

## Ibrutinib Approved for the Treatment of Mantle Cell Lymphoma

On November 13, the US Food and Drug Administration (FDA) granted an accelerated approval to ibrutinib (Imbruvica, Pharmacyclics and Janssen Biotech) as a treatment for patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. Earlier this year, the FDA designated ibrutinib as a breakthrough therapy, which put the drug on a fast track for development and approval.

Ibrutinib is a first-in-class specific inhibitor of Bruton's tyrosine kinase, which is known to be expressed in chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma, MCL, diffuse large B-cell lymphoma, and follicular lymphoma.

The approval was based on results from the PCYC-1104 study, which was a single-arm clinical trial of 111 patients who had previously undergone treatment for MCL. The average age of participants was 68 years, most were male, and 55% had been treated with at least 3 previous regimens (65 patients were bortezomib [Velcade, Millennium Pharmaceuticals]-naive).

According to clinical prognostic factors, 86% of patients had intermediate or high-risk MCL. Most patients had been treated with cyclophosphamide, doxorubicin, vincristine, and dexamethasone (hyper-CVAD); 10% had undergone stem cell transplantation; and 25% of patients had received lenalidomide (Revlimid, Celgene). Some patients were refractory to every treatment attempted.

In this study, patients received ibrutinib 560 mg daily until their disease progressed or unacceptable toxicity occurred. Tumor response was assessed every 2 cycles according to the International Working Group revised criteria for non-Hodgkin lymphoma.

Results of the PCYC-1104 study were reported in June in *The New England Journal of Medicine* by Wang and colleagues, and included an overall response of 68% among patients treated with ibrutinib (complete response, 21%; partial response, 47%). After a median follow-up of 15.3 months, the estimated median duration of response was 17.5 months, the estimated median progression-free survival was 13.9 months, and the median overall survival was not reached. The estimated 18-month overall survival rate was 58%.

Interestingly, the response rate improved with longer drug exposure. After treatment was initiated, there was a

significant incidence of lymphocytosis, which was associated with a dramatic reduction in tumor volume.

The most common adverse events were thrombocytopenia (57%), diarrhea (51%), neutropenia (47%), anemia (41%), fatigue (41%), musculoskeletal pain (37%), peripheral edema (35%), upper respiratory tract infection (34%), nausea (31%), bruising (30%), dyspnea (27%), constipation (25%), rash (25%), abdominal pain (24%), vomiting (23%), and decreased appetite (21%).

Nine percent of patients discontinued treatment owing to adverse events, and 14% underwent dose reductions as a result of adverse events. The recommended dose in this patient population is 560 mg (four 140 mg capsules) orally once daily.

Based on the same new drug application that resulted in its approval in MCL, ibrutinib has also received a Breakthrough Therapy designation as a treatment for CLL and Waldenström macroglobulinemia.

## Marketing and Commercial Distribution of Ponatinib Suspended Following FDA Request

On October 31, the FDA requested that Ariad Pharmaceuticals temporarily withdraw ponatinib (Iclusig) from the market. The reason was the increased frequency of serious adverse vascular events that occurred after the drug received approval in December 2012 for the treatment of chronic phase, accelerated phase, or blast crisis chronic myelogenous leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy.

The decision to approve ponatinib was based primarily on the positive results of the PACE (Ponatinib Ph+ ALL and CML Evaluation) trial. This was a multicenter, international, phase 2 trial that evaluated ponatinib in CML patients who were resistant or intolerant to prior tyrosine kinase inhibitor therapy. The study enrolled different subtypes of CML patients, including chronic phase, accelerated phase, and blast crisis. In a 12-month follow-up analysis, it was reported that ponatinib was active and well tolerated in all CML subtypes.

A Boxed Warning was included in the approval of ponatinib, based on the development of arterial thrombosis in 8% of patients and hepatotoxicity in the trial. However, at an FDA-required median 24-month planned follow-up, the rate of arterial thrombosis had increased to 11.8% in patients treated with ponatinib, which warranted a pause in patient enrollment.

According to the FDA's investigation, new clinical trial data indicated that approximately 24% of patients in the phase 2 study (median treatment duration, 1.3 years) and roughly 48% of patients in the phase 1 trial (median treatment duration, 2.7 years) experienced serious adverse vascular events, including: fatal and life-threatening heart attack; stroke; loss of blood flow to the extremities resulting in tissue death; and severe narrowing of blood vessels in the extremities, heart, and brain that required urgent surgical procedures to restore blood flow. In some patients, fatal and serious adverse events occurred as early as 2 weeks after starting ponatinib therapy.

Although the relationship of these adverse events to ponatinib was not determined, the increased frequency and pattern of the events strongly suggested that many were drug-related. The FDA stated that it was not able to identify a safe dose level or exposure duration with ponatinib.

The phase 3 trial that was evaluating ponatinib in untreated patients with CML was discontinued. The EPIC trial was a randomized, 2-arm, multicenter study comparing the efficacy of ponatinib with that of imatinib in adult patients with newly diagnosed CML in the chronic phase. The trial was being conducted at approximately 150 investigational sites in more than 20 countries. Patients selected for treatment with ponatinib in the trial will no longer receive the drug. The termination of the trial was agreed upon by the manufacturer, the FDA, and an independent data monitoring committee. In addition, all other trials exploring ponatinib were placed on hold.

## Updated Guidelines Recommend HER2 Testing in All Breast Cancer Patients

The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) have released updated recommendations aimed at improving the accuracy and reporting of human epidermal growth factor receptor 2 (HER2) testing in patients with invasive breast cancer.

The updated guidelines, which were published jointly in the *Journal of Clinical Oncology* and the *Archives of Pathology & Laboratory Medicine*, are based on a systematic review of medical research literature and provide detailed recommendations for how to test for HER2 overexpression, interpret test results, and guide treatment decisions involving targeted therapies.

The updated guidelines strongly emphasize the importance of accurately determining HER2 status in order to treat patients with HER2-targeted therapies, including trastuzumab (Herceptin, Genentech), lapa-

**Table.** ASCO/CAP Updated Guidelines for HER2 Testing in Patients With Breast Cancer

Key Recommendations for Oncologists
Request HER2 testing for every primary invasive cancer (and on the metastatic site if stage IV)
Recommend HER2-targeted therapy if HER2 test result is positive
Delay decisions about HER2-targeted therapy if the initial HER2 test result is equivocal
Must not recommend anti-HER2 therapy for patients who have negative test results
Delay decisions about anti-HER2 therapy if the test cannot be confirmed as positive or negative
Consider HER2-targeted therapy if a test result remains equivocal, even after reflex testing with an alternative assay

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; HER2, human epidermal growth factor receptor 2.

Adapted from Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol.* 2013;31(31):3997-4013.

tinib (Tykerb, GlaxoSmithKline), pertuzumab (Perjeta, Genentech), and T-DM1 (Kadcyla, Genentech).

The guidelines strengthen recommendations based on a new diagnostic technique known as bright-field in situ hybridization (ISH), which involves a regular light microscope to evaluate for amplification of the HER2 gene.

HER2 testing is now recommended for every primary, recurrent, and metastatic tumor. Additionally, the report advocates retesting in patients who previously tested HER2-negative but demonstrate clinical behavior suggestive of HER2-positive or triple-negative disease at the time of recurrence. If the HER2 test result is equivocal, HER2-targeted therapy should be delayed. Furthermore, any test results that are equivocal should be retested on a mandatory basis. The 6 key recommendations for oncologists are summarized in the Table.

ASCO and CAP have also developed clinical tools and resources that include supplemental information on clinical questions, as well as test result interpretation criteria and reporting elements. A companion patient guide is also available at [www.cancer.net](http://www.cancer.net) and at [www.cap.org](http://www.cap.org).

## Approval of Obinutuzumab as a Breakthrough Therapy for Chronic Lymphocytic Leukemia

On November 1, obinutuzumab (Gazyva, Genentech; previously known as GA101) was approved by the FDA for use in combination with chlorambucil for the treatment of patients with previously untreated chronic CLL.

Obinutuzumab is the first agent to be approved under the FDA's Breakthrough Therapy designation.

The decision to approve obinutuzumab was based on outcomes from the CLL11 trial showing that obinutuzumab in combination with chlorambucil more than doubled median progression-free survival over chlorambucil alone. This phase 3 trial enrolled patients with previously untreated CD20-positive CLL. In this 3-arm study, patients were randomized in a 1:2:2 ratio to receive 6 cycles of chlorambucil every 28 days (n=118), chlorambucil plus obinutuzumab (n=238), or chlorambucil plus rituximab (Rituxan, Genentech/Biogen Idec [n=233]). In order to allow for the direct comparison of the obinutuzumab and rituximab combinations, an additional 192 patients were enrolled. Final data from the expanded 781-patient CLL11 trial will be presented at the American Society of Hematology annual meeting in December 2013.

The median progression-free survival was 23 months in the obinutuzumab plus chlorambucil group compared

with 11.1 months among those treated with chlorambucil alone, representing an 84% reduction in risk (hazard ratio, 0.16). Overall response was also higher among patients who received obinutuzumab (approximately 76% vs 32.1%, respectively), as was complete response (27.8% vs 0.9%, respectively) and median duration of response (15.2 vs 3.5 months, respectively).

The most common adverse events reported among patients treated with obinutuzumab were infusion-related reactions, neutropenia, thrombocytopenia, anemia, musculoskeletal pain, and pyrexia.

Obinutuzumab is approved with a Boxed Warning about hepatitis B virus reactivation. Patients should be assessed for hepatitis B virus and their related reactivation risk. The warning also lists the risk of inducing progressive multifocal leukoencephalopathy. According to the FDA, these are known risks with other monoclonal antibodies in this class and rare cases were identified in patients enrolled in other trials of obinutuzumab.