, and 15 of cycle 1 of chemotherapy, followed by 1000 mg on day 1 of each subsequent chemotherapy cycle. Obinutuzumab is used with one of the following chemotherapy regimens:

- Six 28-day cycles of bendamustine
- Six 21-day cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), followed by 2 additional 21-day cycles of obinutuzumab alone
- Eight 21-day cycles of cyclophosphamide, vincristine, and prednisone (CVP).

Patients who have a complete or partial response to initial treatment should receive obinutuzumab monotherapy at a dose of 1000 mg every 2 months for up to 2 years.\(^5\)

### Pivotal Clinical Trial: GALLIUM

The efficacy of obinutuzumab in untreated follicular lymphoma or in marginal-zone lymphoma was evaluated in the randomized, open-label, multicenter, phase 3 GALLIUM clinical trial, which involved 1202 patients with stage II bulky, stage III, or stage IV follicular lym-
Patients were randomized to receive obinutuzumab plus chemotherapy or rituximab plus chemotherapy, followed by obinutuzumab or rituximab maintenance for up to 2 years in patients whose disease responded to treatment. The study was powered to evaluate progression-free survival (PFS) among patients with follicular lymphoma only.\(^8\)

Overall, 91% of patients with follicular lymphoma had stage III or IV disease, 79% had high- or intermediate-risk disease based on their Follicular Lymphoma International Prognostic Index score, and 44% had bulky disease.\(^3,5\) The chemotherapy regimen (bendamustine, CHOP, or CVP) was stipulated at each site: all patients at each site received the same regimen. Overall, 57% of patients received bendamustine, 33% received CHOP, and 10% received CVP.\(^5,8\)

After a median follow-up of 38 months, the independent review committee–assessed PFS was significantly longer in the obinutuzumab arm than in the rituximab arm. The median PFS was not reached in either cohort.\(^5,8\) The Table summarizes these PFS data, as well as secondary outcomes, including overall response rate and complete response rate.\(^5\)

### Adverse Reactions

Overall, 1385 patients with follicular lymphoma or with marginal-zone lymphoma were evaluated for safety in GALLIUM. Serious adverse events were reported in 50% of patients in the obinutuzumab arm versus 43% in the rituximab arm; grade ≥4 events were 79% versus 72%, respectively.\(^5\) Fatal infections occurred in 2% of patients versus <1%, respectively.\(^5\)

The most common adverse events (incidence ≥20% and ≥5% greater than in the rituximab arm) in the obinutuzumab arm included infusion reactions, neutropenia, upper respiratory tract infection, cough, constipation, and diarrhea. The most common grade ≥3 adverse events (incidence ≥5%) reported more often with obinutuzumab than rituximab were neutropenia, febrile neutropenia, thrombocytopenia, and infusion reactions. Patients who received obinutuzumab plus bendamustine were more likely to have serious or fatal infections than those who received obinutuzumab plus CHOP or obinutuzumab plus CVP.\(^5\)

### Contraindications

Obinutuzumab is contraindicated in patients with known hypersensitivity reactions (eg, anaphylaxis) to obinutuzumab or to any of its excipients, including serum sickness with previous obinutuzumab use.\(^5\)

### Use in Specific Populations

Obinutuzumab is likely to cause fetal B-cell depletion.

Live vaccines should not be given to neonates and infants exposed to obinutuzumab until B-cell recovery occurs.\(^5\)

Obinutuzumab was not investigated in children.

Patients aged ≥65 years had higher rates of serious adverse events and were more likely to discontinue therapy than younger patients. Of patients aged ≥65 years, 63% had serious adverse events and 26% had events that led to treatment withdrawal; among younger patients, the rates were 43% and 13%, respectively.\(^5\)

No difference in the efficacy of obinutuzumab was observed between older and younger patients.\(^5\)

### Warnings and Precautions

The prescribing information for obinutuzumab includes a boxed warning regarding the risk for hepatitis B virus (HBV) infection reactivation and progressive multifocal leukoencephalopathy (PML). HBV reactivation can occur with anti-CD20 antibodies, including obinutuzumab. Patients with evidence of current or past HBV infection should be monitored for hepatitis or HBV reactivation during and for several months after obinutuzumab treatment.\(^5\)

John Cunningham virus infection resulting in PML, a potentially fatal condition, has been reported in patients who received obinutuzumab. PML should be ruled out in patients presenting with new-onset neurologic manifestations.\(^5\)

Obinutuzumab can cause life-threatening infusion reactions during infusion. Premedication with acetaminophen, an antihistamine, and a glucocorticoid is recommended.\(^5\)

Immediate- and late-onset hypersensitivity reactions have been reported after obinutuzumab therapy and may be difficult to distinguish from infusion-related reactions. Hypersensitivity reactions only rarely occur after the first obinutuzumab infusion.\(^5\)

### Table: Efficacy of Obinutuzumab plus Chemotherapy in Patients with Treatment-Naïve Follicular Lymphoma

<table>
<thead>
<tr>
<th>End point(^6)</th>
<th>Obinutuzumab + chemotherapy, then obinutuzumab monotherapy (N = 601)</th>
<th>Rituximab + chemotherapy, then rituximab monotherapy (N = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, N (%)</td>
<td>108 (18)</td>
<td>141 (23)</td>
</tr>
<tr>
<td>HR, 0.72 (95% CI, 0.56-0.93)</td>
<td>P = .0118</td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>CR, %</td>
<td>28</td>
<td>27</td>
</tr>
</tbody>
</table>

\(^6\)Per independent review committee (IRC).  
\(^7\)Investigator-assessed PFS was consistent with data from the IRC.  
\(^8\)After completion of combination therapy; assessed by computed tomography, without positron emission tomography.  
CI indicates confidence interval; CR, complete response; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival.  
Source: Gazyva (obinutuzumab) injection prescribing information; November 2017.
Tumor lysis syndrome (TLS) can occur after obinutuzumab treatment. For patients at high risk for TLS, prophylaxis with antihyperuricemics and hydration before obinutuzumab infusion are recommended.5

Serious bacterial, fungal, and new or reactivated viral infections can occur during and after obinutuzumab therapy. Obinutuzumab should not be given to patients with active infection.5

Neutropenia associated with obinutuzumab therapy can occur >28 days after completion of obinutuzumab treatment and can last >28 days.5

Life-threatening thrombocytopenia has been reported with use of obinutuzumab in combination with chemotherapy.5

Immunization with live virus vaccines is not recommended until the completion of obinutuzumab treatment and B-cell recovery.5

Conclusion
The FDA approval of obinutuzumab, an intravenous monoclonal antibody that targets CD20, as first line treatment, in combination with chemotherapy, for patients with newly diagnosed follicular lymphoma, provides a novel treatment option for patients diagnosed with this disease. Results of a large, phase 3, randomized study demonstrated that the use of obinutuzumab, in combination with chemotherapy, is safe and significantly prolongs PFS in patients with untreated follicular lymphoma. ■

References