

FDA Approval: Ibrutinib for Patients with Previously Treated Mantle Cell Lymphoma and Previously Treated Chronic Lymphocytic Leukemia ^{CME}

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Abstract

On November 13, 2013, the FDA granted accelerated approval to ibrutinib (IMBRUVICA capsules; Pharmacyclics, Inc.) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. On February 12, 2014, the FDA granted accelerated approval for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy. Ibrutinib is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor that received all four expedited programs of the FDA: Fast-Track designation, Breakthrough Therapy designation, Priority Review, and Accelerated Approval. Both approvals were based on overall response rate (ORR) and duration of

response (DOR) in single-arm clinical trials in patients with prior treatment. In MCL ($N = 111$), the complete and partial response rates were 17.1% and 48.6%, respectively, for an ORR of 65.8% [95% confidence interval (CI), 56.2%–74.5%]. The median DOR was 17.5 months (95% CI, 15.8–not reached). In CLL ($N = 48$), the ORR was 58.3% (95% CI, 43.2%–72.4%), and the DOR ranged from 5.6 to 24.2 months. The most common adverse reactions ($\geq 30\%$ in either trial) were thrombocytopenia, diarrhea, neutropenia, bruising, upper respiratory tract infection, anemia, fatigue, musculoskeletal pain, peripheral edema, and nausea. *Clin Cancer Res*; 21(16): 3586–90. ©2015 AACR.

Disclosure of Potential Conflicts of Interest

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CME Staff Planners' Disclosures

The members of the planning committee have no real or apparent conflicts of interest to disclose.

Learning Objectives

Upon completion of this activity, the participant should have a better understanding of the efficacy, safety, and dosing of ibrutinib, and of the regulatory mechanisms that supported the initial U.S. approvals of ibrutinib for the treatment of previously treated mantle cell lymphoma and previously treated chronic lymphocytic leukemia.

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Introduction

The ibrutinib drug development program and approval used all four expedited approval programs of the FDA: Fast-Track designation, Breakthrough Therapy designation, Priority Review, and Accelerated Approval. In this article, FDA reviewers discuss how these programs expedited ibrutinib approvals in mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). All four expedited programs are granted for drugs that treat serious and life-threatening medical conditions (1, 2).

MCL is a distinct subtype of non-Hodgkin lymphoma (NHL) and is characterized by the translocation $t(11,14)(q13;q32)$, which results in constitutive overexpression of cyclin D1 (3).

The median age at diagnosis is 68 years. Patients typically present with generalized lymphadenopathy, and extranodal involvement is common. The median overall survival (OS) in patients with newly diagnosed MCL historically has been 3 to 4 years (4). First-line treatment regimens include multi-agent chemotherapies; however, almost all patients eventually experience a relapse.

Bortezomib and lenalidomide were the only FDA-approved treatments for patients with MCL who had received prior therapy. The bortezomib approval in 2006 was based on a single-arm trial of bortezomib monotherapy in 155 patients with MCL who had received at least one prior therapy. The overall response rate (ORR) was 31%, and the median duration of response (DOR) was 9.3 months (5). The lenalidomide approval in 2013 was based on a single-arm trial of lenalidomide monotherapy in 134 patients after two prior therapies, one of which included bortezomib. Lenalidomide showed similar results, with an ORR of 26% and a median DOR of 16.6 months (6).

CLL is the most common form of leukemia in adults and is characterized by an accumulation of monoclonal mature B cells in the blood, bone marrow, and secondary lymphatic organs. The median age at diagnosis is 71 years. Current treatments for CLL are not curative. Among patients with disease relapse or disease that is refractory to first-line treatment, the choice of subsequent therapy depends on comorbidities, duration of response to prior therapy, tolerance to treatment, disease-related manifestations, and the presence of molecular poor-risk features, including del(17)(p13.1). The immunophenotype of CLL is characterized by CD19, CD23, CD5, and dim expression of surface immunoglobulin (7). The following treatments are FDA-approved for CLL: chlorambucil (1957), cyclophosphamide (1959), fludarabine (1991), alemtuzumab (2007), bendamustine (2008), ofatumumab (2009), rituximab in combination with fludarabine and cyclophosphamide (2010), and obinutuzumab in combination with chlorambucil (2013).

Chemistry

Ibrutinib is supplied as an immediate-release gelatin capsule for oral administration containing 140 mg of ibrutinib.

Nonclinical Pharmacology and Toxicology

Ibrutinib is an inhibitor of BTK, a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways that activate pathways necessary for B-cell trafficking, chemotaxis, and adhesion (8, 9). The mechanism of action of ibrutinib includes reduced homing of leukocytes, which may contribute to the peripheral lymphocytosis that is observed in some patients with MCL and CLL. Ibrutinib-related toxicities in animals included ulceration and inflammation of the gastrointestinal tract; depletion, necrosis, and inflammation in lymphoid tissues; and epidermal necrosis and exudate. Muscular degeneration, thinning of cortical bone, and pancreatic acinar atrophy/reduced zymogen granules also occurred in animals to a lesser degree.

Clinical Pharmacology

Ibrutinib is absorbed after oral administration with a median T_{max} of 1 to 2 hours. Exposure increases with increasing doses up

to 840 mg. The steady-state AUC (mean \pm SD) in patients receiving 560 mg was 953 ± 705 ng·h/mL and in patients receiving 420 mg was 680 ± 517 ng·h/mL. Administration with food increases ibrutinib exposure approximately 2-fold compared with administration after overnight fasting. Reversible binding of ibrutinib to human plasma proteins *in vitro* was 97.3% with no concentration dependence in the range of 50 to 1,000 ng/mL. The apparent volume of distribution at steady state ($V_d, ss/F$) was approximately 10,000 L.

Metabolism is the main route of elimination. Ibrutinib is metabolized primarily by CYP3A and to a minor extent by CYP2D6. An active metabolite has BTK-inhibitory activity approximately 15 times lower than that of ibrutinib, and the mean metabolite:parent ratio at steady-state ranges from 1 to 2.8. In healthy fasted subjects, coadministration with ketconazole, a strong CYP3A inhibitor, increased the C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. If a moderate CYP3A inhibitor must be used, the ibrutinib dose should be reduced. In healthy fasted subjects, coadministration of rifampin, a CYP3A inducer, decreased the C_{max} and AUC of ibrutinib by more than 10-fold. Concomitant administration with strong or moderate inhibitors or strong CYP3A inducers should be avoided.

Apparent clearance (CL/F) is approximately 1,000 L per hour, and the half-life is 4 to 6 hours. Because ibrutinib is metabolized in the liver, significant increases in ibrutinib exposure are expected in patients with hepatic impairment. Patients with liver impairment were excluded from ibrutinib clinical trials; however, preliminary pharmacokinetics data from an ongoing trial in patients with hepatic impairment indicated that ibrutinib exposure was approximately 6-fold higher in those ($n = 3$) with moderate hepatic impairment (Child-Pugh B) than in healthy volunteers. Therefore the use of ibrutinib in patients with baseline hepatic impairment should be avoided.

Clinical Trials

Trial design

The safety and efficacy of ibrutinib in MCL were evaluated in a single-arm, open-label, multicenter trial (NCT01236391, PCYC-1104-CA) in 111 patients who had received at least one prior therapy (10). Ibrutinib, 560 mg, was administered orally once daily until disease progression or unacceptable toxicity. Tumor response was assessed by investigators and an Independent Review Committee (IRC) according to the revised International Working Group for NHL criteria (11). The primary endpoint was investigator-assessed ORR.

The safety and efficacy of ibrutinib in CLL were evaluated in a single-arm, open-label, multicenter trial (NCT01105247, PCYC-1102-CA) in 48 patients who had received at least one prior therapy (12). Ibrutinib, 420 mg, was administered orally once daily until disease progression or unacceptable toxicity. The ORR and DOR were assessed by an IRC using a modified version of the International Workshop on CLL criteria (13, 14).

Baseline characteristics

The median age in the MCL trial was 68 years, and 89% of the patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The median time since diagnosis was 42 months, and the median number of prior treatments was three. Thirty-nine percent had at least one tumor ≥ 5 cm, 49% had bone marrow involvement, and 54% had extranodal involvement.

Table 1. Efficacy results for ibrutinib clinical trials

Efficacy endpoint	MCL	CLL
	N = 111	N = 48
ORR (95% CI)	65.8% (56.2%–74.5%)	58.3% (43.2%–72.4%)
Complete response	17.1%	0
Partial response	48.6%	58.3%
Duration of response	N = 73	N = 28
Median	17.5 months	Not reached
Range	0.4 to 19.6+ months	5.6 to 24.2+ months

The median age in the CLL trial was 67 years, and all patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 80 months, and the median number of prior treatments was four. Forty-six percent had at least one tumor ≥ 5 cm.

Efficacy

In the MCL trial, the ORR was 65.8% [95% confidence interval (CI), 56.2%–74.5%], and the complete response rate was 17.1% (Table 1). The DOR ranged from 0.4 to 19.6+ months, and the median DOR was 17.5 months (95% CI, 15.8–not reached). In the CLL trial, the ORR was 58.3% (95% CI, 43.2%–72.4%), all partial responses. The DOR ranged from 5.6 to 24.2+ months, and the median DOR had not been reached.

Safety

The median treatment duration was 8.3 and 15.6 months in the MCL and CLL trials, respectively. The most common adverse reactions ($\geq 30\%$ in either trial) were thrombocytopenia, diarrhea, neutropenia, bruising, upper respiratory tract infection, anemia, fatigue, musculoskeletal pain, peripheral edema, and nausea.

The most common grade 3 or 4 nonhematologic adverse reactions ($\geq 5\%$ in either study) were pneumonia, atrial fibrillation, hypertension, musculoskeletal pain, skin infection, diarrhea, abdominal pain, and fatigue (Table 2). The most common grade 3 or 4 hematologic laboratory abnormalities ($\geq 5\%$ in either study) were neutropenia, thrombocytopenia, and anemia.

In the MCL trial, 9% of patients discontinued treatment due to adverse reactions, and the most frequent was subdural hematoma (1.8%). In the CLL trial, 10% of patients discontinued treatment due to adverse reactions. These included 3 patients (6%) with infections and 2 patients (4%) with subdural hematomas.

Bleeding events, infections, renal failure, and second primary malignancies were of sufficient concern to be included in the Warnings and Precautions section of the prescribing information. Grade 3 or greater bleeding events (subdural hematoma, ecchymoses, gastrointestinal bleeding, and hematuria) occurred in 5% of patients with MCL and in 6% of patients with CLL.

Overall, bleeding events of any grade, including bruising and petechiae, occurred in 48% of patients with MCL and in 63% of patients with CLL. The safety issue of hemorrhage was identified during early phase I and II clinical trials in 2011, with the occurrence of a cluster of central nervous system (CNS) hemorrhages in the setting of recent head trauma or use of warfarin. Subsequently, ongoing clinical trial protocols were modified to exclude patients on warfarin or with a recent history of stroke or CNS hemorrhage. The protocols also included a provision to hold study drug in any patient requiring the initiation of anticoagulation until the patient was stably anticoagulated. The mechanism

of bleeding for the bleeding events is not well understood; however, data are emerging on the effects of ibrutinib on collagen and von Willebrand factor–dependent platelet function (15).

Fatal and nonfatal infections occurred with ibrutinib therapy. At least 25% of patients with MCL and 35% of patients with CLL had grade 3 or greater infections. Fatal and serious cases of renal failure were noted in the uncontrolled clinical trials. In contrast, no differences were seen in the incidence of renal toxicity between the ibrutinib and ofatumumab arms in the subsequent phase III RESONATE trial (16). Second primary malignancies (SPM) occurred in 5% of patients with MCL and 10% of patients with CLL who received ibrutinib. SPMs were mostly nonmelanoma skin cancers in both populations.

Treatment-emergent lymphocytosis occurred in 33% and 77% of patients with MCL and CLL, respectively. The onset of lymphocytosis was within the first month of treatment and resolved after about 6 months of therapy in most patients. However, in a subgroup of patients, lymphocytosis lasted more than 12 months (17). When lymphocytosis was greater than 400,000/mcL, some patients developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were confounded as they occurred in patients with disease progression.

Discussion

The following four FDA programs are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition: Fast-Track designation, Breakthrough Therapy designation, Priority Review, and Accelerated Approval. Ibrutinib received fast-track designation for previously treated CLL in October 2012 and for previously treated MCL in December 2012 as it met the criteria of treating a serious condition and demonstrated the potential to meet an unmet medical need. Fast-track designation allows sponsors to have frequent interactions with the review team including meetings. In addition, the Agency may consider reviewing portions of the marketing application for a fast-track product before the sponsor submits the complete application (rolling review).

Ibrutinib was granted breakthrough therapy designation for previously treated MCL in February 2013 and for CLL with deletion of the short arm of chromosome 17 (del 17p) in March 2013 because preliminary clinical evidence indicated that the drug demonstrated substantial improvement on a clinically significant endpoint over available therapies. The bases for breakthrough therapy designation were the top-line efficacy and safety results from the clinical trials that were eventually submitted to support the approvals, PCYC-1104-CA (NCT01236391) for the MCL indication (10) and PCYC-1102-CA (NCT01105247) for the CLL indication (12). With breakthrough therapy designation, the sponsor received organizational commitment from the FDA to provide intensive guidance during drug development, early involvement of senior FDA management, and an expedited review of the application, including granting of priority review. From the time of IND submission in September 2008 through the submission of the New Drug Application (NDA) in June 2013, the FDA granted more than 10 meetings to discuss various aspects of the development program, including design of registrational trials for CLL and MCL, and specific meetings regarding the manufacturing and clinical pharmacology aspects of the NDA.

Table 2. All-grade adverse reactions in $\geq 20\%$ of patients or grade 3/4 adverse reactions in $\geq 5\%$ of patients in either study

System organ class Preferred term	MCL (N = 111)		CLL (N = 48)	
	All grades %	Grades 3/4 %	All grades %	Grades 3/4 %
Gastrointestinal disorders				
Diarrhea	51	5	63	4
Nausea	31	0	21	2
Constipation	25	0	23	2
Abdominal pain	24	5	15	0
Vomiting	23	0	19	2
Stomatitis	17	1	21	0
Infections and infestations				
Upper respiratory tract infection	34	0	48	2
Pneumonia	14	7	10	8
Sinusitis	13	1	21	6
Skin infection	14	5	17	6
General disorders and administrative site conditions				
Fatigue	41	5	31	4
Peripheral edema	35	3	23	0
Pyrexia	18	1	25	2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	37	1	27	6
Arthralgia	11	0	23	0
Skin and subcutaneous tissue disorders				
Bruising	30	0	54	2
Rash	25	3	27	0
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	27	4	10	0
Metabolism and nutrition disorders				
Decreased appetite	21	2	17	2
Nervous system disorders				
Dizziness	14	0	21	0
Cardiac disorders				
Atrial fibrillation	8	6	19	8
Vascular disorders				
Hypertension	10	4	17	8
Hematology laboratory abnormalities				
Platelets decreased	57	17	71	10
Neutrophils decreased	47	29	54	27
Hemoglobin decreased	41	9	44	0

Accelerated approval allows patients earlier access to promising drugs and biologics while the drug is studied further to demonstrate clinical benefit. Accelerated approval is based on adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity (18). A drug or biologic approved under accelerated approval is subject to the requirement that the sponsor study the drug or biologic further to verify and describe its clinical benefit. In patients with advanced malignancies, objective responses of sufficient magnitude and duration in single-arm trials have been accepted as the basis for accelerated approval (19).

For both MCL and CLL indications, the FDA granted accelerated approval rather than regular approval primarily due to the small number of patients studied and the lack of a control arm. All FDA review teams recommended approval for both indications. At the time of approvals (November 13, 2013, for the MCL indication and February 12, 2014, for the CLL indication), the sponsor had multiple ongoing randomized controlled trials in CLL and MCL, which FDA required to be submitted as postmarketing requirements (PMR) to fulfill the requirements for accelerated approval.

One of the PMRs in the CLL approval was for submission of the results of the completed randomized controlled trial of ibrutinib compared with ofatumumab in patients with relapsed or refractory CLL (RESONATE trial). The results of the RESONATE trial (NCT01578707, PCYC-1112-CA) were recently published (16). A notable finding in the RESONATE trial was the increased risk for atrial fibrillation, which occurred 10 times more commonly in the ibrutinib-treated patients [5.1% (10/195) in ibrutinib arm as compared with 0.5% (1/191) in ofatumumab arm]. The mechanism for this increased risk is unclear. Recent data identify a potential role for inhibition of cardiac PI3K-Akt signaling by ibrutinib (20). After submission and review of the RESONATE trial results, ibrutinib was granted regular approval on July 28, 2014, for the treatment of patients with CLL who have received at least one prior therapy and for CLL with the 17p deletion. For ibrutinib, randomized controlled trials serve a role in confirming clinical benefit and ascertaining the significance of safety findings from earlier phase I or II clinical trials.

Ibrutinib received three approvals between November 2013 and July 2014. Two approvals were accelerated approvals and one was a regular approval, and all three approvals were expedited by the four expedited programs for serious conditions.

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