



IMBRUVICA®
Ibrutinib capsules

DOSAGE FORMS AND STRENGTHS

Capsules

140mg capsules

IMBRUVICA capsules contain 140 mg of ibrutinib.

White opaque, size 0, hard gelatin capsule marked with “ibr 140 mg” in black ink.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

INDICATIONS

Mantle cell lymphoma (MCL)

Indicated for the treatment of adult patients with relapsed or refractory MCL.

Chronic lymphocytic leukemia (CLL)

IMBRUVICA as a single agent is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) (see *Pharmacodynamic properties*).

IMBRUVICA as a single agent is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

Chronic lymphocytic leukemia with deletion 17p

Indicated for the treatment of patients with CLL with deletion 17p.

DOSAGE AND ADMINISTRATION

Dosage

IMBRUVICA should be administered orally once daily with a glass of water at approximately the same time each day. The capsules should be swallowed whole with water. Do not open, break, or chew the capsules. IMBRUVICA must not be taken with grapefruit juice. IMBRUVICA should continue until disease progression or no longer tolerated by the patient.

Mantle cell lymphoma

The recommended dose of IMBRUVICA for MCL is 560 mg once daily until disease progression or no longer tolerated by the patient.

Chronic lymphocytic leukemia (CLL)

The recommended dose for the treatment of CLL is 420mg (three capsules) once daily.

Treatment should continue until disease progression or no longer tolerated by the patient.

Dose modification guidelines

Dose modifications are required for the concomitant use of moderate and strong CYP3A inhibitors as these can increase the exposure of ibrutinib (see *Interactions*).

IMBRUVICA therapy should be withheld for any new onset or worsening Grade ≥ 3 non-hematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities.

Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue IMBRUVICA.

Recommended dose modifications are described below:

Toxicity occurrence	MCL dose modification after recovery	CLL dose modification after recovery
First	restart at 560 mg daily	restart at 420 mg daily
Second	restart at 420 mg daily	restart at 280 mg daily
Third	restart at 280 mg daily	restart 140 mg daily
Fourth	discontinue IMBRUVICA	

Missed dose

If a dose of IMBRUVICA is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose.

Special populations

Pediatrics (18 years of age and younger)

The safety and efficacy of IMBRUVICA in children have not yet been evaluated.

Renal impairment

Ibrutinib has minimal renal clearance. No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in IMBRUVICA clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained and serum creatinine levels monitored periodically. There are no data in patients with severe renal impairment or patients on dialysis (see *Pharmacokinetic Properties*).

Hepatic impairment

Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure (see *Pharmacokinetic Properties*). For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily (two capsules). For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule). Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with severe hepatic impairment (Child-Pugh class C).

CONTRAINDICATIONS

IMBRUVICA is contraindicated in patients who have known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to ibrutinib or to the excipients in its formulation.

Use of preparations containing St. John's Wort is contraindicated in patients treated with Imbruvica.

WARNINGS AND PRECAUTIONS

Bleeding-related events

There have been reports of bleeding events in patients treated with IMBRUVICA, both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae; and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.

In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed (see *Pharmacodynamic Properties*). Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Supplements such as fish oil and vitamin E preparations should be avoided.

IMBRUVICA should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

The mechanism for the bleeding-related events is not fully understood. Patients with congenital bleeding diathesis have not been studied.

Leukostasis

There were isolated cases of leukostasis reported in patients treated with IMBRUVICA. A high number of circulating lymphocytes (> 400,000/mcL) may confer increased risk. Consider temporarily withholding IMBRUVICA. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in patients treated with IMBRUVICA. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in patients treated with IMBRUVICA. Patients should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of ibrutinib within the context of a prior or concomitant immunosuppressive therapy.

Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be considered.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anemia) were reported in patients treated with IMBRUVICA. Monitor complete blood counts monthly.

Interstitial Lung Disease (ILD)

Cases of ILD have been reported in patients treated with IMBRUVICA. Monitor patients for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt IMBRUVICA and manage ILD appropriately. If symptoms persist, consider the risks and benefits of IMBRUVICA treatment and follow the dose modification guidelines.

Cardiac arrhythmias and cardiac failure

Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia and cardiac failure including some fatal events, have been reported in patients treated with IMBRUVICA. Cases of atrial fibrillation and atrial flutter have been reported particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. At baseline and then periodically, monitor all patients clinically for cardiac arrhythmia and cardiac failure. Patients who develop arrhythmic symptoms or new onset of dyspnea, dizziness or fainting should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed.

In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, IMBRUVICA should be temporarily discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.

In patients with preexisting atrial fibrillation requiring anticoagulant therapy, alternative treatment options to IMBRUVICA should be considered. In patients who develop atrial fibrillation on therapy with IMBRUVICA a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to IMBRUVICA are non-suitable, tightly controlled treatment with anticoagulants should be considered.

Tumor lysis syndrome

Tumor lysis syndrome has been reported with IMBRUVICA therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

Non-melanoma skin cancer

Non-melanoma skin cancers were reported more frequently in patients treated with IMBRUVICA than in patients treated with comparators in pooled comparative randomised phase 3 studies. Monitor patients for the appearance of non-melanoma skin cancer.

Hypertension

Hypertension has occurred in patients treated with IMBRUVICA. Regularly monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust antihypertensive medication throughout treatment with IMBRUVICA as appropriate.

Viral reactivation

Cases of hepatitis B reactivation have been reported in patients receiving IMBRUVICA. Hepatitis B virus (HBV) status should be established before initiating treatment with IMBRUVICA. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. If patients have positive hepatitis B serology, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Drug-drug interactions

Co-administration of strong or moderate CYP3A4 inhibitors with IMBRUVICA may lead to increased ibrutinib exposure and consequently a higher risk for toxicity. On the contrary, co-administration of CYP3A4 inducers may lead to decreased IMBRUVICA exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of IMBRUVICA with strong CYP3A4 inhibitors and strong or moderate CYP3A4 inducers should be avoided whenever possible and co-administration should only be considered when the potential benefits clearly outweigh the potential risks. Patients should be closely monitored for signs of IMBRUVICA toxicity if a CYP3A4 inhibitor must be used, closely monitor patients for signs of IMBRUVICA lack of efficacy.

Women of Childbearing potential

Women of childbearing potential must use a highly effective method of contraception while taking Imbruvica.

INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4 (CYP3A4).

Agents that may increase ibrutinib plasma concentrations

Concomitant use of IMBRUVICA and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and strong CYP3A should be avoided.

Strong CYP3A inhibitors

Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects, increased exposure (C_{max} and AUC_{0-12h}) of ibrutinib by 29- and 24-fold, respectively. In a dedicated drug-drug interaction study in patients with B-cell malignancies, co-administration of voriconazole increased C_{max} and AUC by 6.7-fold and 5.7-fold, respectively. In clinical studies, the maximal observed ibrutinib exposure (AUC) was ≤ 2 -fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Voriconazole and posaconazole can be used concomitantly with IMBRUVICA as per dose recommendations in the table below. All other strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, and cobicistat) should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, see recommended dose modifications in the table below.

Moderate and mild CYP3A inhibitors

In patients with B-cell malignancies, co-administration of CYP3A inhibitor erythromycin increased C_{max} and AUC by 3.4-fold and 3.0-fold, respectively. If a moderate CYP3A inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) is indicated, reduce IMBRUVICA dose as per recommended dose modifications in the table below.

No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during IMBRUVICA treatment as these contain moderate inhibitors of CYP3A (see *Dosage and Administration* and *Pharmacokinetic Properties*).

Recommended dose modifications are described below:

Patient Population	Co-administered Drug	Recommended IMBRUVICA Dose for the Duration of the Inhibitor Use ^a
B-Cell Malignancies	• Mild CYP3A inhibitors	420 mg or 560 mg once daily per indication. No dose adjustment required.
	• Moderate CYP3A inhibitors	280 mg once daily.
	• Voriconazole • Posaconazole at doses less than or equal to suspension 200 mg BID	140 mg once daily.
	• Other strong CYP3A inhibitors • Posaconazole at higher doses ^b	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA. If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce IMBRUVICA dose to 140 mg once daily for the duration of the inhibitor use.

^a Monitor for adverse reactions to IMBRUVICA and interrupt or modify dose as recommended (see *Dosage and Administration*).

^b Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

After discontinuation of a CYP3A inhibitor, resume previous dose of IMBRUVICA (see *Dosage and Administration*).

Agents that may decrease ibrutinib plasma concentrations

Administration of IMBRUVICA with strong inducers of CYP3A decreases ibrutinib plasma concentrations by up to 90%. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction.

Drugs that may have their plasma concentrations altered by ibrutinib

In vitro studies indicated that ibrutinib is a weak reversible inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time-dependent CYP450 inhibition. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak

inducers of CYP450 isoenzymes *in vitro*. However, in a drug interaction study in patients with B-cell malignancies, a single 560 mg dose of ibrutinib did not have a clinically meaningful effect on the exposure of the CYP3A4 substrate midazolam. In the same study, 2 weeks of treatment with ibrutinib at 560 mg daily had no clinically relevant effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel), the CYP3A4 substrate midazolam, nor the CYP2B6 substrate bupropion.

In vitro studies indicated that ibrutinib is not a substrate of P-gp nor other major transporters, except OCT2. The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is a mild inhibitor of P-gp and breast cancer resistance protein (BCRP). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. There are no clinical data available. To minimize the potential for an interaction in the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after IMBRUVICA. Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no adequate and well-controlled studies of IMBRUVICA in pregnant women. Based on findings in animals, IMBRUVICA may cause fetal harm when administered to pregnant women.

IMBRUVICA should not be used during pregnancy. Women of child-bearing potential must use highly effective contraceptive measures while taking IMBRUVICA. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. The time period following treatment with IMBRUVICA where it is safe to become pregnant is unknown.

Men should be advised not to father a child or donate sperm while receiving IMBRUVICA, and for 3 months following completion of treatment (see *Non-Clinical Information - Fertility*).

Ibrutinib was studied for effects on embryo-fetal development in pregnant rats given oral doses of 10, 40, and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day (approximately 14 times the AUC of ibrutinib and 9.5 times the AUC of the dihydrodiol metabolite compared to patients at the dose of 560 mg daily) was associated with increased post-implantation loss and increased visceral malformations (heart and major vessels). Ibrutinib at a dose of ≥ 40 mg/kg/day ($\geq$ approximately 5.6 times the AUC of ibrutinib and 4.0 times the AUC of the dihydrodiol metabolite compared to patients at a dose of 560 mg daily) was associated with decreased fetal weights.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at oral doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal malformations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased post-implantation loss. Ibrutinib caused malformations in rabbits at a dose of 15 mg/kg/day (approximately 2.0 times the exposure (AUC) in patients with MCL administered ibrutinib 560 mg daily and 2.8 times the exposure in patients with CLL receiving ibrutinib dose 420 mg per day).

Breast-feeding

It is not known whether ibrutinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, breast-feeding should be discontinued during IMBRUVICA treatment.

Effects on Ability to Drive and Use Machines

Fatigue, dizziness, and asthenia have been reported in some patients taking IMBRUVICA and should be considered when assessing a patient's ability to drive or operate machines.

ADVERSE REACTIONS

Throughout this section, adverse reactions (AR) are presented. Adverse reactions are adverse events that have been considered to be reasonably causally associated with the use of ibrutinib based on the comprehensive assessment of the available adverse event information. A causal relationship with ibrutinib cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Non-melanoma skin cancer

Based on an integrated analysis of the randomized, controlled phase 3 studies, the incidence of non-melanoma skin cancer was 6% in IMBRUVICA-treated patients and 3% in comparator-treated patients.

Leukostasis

Isolated cases of leukostasis have been observed (see *Warnings and Precautions*).

Elderly

Of the 1200 patients treated with IMBRUVICA, 64% were 65 years of age or older. Grade 3 or higher pneumonia occurred more frequently ($\geq 5\%$) among elderly patients treated with IMBRUVICA (12% of patients ≥ 65 years of age versus 7% of patients <65 years of age).

Mantle cell lymphoma

The data described below reflect exposure to IMBRUVICA in a phase 2 clinical study (PCYC-1104-CA) and a randomized phase 3 study (MCL3001) in patients with MCL (n=250).

The most commonly occurring adverse reactions for MCL ($\geq 20\%$) were diarrhea, hemorrhage (e.g., bruising), fatigue, musculoskeletal pain, nausea, upper respiratory tract infection, cough, and rash.

The most common Grade 3/4 adverse reactions ($\geq 5\%$) were: neutropenia, thrombocytopenia, pneumonia, and anemia.

Discontinuation and dose reduction due to ARs

Of the 250 patients treated with IMBRUVICA for MCL, seven (3%) discontinued treatment due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation included hemorrhage, pneumonia, and thrombocytopenia. Adverse reactions leading to dose reduction occurred in 6% of patients.

Adverse reactions from Study 1104 are described below in Table 1 to reflect exposure to IMBRUVICA in patients with MCL who received at least one prior therapy with a median treatment duration of 8.3 months.

Table 1: Treatment-emergent adverse reactions reported in $\geq 10\%$ of patients with MCL treated with 560 mg IMBRUVICA – Study 1104 (N = 111)

System Organ Class	Adverse Reaction	Frequency	
		All Grades (%)	Grades 3-4 (%)
Infections and infestations	Pneumonia	12	5
	Urinary tract infection	14	3
	Sinusitis	14	1
	Upper respiratory tract infection	26	0
Blood and lymphatic system disorders	Neutropenia	19	17
	Thrombocytopenia	21	12
	Anemia	15	10
Metabolism and nutrition disorders	Dehydration	14	4
	Hyperuricemia	17	5
	Decreased appetite	23	2
Nervous system disorders	Dizziness	14	0
	Headache	12	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	28	4
	Epistaxis	11	0
	Cough	18	0
Gastrointestinal disorders	Diarrhea	53	5
	Abdominal pain	18	5
	Vomiting	23	0
	Stomatitis	13	1
	Constipation	28	0
	Nausea	32	1
	Dyspepsia	11	0
Skin and subcutaneous tissue disorders	Rash	16	2
Musculoskeletal and connective tissue disorders	Muscle spasms	14	0
	Myalgia	14	0
	Arthralgia	14	0
	Back pain	14	1
	Pain in extremity	12	0
General disorders and administration site conditions	Pyrexia	19	1
	Fatigue	43	5
	Asthenia	12	3

	Edema peripheral	30	2
Injury, poisoning and procedural complications	Contusion	18	0

Serious adverse reactions

In the phase 2 study, serious adverse reactions were reported in 60% of patients (treatment-emergent frequencies). Serious adverse reactions that occurred in greater than 2% of patients were atrial fibrillation (6%), pneumonia (5%), urinary tract infection (4%), abdominal pain (3%), subdural hematoma (3%), febrile neutropenia (3%), acute renal failure (3%), peripheral edema (3%), and pyrexia (3%).

Adverse reactions from Study MCL3001 are described below in Table 2 reflecting exposure to IMBRUVICA in patients with MCL who received at least one prior therapy, treated with a median treatment duration of 14.4 months.

Table 2: Adverse reactions reported in patients with MCL treated with 560 mg IMBRUVICA – Study MCL3001 (n=139)

System Organ Class	Adverse Reactions	IMBRUVICA (n=139)		Temsilolimus (n=139)	
		All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection	19	2	12	1
	Pneumonia*	14	10	19	12
Eye disorders	Conjunctivitis	12	0	5	0
Cardiac disorders	Atrial fibrillation	4	4	2	1
Gastrointestinal disorders	Abdominal pain	8	4	8	1
Musculoskeletal and connective tissue disorders	Muscle spasms	19	0	3	0

* Includes multiple adverse reaction terms.

Chronic lymphocytic leukemia

The data described below reflect exposure to IMBRUVICA in a single arm, open-label clinical study (Study PCYC-1102-CA) that included 51 patients and a randomized clinical study (Study PCYC-1112-CA) and three randomized clinical studies (Study PCYC 1115 CA, Study PCYC 1112 CA, and Study CLL3001) in patients with CLL (n=668).

The most commonly occurring adverse reactions in studies PCYC-1102-CA, PCYC-1112-CA, PCYC 1115 CA and CLL3001 ($\geq 20\%$) were diarrhea, neutropenia, rash, musculoskeletal pain, hemorrhage (e.g., bruising), nausea, thrombocytopenia, and pyrexia.

The most common Grade 3/4 adverse reactions ($\geq 5\%$) were: neutropenia, pneumonia, thrombocytopenia and febrile neutropenia.

Discontinuation and dose reduction due to AEs

Six percent of patients receiving IMBRUVICA in studies PCYC-1102-CA, PCYC-1112-CA, PCYC-1115-CA and CLL3001 discontinued treatment due to adverse events. The most frequent adverse reactions leading to treatment discontinuation included pneumonia, atrial fibrillation, rash and hemorrhage. Adverse events leading to dose reduction occurred in approximately 6% of patients.

Patients with previously untreated CLL

Single agent

Adverse reactions described below in Table 3 reflect exposure to IMBRUVICA with a median duration of 17.4 months, which is approximately 2.5 times the median exposure to chlorambucil of 7.1 months in Study PCYC-1115-CA.

Table 3: Adverse reactions reported in previously untreated patients with CLL treated with 420 mg IMBRUVICA - Study PCYC-1115-CA^a

System Organ Class Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations				

Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Neoplasms benign, malignant, and unspecified (including cysts and polyps)				
Basal cell carcinoma	9	1	2	0
Metabolism and nutrition disorders				
Hyponatremia	7	3	1	0
Eye disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Cardiac disorders				
Atrial fibrillation	6	1	1	0
Vascular disorders				
Hypertension*	14	4	1	0
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Dyspepsia	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
General disorders and administrative site conditions				
Peripheral edema	19	1	9	0

^a Subjects with multiple events for a given adverse reaction term are counted once only for each adverse reaction term.

* Includes multiple adverse reaction terms

Patients with CLL who received at least one prior therapy

Single agent

Adverse reactions described in Table 4 below reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median duration of 5.3 months in Study PCYC-1112-CA.

Table 4: Adverse reactions reported in patients with CLL treated with IMBRUVICA as single agent in Study PCYC-1112-CA^a

System Organ Class Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations				
Upper respiratory tract infection	16	1	10	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin infection*	7	2	3	1
Sepsis*	4	2	4	3
Blood and lymphatic system disorders				
Anemia	23	5	17	8
Neutropenia	22	16	15	14
Thrombocytopenia	17	6	12	4
Lymphocytosis	4	2	3	1

Leukocytosis	4	3	1	0
Febrile neutropenia	2	2	3	3
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Eye disorders				
Vision blurred	10	0	3	0
Cardiac disorders				
Atrial fibrillation	5	3	1	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	9	0	3	1
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Bruising*	21	0	4	0
Petechiae	14	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Injury, poisoning and procedural complications				
Subdural hematoma	1	0	0	0

^a Occurring at $\geq 10\%$ incidence and 5% greater in the IMBRUVICA arm when compared to the ofatumumab arm or serious adverse reactions $\geq 2\%$ incidence and 2% greater in the IMBRUVICA arm when compared to the ofatumumab arm or biologically plausible.

* Includes multiple adverse reaction terms.

Patients with multiple events for a given adverse reaction term are counted once only for each adverse reaction term. Events are sorted by system organ class and by decreasing frequency of adverse reaction term in the IMBRUVICA arm.

Long-term safety

The long-term safety data over 5 years from 1178 patients (treatment-naïve CLL n=162, relapsed/refractory CLL n=646, and relapsed/refractory MCL n=370) treated with IMBRUVICA were analyzed. The median duration of treatment for CLL was 51 months (range, 0.2 to 98 months) with 70% and 52% of patients receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for MCL was 11 months (range, 0 to 87 months) with 31% and 17% of patients receiving treatment for more than 2 years and 4 years, respectively. The overall known safety profile of IMBRUVICA-exposed patients remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), 8% (year 2-3), 9% (year 3-4), and 9% (year 4-5). The incidence for the 5-year period was 11%.

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 6). Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the table, the frequencies are provided according to the following convention:

Very common	$\geq 1/10$ ($\geq 10\%$)
Common	$\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)
Uncommon	$\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$)
Rare	$\geq 1/10000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)
Very rare	$< 1/10000$, including isolated reports ($< 0.01\%$)

Not known Cannot be estimated from the available data.

In Table 5, adverse reactions are presented by frequency category based on spontaneous reporting rates and by frequency category based on incidence in clinical trials or epidemiology studies, when known.

Table 5: Adverse reactions identified during postmarketing experience with IMBRUVICA

System Organ Class Adverse Reaction	Frequency Category Estimated from Spontaneous Reporting Rates	Frequency Category Estimated from Clinical Trials with IMBRUVICA
Cardiac disorders		
Ventricular tachyarrhythmias*†	Rare	Common
Cardiac failure*†	Uncommon	Common
Immune system disorders		
Interstitial lung disease*†	Uncommon	Common
Metabolism and nutrition disorders		
Tumor lysis syndrome	Very rare	Common
Hepatobiliary disorders		
Hepatic failure*†	Very rare	Not known
Skin and subcutaneous tissue disorders		
Angioedema	Very rare	Uncommon
Erythema	Very rare	Common
Onychoclasia	Uncommon	Common
Panniculitis*	Rare	Uncommon
Stevens-Johnson syndrome	Rare	Not known
Urticaria	Very rare	Common
Neutrophilic dermatoses*	Rare	Uncommon
Nervous system disorders		
Peripheral neuropathy*	Uncommon	Common
Cerebrovascular accident†	Uncommon	Uncommon
Transient ischemic attack	Rare	Uncommon
Ischemic stroke†	Rare	Rare
Infections and infestations		
Hepatitis B reactivation	Not known	Uncommon

* Includes multiple adverse reaction terms.

† Includes events with fatal outcome.

OVERDOSE

Symptoms and signs

There are limited data on the effects of IMBRUVICA overdose. No Maximum Tolerated Dose was reached in the phase 1 study in which patients received up to 12.5 mg/kg/day (1400 mg/day). In a separate study, one healthy subject who received a dose of 1680 mg experienced reversible Grade 4 hepatic enzyme increases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. There is no specific antidote for IMBRUVICA. Patients who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: **L01EL01**.

Mechanism of action

Ibrutinib is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including MCL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and B-cell CLL. BTK's pivotal role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis and adhesion. Preclinical studies have shown that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

Lymphocytosis

Upon initiation of single agent treatment with IMBRUVICA, a reversible increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute count > 5000/mcL), often associated with reduction of lymphadenopathy, has been

observed in most patients (66%) with CLL. This effect has also been observed in some patients (35%) with MCL treated with IMBRUVICA. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few month of IMBRUVICA therapy and typically resolves within a median of 8.0 weeks in patients with MCL and 14 weeks in patients with CLL (range 0.1 to 104 weeks).

When IMBRUVICA was administered with chemoimmunotherapy, lymphocytosis was infrequent

In vitro platelet aggregation

In an in vitro study, ibrutinib demonstrated inhibition of collagen induced platelet aggregation in samples from the cohorts of subjects with either renal dysfunction, those on warfarin, or healthy subjects. The magnitude of inhibition of collagen-induced platelet aggregation in the cohort of subjects on aspirin was less pronounced since collagen-induced platelet aggregation was already reduced without ibrutinib. Ibrutinib did not show meaningful inhibition of platelet aggregation for the 4 agonists adenosine diphosphate (ADP), arachidonic acid, ristocetin, and thrombin receptor-activating peptide 6 (TRAP 6) across any of these cohorts of subjects or healthy subjects.

Effect on QT/QTc interval and cardiac electrophysiology

The effect of ibrutinib on the QTc interval was evaluated in 20 healthy male and female subjects in a randomized, double blind thorough QT study with placebo and positive controls. At a supratherapeutic dose of 1680 mg, ibrutinib did not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the baseline adjusted mean differences between ibrutinib and placebo was below 10 ms. In this same study, a concentration dependent shortening in the QTc interval was observed (-5.3 ms [90% CI: -9.4, -1.1] at a C_{max} of 719 ng/mL following the supratherapeutic dose of 1680 mg) that was considered not clinically relevant.

Clinical studies

Mantle cell lymphoma

The safety and efficacy of IMBRUVICA in MCL patients who received at least one prior therapy were evaluated in a single open-label, multi-center Phase 2 study (PCYC-1104-CA) of 111 patients. The median age was 68 years (range, 40 to 84 years), 77% were male and 92% were Caucasian. Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 3 or greater were excluded from the study. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 35% with prior high-dose chemotherapy, 43% with prior bortezomib, 24% with prior lenalidomide, and 11% with prior stem cell transplant. At baseline, 39% of patients had bulky disease (≥ 5 cm), 49% had high-risk score by Simplified MCL International Prognostic Index (MIPI), and 72% had advanced disease (extranodal and/or bone marrow involvement) at screening.

IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Responses to IMBRUVICA are shown in Table 6.

Table 6: Overall response rate (ORR) and duration of response (DOR) based on investigator assessment in patients with mantle cell lymphoma

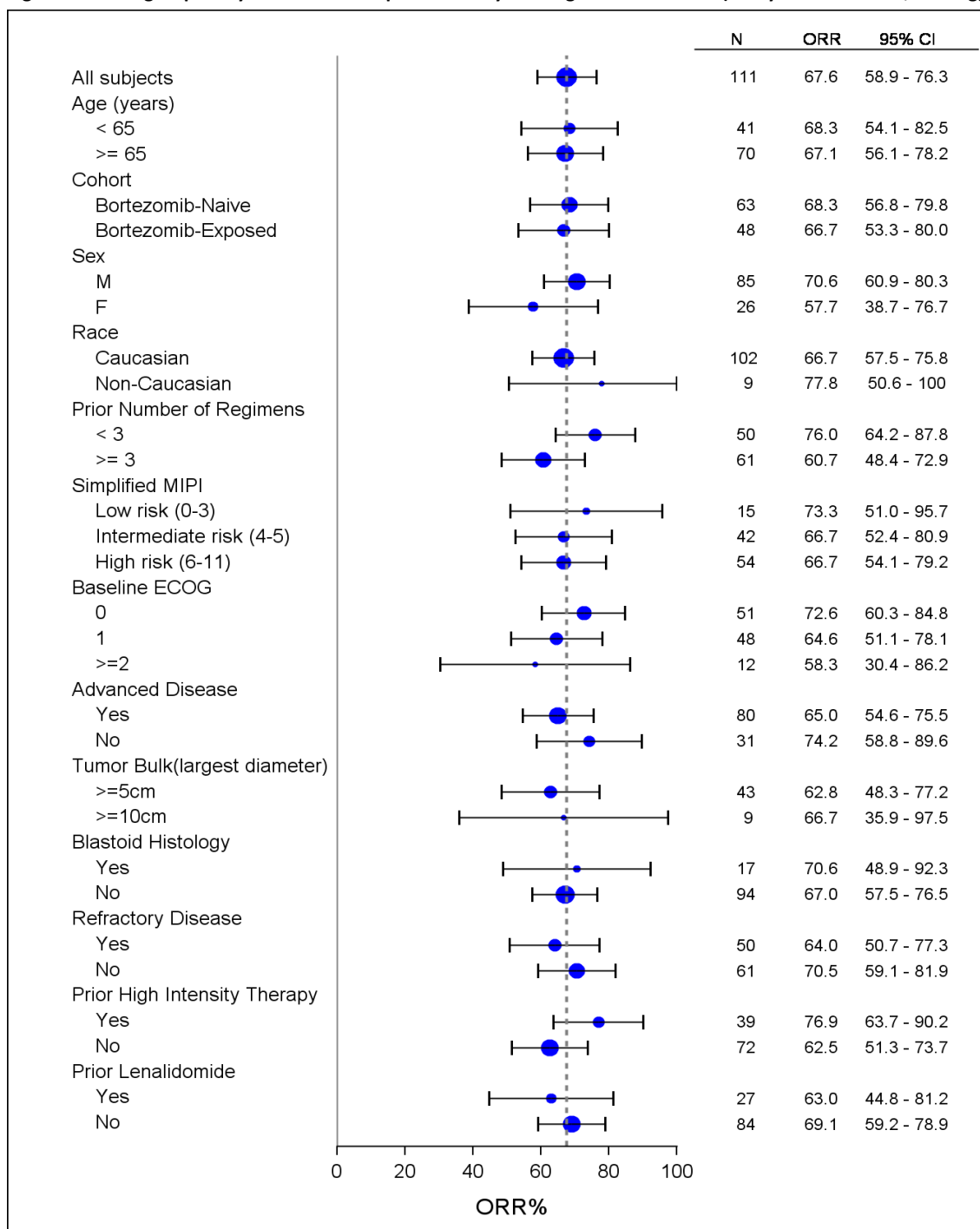
	Total N = 111
ORR (%)	67.6
95% CI (%)	(58.0, 76.1)
CR (%)	20.7
PR (%)	46.8
Median DOR (CR+PR) (months)	17.5 (15.8, NR)
Median Time to Initial Response, months (range)	1.9 (1.4-13.7)
Median Time to CR, months (range)	5.5 (1.7, 11.5)

CI = confidence interval; CR = complete response; PR = partial response; NR = not reached

The efficacy data was further evaluated by an Independent Review Committee (IRC) demonstrating an ORR of 69%, with a 21% CR rate and a 48% PR rate. The IRC estimated median DOR was 19.6 months.

The overall response to IMBRUVICA was independent of prior treatment including bortezomib and lenalidomide or underlying risk/prognosis, bulky disease, gender or age (Figure 1).

Figure 1: Subgroup analysis of overall response rate by investigator assessment (Study PCYC-1104-CA; 560 mg)



The safety and efficacy of IMBRUVICA were demonstrated in a randomized phase 3, open-label, multicenter study including 280 patients with MCL who received at least one prior therapy (Study MCL3001). Patients were randomized 1:1 to receive either IMBRUVICA orally at 560 mg once daily on a 21-day cycle or temsirolimus intravenously at 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle. Treatment on both arms continued until disease progression or unacceptable toxicity. The median age was 68 years (range, 34 to 88 years), 74% were male and 87% were Caucasian. The median time since diagnosis was 43 months, and median number of prior treatments was 2 (range: 1 to 9 treatments), including 51% with prior high-dose chemotherapy, 18% with prior bortezomib, 5% with prior lenalidomide, and 24% with prior stem cell transplant. At baseline, 53% of patients had bulky disease (≥ 5 cm), 21% had high-risk score by Simplified MIPI, 60% had extranodal disease and 54% had bone marrow involvement at screening.

Progression-free survival (PFS) as assessed by IRC according to the revised IWG for non-Hodgkin's lymphoma (NHL) criteria showed a 57% statistically significant reduction in the risk of death or progression for patients in the IMBRUVICA arm. Efficacy results for Study MCL3001 are shown in Table 7 and the Kaplan-Meier curve for PFS in Figure 2.

Table 7: Efficacy results in Study MCL3001

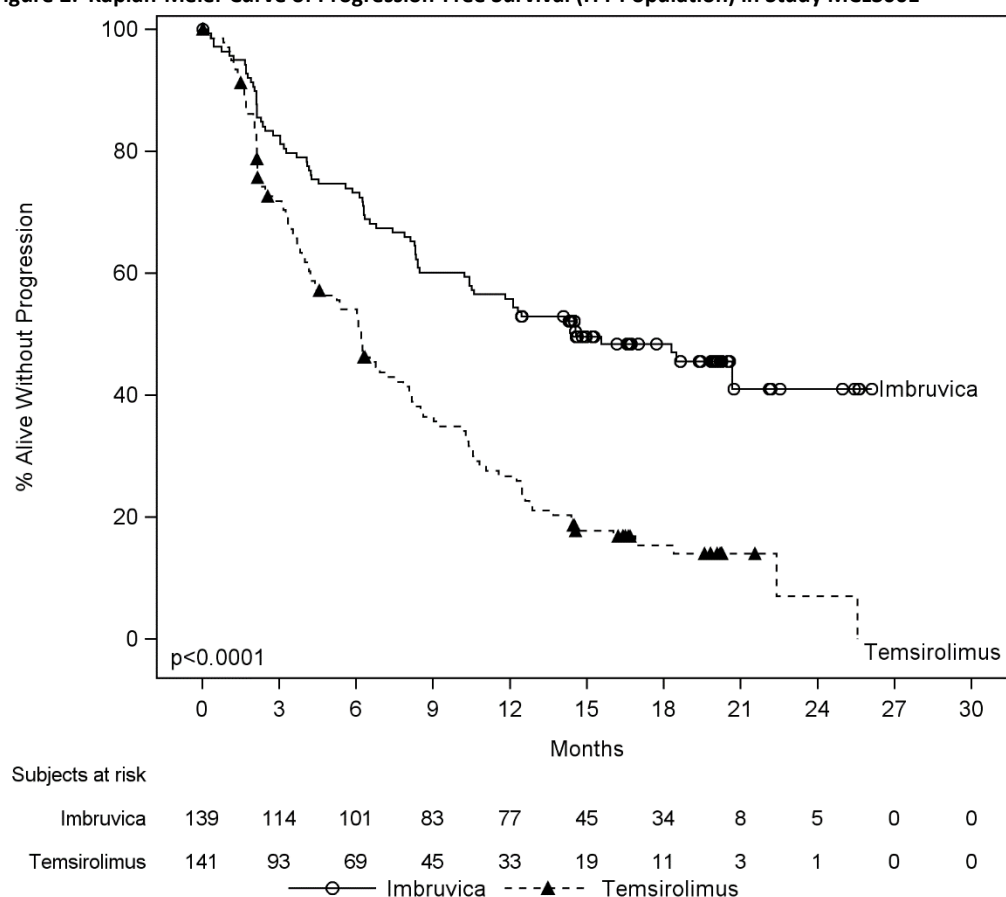
Endpoint	IMBRUVICA N=139	Temsirolimus N=141
Progression-Free Survival^a		
Number of events (%)	73 (52.5)	111 (78.7)
Median Progression-Free Survival (95% CI), months	14.6 (10.4, NE)	6.2 (4.2, 7.9)
HR (95% CI)	0.43 (0.32, 0.58)	
Overall Response Rate (CR+PR)	71.9%	40.4%
p-value	p<0.0001	

NE = not estimable; HR = hazard ratio; CI = confidence interval; CR = complete response; PR = partial response

^a IRC evaluated.

A smaller proportion of patients treated with IMBRUVICA experienced a clinically meaningful worsening of lymphoma symptoms versus temsirolimus (27% versus 52%) and time to worsening of symptoms occurred more slowly with IMBRUVICA versus temsirolimus (HR 0.27, p<0.0001).

Figure 2: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study MCL3001



Chronic lymphocytic leukemia

The safety and efficacy of IMBRUVICA in patients with CLL were demonstrated in one uncontrolled study and two randomized, controlled studies.

Patients with treatment-naïve CLL

Single agent

Study PCYC-1115-CA

A randomized, multicenter, open-label phase 3 study of IMBRUVICA versus chlorambucil was conducted in patients with treatment-naïve CLL who were 65 years of age or older. Patients (n=269) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for a maximum of 12 cycles, with an allowance for inpatient dose increases up to 0.8 mg/kg based on tolerability. After confirmed disease progression, patients on chlorambucil were able to crossover to ibrutinib.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety-one percent of patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and 9% had an ECOG performance status of 2. The study enrolled 269 patients with CLL. At baseline, 45% had advanced clinical stage (Rai Stage III or IV), 35% of patients had at least one tumor ≥ 5 cm, 39% with baseline anemia, 23% with baseline thrombocytopenia, 65% had elevated $\beta 2$ microglobulin > 3500 mcg/L, 47% had a CrCL < 60 mL/min, 20% of patients presented with del 11q, 6% of patients presented with del 17p/tumor protein 53 (TP53) mutation, and 44% of patients presented with unmutated immunoglobulin heavy chain variable region (IGHV).

Progression-free survival (PFS) as assessed by IRC according to IWCLL criteria indicated an 84% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm. With a median follow-up of 18 months, the median PFS was not reached in the ibrutinib arm and was 19 months in the chlorambucil arm. Significant improvement in ORR was observed in the ibrutinib arm (82%) versus the chlorambucil arm (35%). The results from investigator and IRC assessments for PFS and ORR were consistent. Analysis of overall survival (OS) also demonstrated an 84% statistically significant reduction in the risk of death for patients in the IMBRUVICA arm. Efficacy results for Study PCYC-1115-CA are shown in Table 8 and the Kaplan-Meier curves for PFS and OS are shown in Figures 3 and 4, respectively.

There was a statistically significant sustained platelet or hemoglobin improvement in the ITT population in favor of ibrutinib vs. chlorambucil. In patients with baseline cytopenias, sustained hematologic improvement was: platelets 77% versus 43%; hemoglobin 84% versus 45% for ibrutinib and chlorambucil respectively.

Table 8: Efficacy results in Study PCYC-1115-CA

Endpoint	IMBRUVICA N=136	Chlorambucil N=133
Progression-Free Survival ^a		
Number of events (%)	15 (11.0)	64 (48.1)
Median (95% CI), months	Not reached	18.9 (14.1, 22.0)
HR (95% CI)	0.161 (0.091, 0.283)	
Overall Response Rate ^a (CR+PR)	82.4%	35.3%
p-value	<0.0001	
Overall Survival ^b		
Number of deaths (%)	3(2.2)	17 (12.8)
HR (95% CI)	0.163 (0.048, 0.558)	

CI = confidence interval; HR = hazard ratio; CR = complete response; PR = partial response

^a IRC evaluated.

^b Median OS not reached for both arms.

p < 0.005 for OS.

Figure 3: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1115-CA

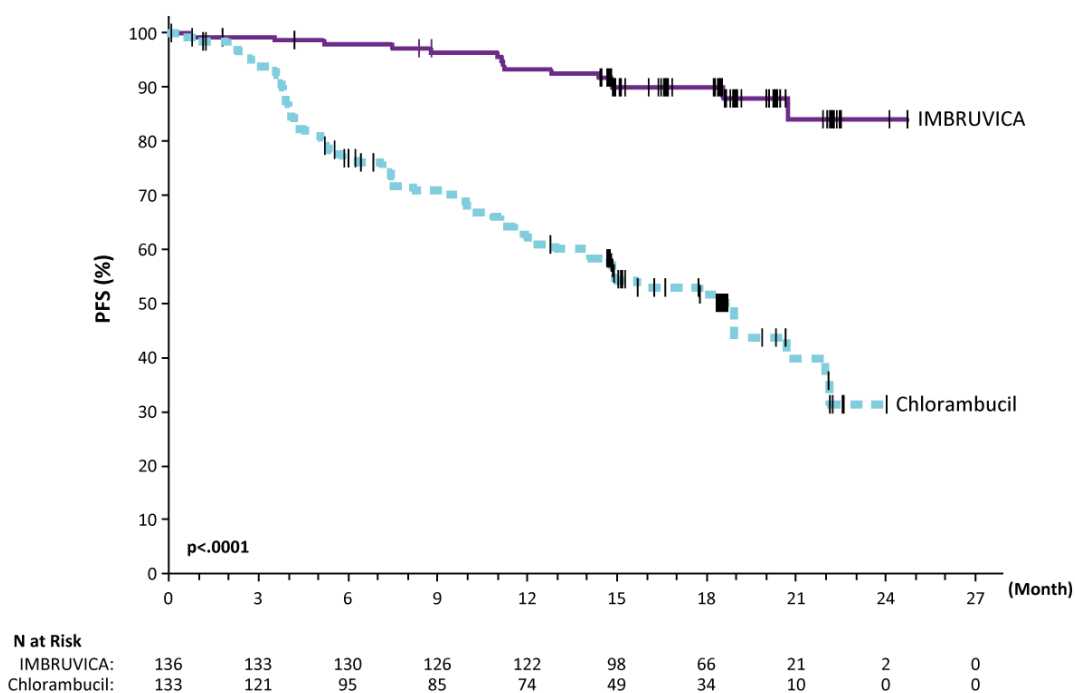
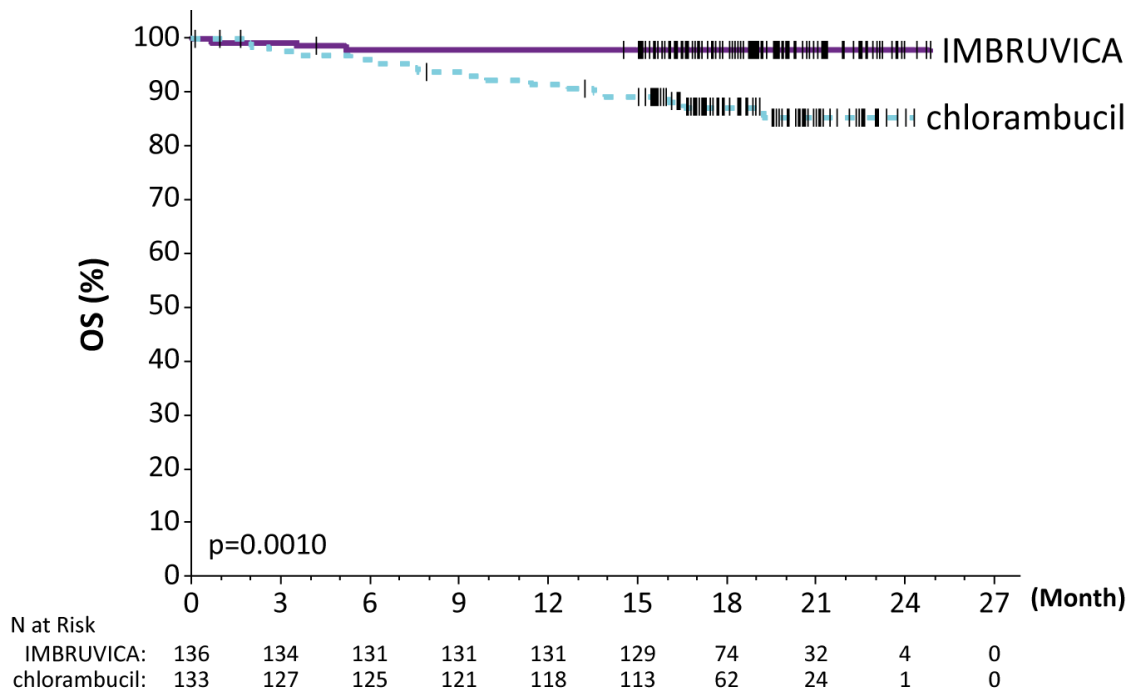


Figure 4: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1115-CA



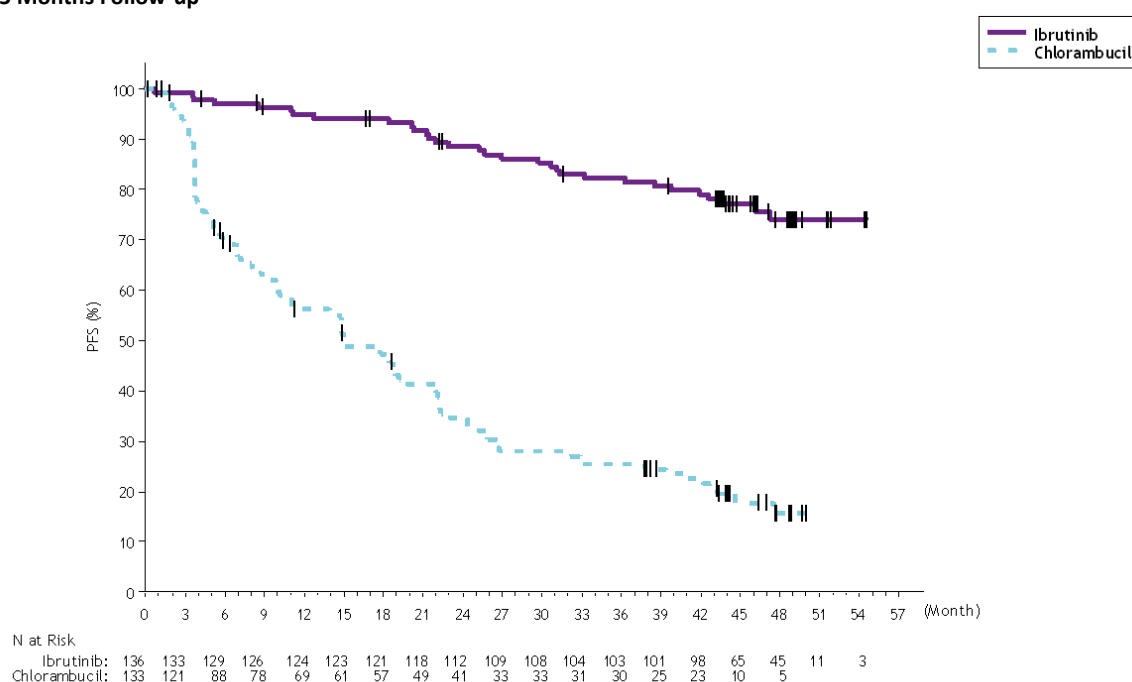
Overall follow-up of 55 months (median of 48 months)

With an overall follow-up of 55 months (median of 48 months) in Study PCYC-1115-CA and its extension study, an 86% reduction in the risk of death or progression by investigator assessment was observed for patients in the IMBRUVICA arm. The median investigator-assessed PFS was not reached in the IMBRUVICA arm and was 15 months [95% CI (10.22, 19.35)] in the chlorambucil arm; (HR = 0.14 [95% CI (0.09, 0.21)]). The 4-year PFS estimate was 73.9% in the IMBRUVICA arm and 15.5% in the chlorambucil arm, respectively. The updated Kaplan-Meier curve for PFS is shown in Figure 5. The investigator-assessed ORR was 91.2% in the IMBRUVICA arm versus 36.8% in the chlorambucil arm. The CR rate according

to IWCLL criteria was 16.2% in the IMBRUVICA arm versus 3.0% in the chlorambucil arm. At the time of long-term follow-up, a total of 73 subjects (54.9%) originally randomized to the chlorambucil arm subsequently received ibrutinib as cross-over treatment. The Kaplan-Meier landmark estimate for OS at 48-months was 85.5% in the IMBRUVICA arm.

The treatment effect of ibrutinib in Study PCYC-1115-CA was consistent across high-risk patients with del 17p/TP53 mutation, del 11q, and/or unmutated IGHV.

Figure 5: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) by Investigator in Study PCYC-1115-CA with 55 Months Follow-up



Patients with CLL who received at least one prior therapy

Single agent

PCYC-1102-CA

An open-label, multi-center study was conducted in 51 patients with CLL who received 420 mg once daily. IMBRUVICA was administered until disease progression or unacceptable toxicity. The median age was 68 (range, 37 to 82 years), median time since diagnosis was 80 months, and median number of prior treatments was 4 (range, 1 to 12 treatments), including 92% with a prior nucleoside analog, 98% with prior rituximab, 86% with a prior alkylator, 39% with prior bendamustine and 20% with prior ofatumumab. At baseline, 39% of patients had Rai Stage IV, 45% had bulky disease (≥ 5 cm), 35% had del 17p, 31% had del 11q.

ORR was investigator-assessed according to the 2008 International Workshop on CLL (IWCLL) criteria. At a median duration of follow up of 16 months, responses to IMBRUVICA for the 51 patients are shown in Table 9.

Table 9: Overall response rate in patients with chronic lymphocytic leukemia treated with 420 mg IMBRUVICA - Study PCYC-1102-CA (N = 51)

ORR (CR+PR) (95% CI) (%)	78.4 (64.7, 88.7)
CR (%)	3.9
PR (%)	74.5
ORR including Partial Response with Lymphocytosis (PRL) (%)	92.2
Median DOR (CR+PR)	NR ¹
Median Time to Initial Response, months (range)	1.8 (1.4, 12.2)

CI = confidence interval; CR = complete response; PR = partial response

¹ 92.5% of responders were censored (i.e., progression free and alive) with a median follow up of 16.4 months.

NR: not reached

The efficacy data were further evaluated using IWCLL criteria by an IRC, demonstrating an ORR of 65% (95% CI: 50%, 78%), all partial responses. The DOR ranged from 4 to 24+ months. The median DOR was not reached.

PCYC-1112-CA

A randomized, multi-center, open-label Phase 3 study of IMBRUVICA versus ofatumumab was conducted in patients with CLL. Patients (n = 391) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or ofatumumab for up to 12 doses (300/2000 mg). Fifty-seven patients randomized to ofatumumab crossed over following progression to receive IMBRUVICA. The median age was 67 years (range, 30 to 88 years), 68% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range, 1 to 13 treatments). At baseline, 58% of patients had at least one tumor ≥ 5 cm. Thirty-two percent of patients had deletion 17p (with 50% of patients having deletion 17p/TP53 mutation), 24% had 11q deletion, and 47% of patients had unmutated IGHV.

Progression free survival (PFS) as assessed by an IRC according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the IMBRUVICA arm. The results from investigator and IRC assessments for PFS were consistent. Analysis of OS demonstrated a 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA arm. Efficacy results for Study PCYC-1112-CA are shown in Table 10.

Table 10: Efficacy results in patients with chronic lymphocytic leukemia (Study PCYC-1112-CA)

Endpoint	IMBRUVICA N=195	Ofatumumab N=196
Progression-Free Survival		
Median Progression-Free Survival, months	Not reached	8.1
HR (95% CI)	0.215 (0.146; 0.317)	
Overall Survival^a		
HR (95% CI)	0.434 (0.238; 0.789) ^b	
HR (95% CI)	0.387 (0.216; 0.695) ^c	
Overall Response Rate^{d,e} (%)	42.6	4.1
Overall Response Rate including Partial Response with Lymphocytosis (PRL)^d (%)	62.6	4.1

HR = hazard ratio; CI = confidence interval; PR = partial response

^a Median OS not reached for both arms.

^b Patients randomized to ofatumumab who progressed were censored when starting ibrutinib if applicable.

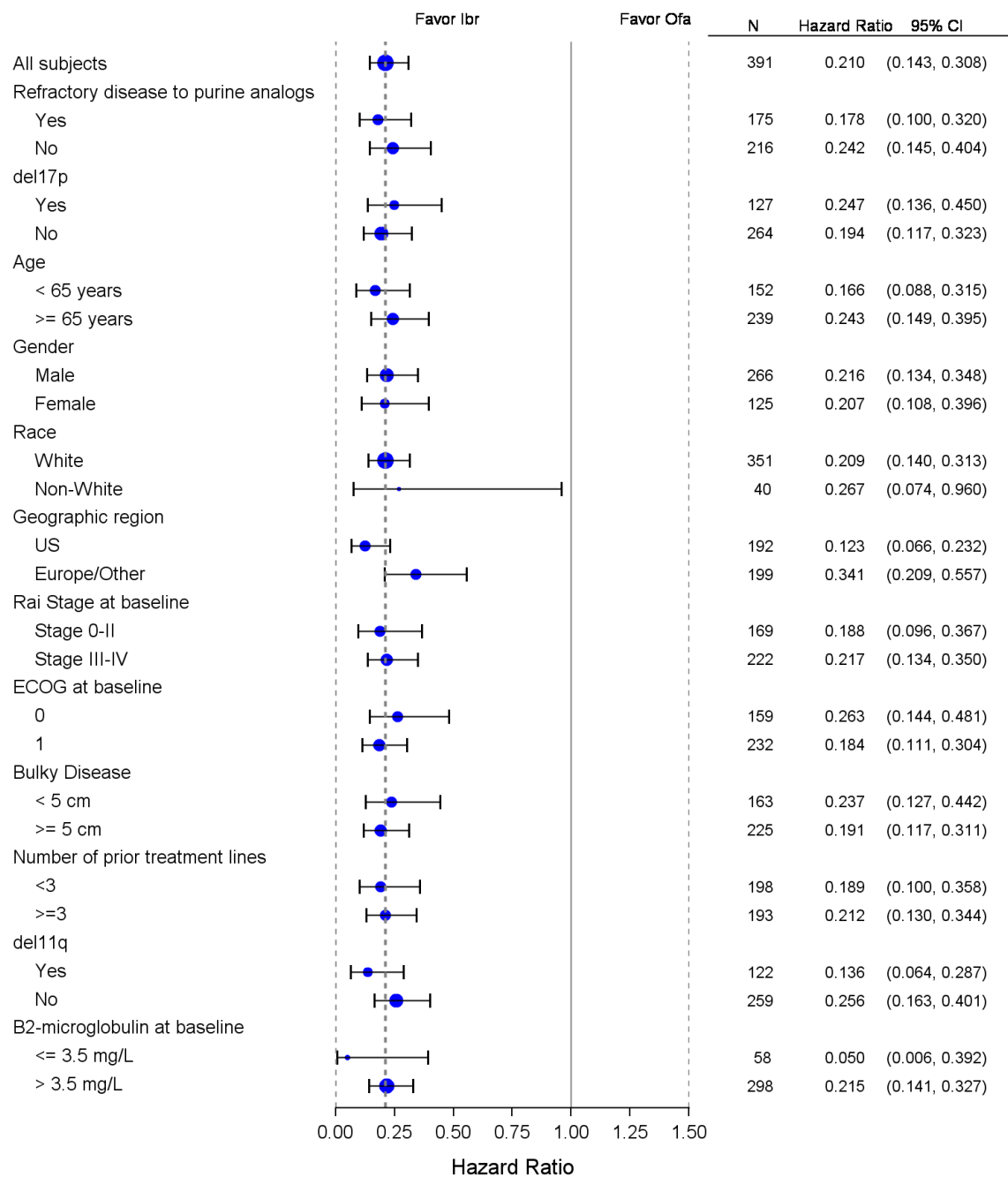
^c Sensitivity analysis in which crossover patients from the ofatumumab arm were not censored at the date of first dose of IMBRUVICA.

^d Per IRC. Repeat CT scans required to confirm response.

^e All PRs achieved. $p < 0.0001$ for ORR.

The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (Figure 6).

Figure 6: Subgroup analysis of progression free survival by IRC (Study PCYC-1112; 420 mg)



The Kaplan Meier curves for PFS and OS are shown in Figures 7 and 8, respectively.

Figure 7: Kaplan Meier curve of progression free survival (ITT Population) in study PCYC 1112 CA

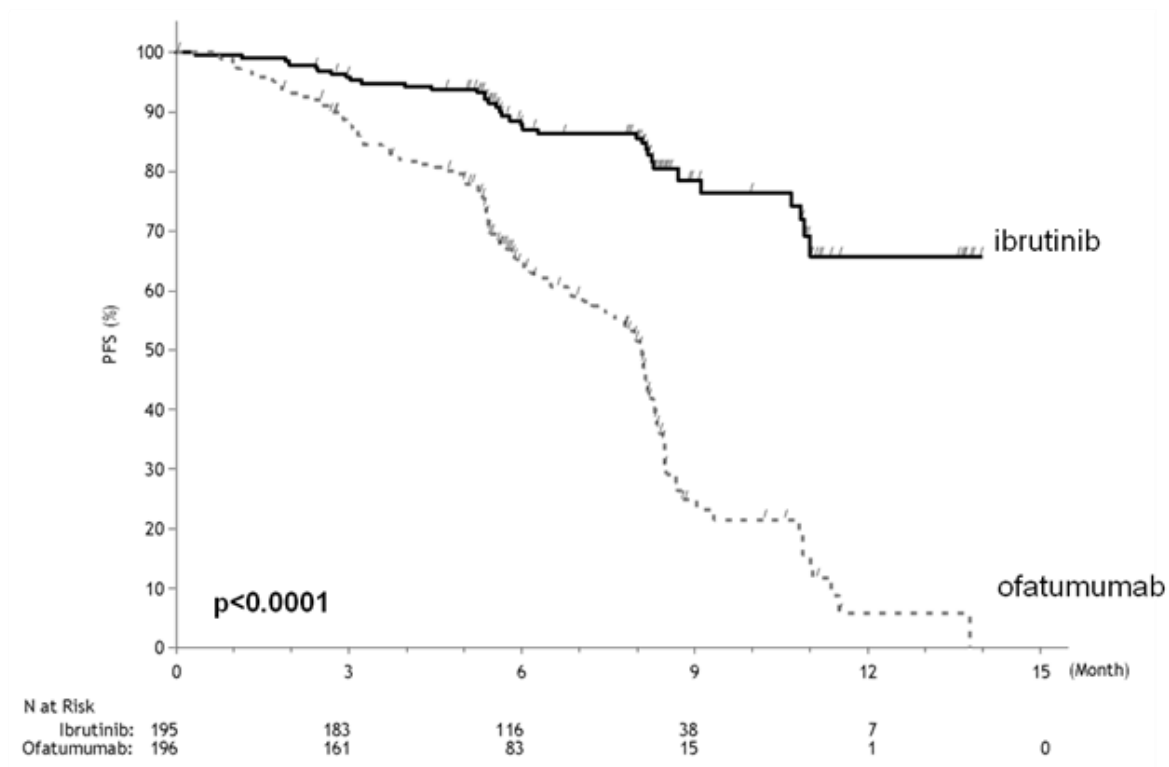
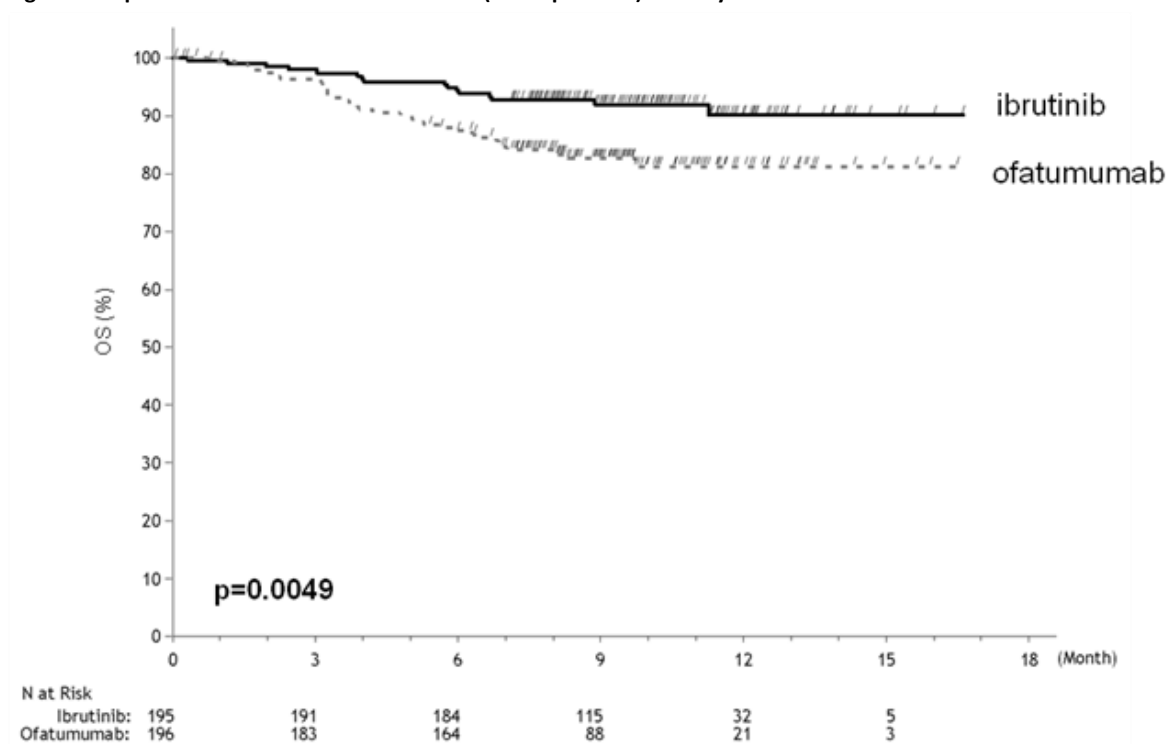


Figure 8: Kaplan-Meier curve of overall survival (ITT Population) in study PCYC-1112-CA

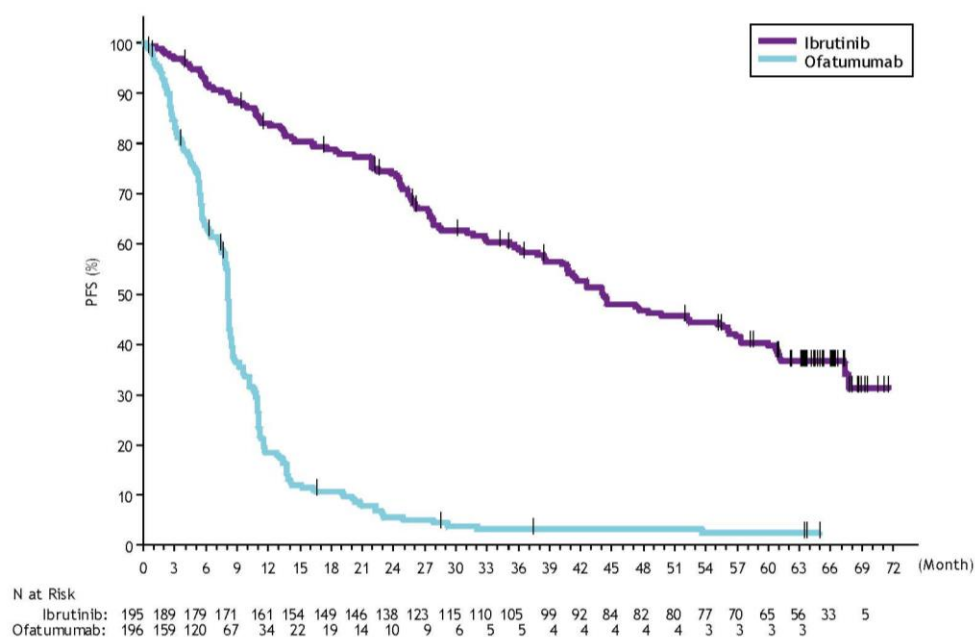


Final analysis at 65-month Follow-up

With median follow-up time on study of 65 months in Study PCYC-1112-CA, an 85% reduction in the risk of death or progression by investigator assessment was observed for patients in the IMBRUVICA arm. The median investigator-assessed PFS according to IWCLL criteria was 44.1 months [95% CI (38.47, 56.18)] in the IMBRUVICA arm and 8.1 months [95% CI (7.79, 8.25)] in the ofatumumab arm, respectively; HR = 0.15 [95% CI (0.11, 0.20)]. The updated Kaplan-Meier curve for PFS is shown in Figure 9. The investigator-assessed ORR in the IMBRUVICA arm was 87.7% versus 22.4% in the

ofatumumab arm. At the time of final analysis, 133 (67.9%) of the 196 subjects originally randomized to the ofatumumab treatment arm had crossed over to ibrutinib treatment. The median investigator-assessed PFS2 (time from randomization until PFS event after first subsequent anti-neoplastic therapy) according to IWCLL criteria was 65.4 months [95% CI (51.61, not estimable)] in the IMBRUVICA arm and 38.5 months [95% CI (19.98, 47.24)] in the ofatumumab arm, respectively; HR=0.54 [95% CI (0.41, 0.71)]. The median OS was 67.7 months [95% CI (61.0, not estimable)] in the IMBRUVICA arm. The treatment effect of ibrutinib in Study PCYC-1112-CA was consistent across high-risk patients with del 17p/TP53 mutation, del 11q, and/or unmutated IGHV.

Figure 9: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) by Investigator in Study PCYC-1112-CA at Final Analysis with 65 Months Follow-up



CLL with deletion 17p

Study PCYC-1112-CA included 127 patients with CLL with deletion 17p. The median age was 67 years (range, 30 to 84 years), 62% were male, and 88% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. PFS and ORR were assessed by IRC. Efficacy results for CLL with deletion 17p are shown in Table 11.

Table 11: Efficacy results in patients with CLL with deletion 17p

Endpoint	IMBRUVICA N=63	Ofatumumab N=64
Progression-Free Survival		
Median Progression-Free Survival, months	Not reached	5.8
HR (95% CI)	0.25 (0.14; 0.45)	
Overall Response Rate^a	47.6%	4.7%
Overall Response Rate including PRL	66.7%	4.7%

^a IRC evaluated. All partial responses achieved; none of the patients achieved a complete response.

HR = hazard ratio; CI = confidence interval; PRL = partial response with lymphocytosis

Overall follow-up of 63 months (median of 56 months)

With an overall follow-up of 63 months (median of 56 months) in Study PCYC-1112-CA, the median investigator-assessed PFS in patients with del 17p according to IWCLL criteria was 40.6 months [95% CI (25.36, 44.55)] in the IMBRUVICA arm and 6.2 months [95% CI (4.63, 8.11)] in the ofatumumab arm, respectively; HR = 0.12, ([95% CI (0.07, 0.21)]. The investigator-assessed ORR in patients with del 17p in the IMBRUVICA arm was 88.9% versus 18.8% in the ofatumumab arm.

Pharmacokinetic Properties

Absorption

Ibrutinib is rapidly absorbed after oral administration with a median T_{max} of 1 to 2 hours. Absolute bioavailability in fasted condition ($n = 8$) was 2.9% (90% CI = 2.1 – 3.9) and doubled when combined with a meal. Pharmacokinetics of ibrutinib does not significantly differ in patients with different B-cell malignancies. Ibrutinib exposure increases with doses up to 840 mg. The steady state AUC observed in patients at 560 mg is (mean $\pm$ standard deviation) 953 ± 705 ng·h/mL and in patients at 420 mg with CLL is 732 ± 521 ng·h/mL (680 ± 517 ng·h/mL in subset of R/R patients). Administration of ibrutinib in fasted condition resulted in approximately 60% of exposure (AUC_{last}) as compared to either 30 minutes before, 30 minutes after (fed condition) or 2 hours after a high fat breakfast.

Distribution

Reversible binding of ibrutinib to human plasma protein *in vitro* was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution (V_d) was 683 L and the apparent volume of distribution at steady state ($V_{d,ss}/F$) is approximately 10000 L.

Metabolism

Ibrutinib is metabolized primarily by cytochrome P450, CYP3A4/5, to produce a prominent dihydrodiol metabolite with an inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. Systemic steady-state exposure to the dihydrodiol metabolite is comparable to that of the parent drug.

In vitro studies indicated that CYP2D6 involvement in ibrutinib oxidative metabolism is < 2%. Moreover, as part of the human mass balance study, subjects genotyped as poor metabolizers for CYP2D6, showed a similar pharmacokinetic profile as extensive metabolizers. Therefore, no precautions are necessary in patients with different CYP2D6 genotypes.

Elimination

Intravenous clearance was 62 and 76 L/h in fasted and fed condition, respectively. In line with the high first-pass effect, the apparent oral clearance is approximately 2000 and 1000 L/h in fasted and fed condition, respectively. The half-life of ibrutinib is 4 to 6 hours.

After a single oral administration of radiolabeled [^{14}C] ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

Special populations

Elderly (65 years of age and older)

Population pharmacokinetics indicated that in older patients (67 to 81 years), a 14% higher ibrutinib exposure is predicted. Dose adjustment by age is not warranted.

Pediatrics (18 years of age and younger)

No pharmacokinetic studies were performed with IMBRUVICA in patients under 18 years of age.

Gender

Population pharmacokinetics data indicated that gender does not significantly influence ibrutinib clearance from the circulation.

Renal impairment

Ibrutinib has minimal renal clearance; urinary excretion of metabolites is < 10% of the dose. No specific clinical studies have been conducted to date in subjects with impaired renal function. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There are no data in patients with severe renal impairment or patients on dialysis.

Hepatic impairment

Ibrutinib is metabolized in the liver. A hepatic impairment trial was performed in non-cancer subjects administered a single dose of 140 mg of IMBRUVICA under fasting conditions. Ibrutinib AUC_{last} increased 2.7-, 8.2- and 9.8-fold in subjects with mild ($n=6$; Child-Pugh class A), moderate ($n = 10$; Child-Pugh class B) and severe ($n = 8$; Child-Pugh class C) hepatic impairment, respectively. The free fraction of ibrutinib also increased with degree of impairment, with 3.0, 3.8 and 4.8% in subjects with mild, moderate and severe liver impairment, respectively, compared to 3.3% in plasma from matched healthy controls within this study. The corresponding increase in unbound ibrutinib exposure ($AUC_{unbound,last}$) is estimated to be 4.1-, 9.8-, and 13-fold in subjects with mild, moderate, and severe hepatic impairment, respectively.

NON-CLINICAL INFORMATION

The following adverse effects were seen in studies up to 13-weeks duration in rats and dogs. Ibrutinib was found to induce gastrointestinal effects (soft feces/diarrhea and/or inflammation) in rats at human equivalent doses (HEDs) ≥ 16 mg/kg/day and in dogs at HEDs ≥ 32 mg/kg/day. Effects on lymphoid tissue (lymphoid depletion) were also induced at HEDs ≥ 28 mg/kg/day in rats and ≥ 32 mg/kg/day in dogs. In rats, moderate pancreatic acinar cell atrophy was observed at HEDs ≥ 6 mg/kg/day. Mildly decreased trabecular and cortical bone was seen in rats administered HEDs ≥ 16 mg/kg/day for 13 weeks. All notable findings in rats and dogs fully or partially reversed following recovery periods of 6 to 13 weeks.

Carcinogenicity and Mutagenicity

Ibrutinib was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse at oral doses up to 2000 mg/kg/day resulting in exposures approximately 23 (males) to 37 (females) times higher than the exposure in humans at a dose of 560 mg daily.

Ibrutinib has no genotoxic properties when tested in bacteria, mammalian cells or in mice.

In pregnant rats, ibrutinib at a dose of 80 mg/kg/day was associated with increased post-implantation loss and increased visceral (heart and major vessels) malformations and skeletal variations with an exposure margin 14 times the AUC found in patients at a daily dose of 560 mg. At a dose of ≥ 40 mg/kg/day, ibrutinib was associated with decreased foetal weights (AUC ratio of ≥ 5.6 as compared to daily dose of 560 mg in patients). Consequently, the foetal NOAEL was 10 mg/kg/day (approximately 1.3 times the AUC of ibrutinib at a dose of 560 mg daily).

In pregnant rabbits, ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal malformations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased post-implantation loss. Ibrutinib caused malformations in rabbits at a dose of 15 mg/kg/day (approximately 2.0 times the exposure (AUC) in patients with MCL administered ibrutinib 560 mg daily and 2.8 times the exposure in patients with CLL or WM receiving ibrutinib dose 420 mg per day). Consequently, the foetal NOAEL was 5 mg/kg/day (approximately 0.7 times the AUC of ibrutinib at a dose of 560 mg daily).

Fertility

No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (HED 16 mg/kg/day).

PHARMACEUTICAL INFORMATION

List of Excipients

Capsules

IMBRUVICA capsules contain the following excipients:

croscarmellose sodium,
magnesium stearate,
microcrystalline cellulose,
sodium lauryl sulfate.

The capsule shell contains gelatin and titanium dioxide (E171).

Black Printing Ink:

iron oxide black (E172)
propylene glycol
shellac glaze

Incompatibilities

Not applicable

Shelf Life

Shelf-life before opening: 24 months.

Shelf-life after opening: 45 days

Storage Conditions

Keep out of the sight and reach of children.

Store below 30°C.

Nature and Contents of Container

Capsules

IMBRUVICA capsules are supplied in a white high-density polyethylene (HDPE) bottle with a child-resistant closure.

Each HDPE bottle with a polypropylene closure contains 90 hard capsules.

Not all pack sizes may be marketed.

Instructions for Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

HOW SUPPLIED

Imbruvica capsule 140 mg
Box, 1 bottle @ 90 capsules
Reg. No.: DKI1951100101A1

HARUS DENGAN RESEP DOKTER

Manufactured by Catalent CTS, LLC 10245 Hickman Mills Drive, Kansas City, MO, 64137, USA
Primary and secondary Packaged by AndersonBrecon Inc 4545 Assembly Drive, Rockford, IL 61109 USA
Finish batch released by Janssen Supply Group, LLC, 200 Tournament Drive Horsham, PA 19044 USA
Imported and distributed by PT Soho Industri Pharmasi
Jl. Pulogadung No. 6, Kawasan Industri Pulogadung, Jakarta 13920 – Indonesia - (021) 460-5550
For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or Phone (021) 2935-3935

Based on CCDS **v.30 11Dec2020**