janssen

IMBRUVICA®
Ibrutinib tablets

DOSAGE FORMS AND STRENGTHS

Film-coated tablets

140mg tablets

IMBRUVICA tablets contain 140 mg of ibrutinib.
Yellow-green to green round film-coated tablet debossed with “ibr” on one side and “140” on the other.

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 or in combination with rituximab or obinutuzumab 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.

Waldenström’s macroglobulinemia (WM)

IMBRUVICA as a single agent is indicated for the treatment of adult patients with Waldenström’s macroglobulinaemia (WM) who have received at least one prior therapy. IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with WM.

DOSAGE AND ADMINISTRATION

Dosage

IMBRUVICA should be administered orally once daily with a glass of water at approximately the same time each day. The tablets should be swallowed whole with water. Do not break or chew the tablets. 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) and Waldenström’s macroglobulinemia (WM)

The recommended dose for the treatment of CLL and WM, either as a single agent or in combination, is 420 mg (three tablets) once daily (for details of the combination regimens, see *Pharmacodynamic properties).*
Treatment should continue until disease progression or no longer tolerated by the patient.
When administering IMBRUVICA in combination with anti-CD20 therapies, it is recommended to administer IMBRUVICA prior to anti-CD20 therapy when given on the same day.

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 2 cardiac failure, Grade 3 cardiac arrhythmias. 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), resume IMBRUVICA therapy at the recommended dose as per the tables below.

Recommended dose modifications for non-cardiac events are described below:

Events[†]	**Toxicity occurrence**	**MCL dose modification after recovery**	**CLL/WM dose modification after recovery**
Grade 3 or 4 non-hematological toxicities Grade 3 or 4 neutropenia with infection or fever Grade 4 hematological toxicities	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 at 140 mg daily
	Fourth	discontinue IMBRUVICA	
[†] Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria, or International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for hematologic toxicities in CLL. [*] When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg.			

Recommended dose modifications for events of cardiac failure or cardiac arrhythmias are described below:

Events	**Toxicity occurrence**	**MCL dose modification after recovery**	**CLL/WM dose modification after recovery**
Grade 2 cardiac failure	First	restart at 420 mg daily	restart at 280 mg daily
	Second	restart at 280 mg daily	restart at 140 mg daily
	Third	discontinue IMBRUVICA	
Grade 3 cardiac arrhythmias	First	restart at 420 mg daily[†]	restart at 280 mg daily[†]
	Second	discontinue IMBRUVICA	
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	discontinue IMBRUVICA	
[†] Evaluate the benefit-risk before resuming treatment.			

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 doses 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. For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily. 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 (> 400000/mcL) may confer increased risk. Consider temporarily with holding 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) have occurred in patients treated with IMBRUVICA. Patients should be monitored for signs and symptoms (such as fever, chills, weakness and confusion) 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.

Hepatic events

Cases of hepatotoxicity, hepatitis B reactivation, and cases of hepatitis E, which may be chronic, have occurred in patients treated with IMBRUVICA. Hepatic failure, including fatal events, has occurred in patients treated with IMBRUVICA. Liver function status should be assessed before initiating treatment with IMBRUVICA. Patients should be monitored for signs and symptoms (such as vomiting and jaundice) and periodically for changes in liver function parameters during treatment. As clinically indicated, viral load and serological testing for infectious hepatitis should be performed per local medical guidelines. For patients diagnosed with hepatic events, consider consulting a liver disease expert for management.

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 arrhythmia and cardiac failure
Fatal and serious cardiac arrhythmias or cardiac failure have occurred in patients treated with IMBRUVICA. Patients with significant cardiac co-morbidities may be at greater risk of events, including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia and cardiac failure have been reported, particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia.

Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating IMBRUVICA. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns. Consider the risks and benefits of IMBRUVICA treatment and follow the dose modification guidelines.

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.

Cerebrovascular accidents
Cases of cerebrovascular accident, transient ischaemic attack and ischaemic stroke including fatalities have been reported in patients treated with IMBRUVICA, with and without concomitant atrial fibrillation and/or hypertension. Among cases with reported latency, the initiation of treatment with IMBRUVICA to the onset of ischaemic central nervous vascular conditions was in the most cases after several months (more than 1 month in 78% and more than 6 months in 44% of cases) emphasising the need for regular monitoring of patients.

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 $AUC_{0\text{-last}}$) 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 (≥ 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 (PCYC-1112-CA, PCYC-1115-CA, PCYC-1130-CA, MCL3001, PCYC-1127-CA, and E1912), the incidence of non-melanoma skin cancer was 6% in IMBRUVICA-treated patients and 2% in comparator-treated patients.

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

Elderly
Of the 1552 patients treated with IMBRUVICA, 52% were 65 years of age or older. Grade 3 or higher pneumonia occurred more frequently (≥5%) among elderly patients treated with IMBRUVICA (12% of patients ≥ 65 years of age versus 5% of patients <65 years of age) and thrombocytopenia (12% of patients ≥ 65 years of age versus 6% 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 (≥ 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 (≥ 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 ≥ 10% of patients with MCL treated with 560 mg IMBRUVICA – Study 1104 (N = 111)

		Frequency	
System Organ Class	**Adverse Reaction**	**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 Stomatitis Constipation Nausea Dyspepsia	23 13 28 32 11	0 1 0 1 0
Skin and subcutaneous tissue disorders	Rash	16	2
Musculoskeletal and connective tissue disorders	Muscle spasms Myalgia Arthralgia Back pain Pain in extremity	14 14 14 14 12	0 0 0 1 0
General disorders and administration site conditions	Pyrexia Fatigue Asthenia Edema peripheral	19 43 12 30	1 5 3 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)

		IMBRUVICA (n=139)		**Temsirolimus (n=139)**	
System Organ Class	**Adverse Reactions**	**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) and four randomized clinical studies (Study PCYC-1115-CA, Study PCYC-1112-CA, PCYC-1130-CA and E1912) in patients with CLL (n=1133).

The most commonly occurring adverse reactions in studies PCYC-1102-CA, PCYC-1112-CA, PCYC 1115 CA and PCYC-1130-CA and E1912 (≥ 20%) were diarrhea, neutropenia, musculoskeletal pain, rash, thrombocytopenia, hemorrhage (e.g., bruising), nausea, lymphocytosis, pyrexia, arthralgia, headache, upper respiratory tract infection, and hypertension.

The most common Grade 3/4 adverse reactions (≥ 5%) were: neutropenia, lymphocytosis, thrombocytopenia, hypertension, pneumonia, and leukocytosis.

Discontinuation and dose reduction due to AEs
Six percent of patients receiving IMBRUVICA in studies PCYC-1102-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1130-CA and E1912 discontinued treatment due to adverse events. The most frequent adverse reactions leading to treatment discontinuation included pneumonia, atrial fibrillation, arthralgia, neutropenia, rash, thrombocytopenia, and hemorrhage. Adverse events leading to dose reduction occurred in approximately 8% 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]

	IMBRUVICA (N=135)		Chlorambucil (N=132)	
System Organ Class **Adverse Reaction**	**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

Combination therapy
Adverse reactions described below in Table 4 reflect exposure to IMBRUVICA + obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median duration of 5.1 months in Study PCYC-1130-CA.

Table 4: Adverse reactions reported in previously untreated patients with CLL treated with IMBRUVICA in combination with obinutuzumab in Study PCYC-1130-CA[a]

	IMBRUVICA + Obinutuzumab (N=113)		**Chlorambucil + Obinutuzumab (N=115)**	
System Organ Class Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Blood and lymphatic system disorders				
Thrombocytopenia*	36	19	28	11
Skin and subcutaneous tissue disorders				
Rash*	36	3	11	0
Bruising*	32	3	3	0
Gastrointestinal disorders				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
Respiratory, thoracic and mediastinal disorders				
Cough	27	1	12	0
Vascular disorders				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3
Infections and infestations				
Pneumonia*	16	9	9	3
Upper respiratory tract infection	14	1	6	0
Skin infection*	13	1	3	0
Urinary tract infection	12	3	7	1
Conjunctivitis	11	0	2	0
Metabolism and nutrition disorders				
Hyperuricemia	13	1	0	0
Cardiac disorders				

Atrial fibrillation	12	5	0	0
General disorders and administration site conditions				
Peripheral edema	12	0	7	0
Psychiatric disorders				
Insomnia	12	0	4	0

[a] Occurring at ≥10% incidence and ≥2% greater in the IMBRUVICA + obinutuzumab arm when compared to the chlorambucil + obinutuzumab arm

* Includes multiple adverse reaction terms

Events are sorted by system organ class and by decreasing frequency of adverse reaction term in the IMBRUVICA + obinutuzumab arm.

In Study E1912, with a median exposure duration of 34.3 months for IR and 4.7 months for FCR, safety data were consistent with the known safety profile of IMBRUVICA.

Adverse reactions described below in Table 5 reflect exposure to IMBRUVICA in combination with rituximab (IR) or received fludarabine, cyclophosphamide, and rituximab (FCR) with a median duration of 34.3 months for IR and 4.7 months for FCR in Study E1912.

Table 5: Adverse reactions reported in previously untreated patients with CLL treated with IMBRUVICA in combination with Rituximab in Study E1912

	IMBRUVICA + Rituximab (N=352) (%)		**Fludarabine + Cyclophosphamide + Rituximab (N=158) (%)**	
System Organ Class Adverse Drug Reaction Term	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Gastrointestinal disorders				
Diarrhea	53	4	27	1
Nausea	40	1	64	1
Stomatitis*	22	1	8	1
Vomiting	18	2	28	0
Constipation	17	0	32	0
Abdominal pain	16	1	9	1
Dyspepsia	14	0	3	0
Gastroesophageal reflux disease	13	0	6	0
General disorders and administration site conditions				
Fatigue	80	2	78	3
Edema peripheral	28	1	17	0
Pyrexia	27	1	27	1
Pain	23	2	8	0
Chills	11	<1	17	1
Infections and infestations				
Upper respiratory tract infection	29	1	19	2
Skin infection*	16	1	3	1
Pneumonia*	11	3	6	3
Investigations				
Blood creatinine increased	36	1	20	1
Metabolism and nutrition disorders				

Hyperuricemia	18	1	4	0
Decreased appetite	15	0	20	1
Hypokalemia	13	1	11	1
Hypoalbuminemia	11	0	8	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	61	5	35	2
Arthralgia	41	5	9	1
Muscle spasms	12	0	1	0
Nervous system disorders				
Headache	40	1	27	1
Dizziness	21	1	13	1
Neuropathy peripheral*	19	1	13	1
Psychiatric disorders				
Insomnia	16	1	19	1
Anxiety	14	<1	10	0
Respiratory, thoracic and mediastinal disorders				
Cough	32	<1	25	0
Dyspnea	22	2	21	1
Oropharyngeal pain	13	<1	5	0
Nasal congestion	12	0	7	0
Skin and subcutaneous tissue disorders				
Rash*	49	4	29	5
Bruising*	36	1	4	1
Pruritus	13	<1	8	0
Dry skin	11	<1	6	0
Vascular disorders				
Hypertension*	42	19	22	6
Hemorrhage*	31	2	8	1

* Includes multiple adverse reaction terms

Table 6: Treatment-Emergent* Hematologic Laboratory Abnormalities reported in previously untreated patients with CLL treated with IMBRUVICA in combination with Rituximab in Study E1912

	IMBRUVICA + Rituximab (N=352)		**Fludarabine + Cyclophosphamide + Rituximab (N=158)**	
	All Grades	**Grade 3 or 4**	**All Grades**	**Grade 3 or 4**
Neutrophils decreased (%)	53	30	70	44
Platelets decreased (%)	43	7	69	25
Hemoglobin decreased (%)	26	0	51	2

* Based on laboratory measurements per iwCLL criteria grade (iwCLL: International Workshop on Chronic Lymphocytic. Leukemia)

Treatment-emergent Grade 4 thrombocytopenia (3% in the IMBRUVICA + Rituximab arm and 9% in the Fludarabine + Cyclophosphamide + Rituximab arm) and neutropenia (15% in the IMBRUVICA + Rituximab arm and 22% in the Fludarabine + Cyclophosphamide + Rituximab arm) occurred in subjects.

Patients with CLL who received at least one prior therapy

Single agent

Adverse reactions described in Table 7 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 7: Adverse reactions reported in patients with CLL treated with IMBRUVICA as single agent in Study PCYC-1112-CA[a]

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
System Organ Class **Adverse Reaction**	**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 ≥10% incidence and 5% greater in the IMBRUVICA arm when compared to the ofatumumab arm or serious adverse reactions ≥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.

Waldenström's macroglobulinemia (WM)

The data described below reflect exposure to IMBRUVICA in an open-label clinical study that included 63 patients with previously treated WM (PCYC-1118E) and a randomized phase 3 clinical study in 75 patients with treatment-naïve or previously treated WM (PCYC-1127-CA). Study PCYC-1127-CA also had an additional monotherapy arm of 31 patients with previously treated WM who failed prior rituximab-containing therapy. The safety profile of patients included in the PCYC-1127-CA monotherapy arm is consistent with the overall known WM safety profile for IMBRUVICA-exposed patients.

The most commonly occurring adverse reactions in the WM studies (PCYC-1118E and PCYC-1127-CA) (≥ 20%) were hemorrhage (e.g., bruising), diarrhea, musculoskeletal pain, rash, nausea, and neutropenia.

The most common Grade 3/4 adverse reactions (≥ 5%) were: neutropenia, pneumonia, hypertension, atrial fibrillation, and thrombocytopenia.

Discontinuation and dose reduction due to ARs

Four percent of patients receiving IMBRUVICA in the WM studies (PCYC-1118E and PCYC-1127-CA) discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 11% of patients.

Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study PCYC-1118E.

Table 8: Adverse reactions reported in ≥10% of patients with WM treated with 420 mg IMBRUVICA - Study 1118E (N=63)

System Organ Class	Adverse Reaction	All Grades (%)	Grades 3-4 (%)

Infections and infestations	Sinusitis	19	0
	Upper respiratory tract infection	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin cancer*	11	0
Blood and lymphatic system disorders	Neutropenia	25	17
	Thrombocytopenia	17	13
	Anemia	16	3
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
General disorders and administration site conditions	Fatigue	21	0

* Includes multiple adverse reaction terms.

Adverse reactions from Study PCYC-1127-CA are described below in Table 9 reflecting exposure to IMBRUVICA + rituximab with a median duration of 25.8 months and exposure to placebo + rituximab with a median duration of 15.5 months in patients with treatment-naïve or previously treated WM.

Table 9: Adverse reactions reported in patients with WM treated with IMBRUVICA in combination with Rituximab in Study PCYC-1127-CA[a]

	IMBRUVICA + R (N=75)		**Placebo + R (N=75)**	
System Organ Class **Adverse Reaction Term**	**All Grades %**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
Skin and subcutaneous tissue disorders				
Bruising*	37	1	5	0
Rash*	24	1	11	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	35	4	21	3
Arthralgia	24	3	11	1
Muscle spasms	17	0	12	1
Vascular disorders				
Hemorrhage*	32	3	17	3
Hypertension*	20	13	5	4
Gastrointestinal disorders				
Diarrhea	28	0	15	1
Nausea	21	0	12	0
Dyspepsia	16	0	1	0
Constipation	13	1	11	1

Infections and infestations				
Pneumonia*	19	13	5	3
Skin infection*	17	3	3	0
Urinary tract infection	13	0	0	0
Bronchitis	12	3	7	0
Influenza	12	0	7	1
Viral upper respiratory tract infection	11	0	7	0
General disorders and administration site conditions				
Peripheral edema	17	0	12	1
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	11	0
Blood and lymphatic system disorders				
Neutropenia*	16	12	11	4
Cardiac disorders				
Atrial fibrillation	15	12	3	1
Nervous system disorders				
Dizziness	11	0	7	0
Psychiatric disorders				
Insomnia	11	0	4	0
Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1

[a] Occurring at ≥10% incidence and ≥2% greater in the IMBRUVICA + rituximab arm when compared to the placebo + rituximab arm

Events are sorted by system organ class and by decreasing frequency of adverse reaction term in the IMBRUVICA + rituximab arm.

* Includes multiple adverse reaction terms

Grade 3 or 4 infusion-related reactions were observed in 1% of patients treated with IMBRUVICA + rituximab and 16% of patients treated with placebo + rituximab.

Long-term safety

The safety data from long-term treatment with IMBRUVICA over 5 years from 1284 patients (treatment-naïve CLL n=162, relapsed/refractory CLL n=646, relapsed/refractory MCL n=370, and WM n=106) 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 median duration of treatment for WM was 47 months (range, 0.3 to 61 months) with 78% and 46% 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), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5). The overall 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 10). 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 ≥ 1/10 (≥ 10%)
Common ≥ 1/100 and < 1/10 (≥ 1% and < 10%)

Uncommon	≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
Rare	≥ 1/10000 and < 1/1000 (≥ 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 10, 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 10: 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
Eye Disorders		
Eye hemorrhage	Uncommon	Uncommon
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	Uncommon
Hepatobiliary disorders		
Hepatic failure*†	Uncommon	Not known
Skin and subcutaneous tissue disorders		
Angioedema	Very rare	Uncommon
Erythema	Very rare	Common
Onychoclasis	Uncommon	Common
Panniculitis*	Rare	Uncommon
Stevens-Johnson syndrome	Rare	Not known
Urticaria	Very rare	Common
Neutrophilic dermatoses*	Rare	Uncommon
Cutaneous vasculitis	Very rare	Rare
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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions via:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079

Website: https://e-meso.pom.go.id/ADR

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 an 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 month of IMBRUVICA therapy and typically resolves within a median of 8 weeks in patients with MCL and 14 weeks in patients with CLL (range 0.1 to 104 weeks).

When IMBRUVICA was administered with chemoimmunotherapy, in combination with obinutuzumab in subjects with CLL, lymphocytosis was infrequent (7% with IMBRUVICA + obinutuzumab versus 1% with chlorambucil + obinutuzumab).

Lymphocytosis was not observed in patients with WM treated with IMBRUVICA.

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 11.

Table 11: Overall response rate (ORR) and duration of response (DOR) based on investigator assessment in patients with mantle cell lymphoma

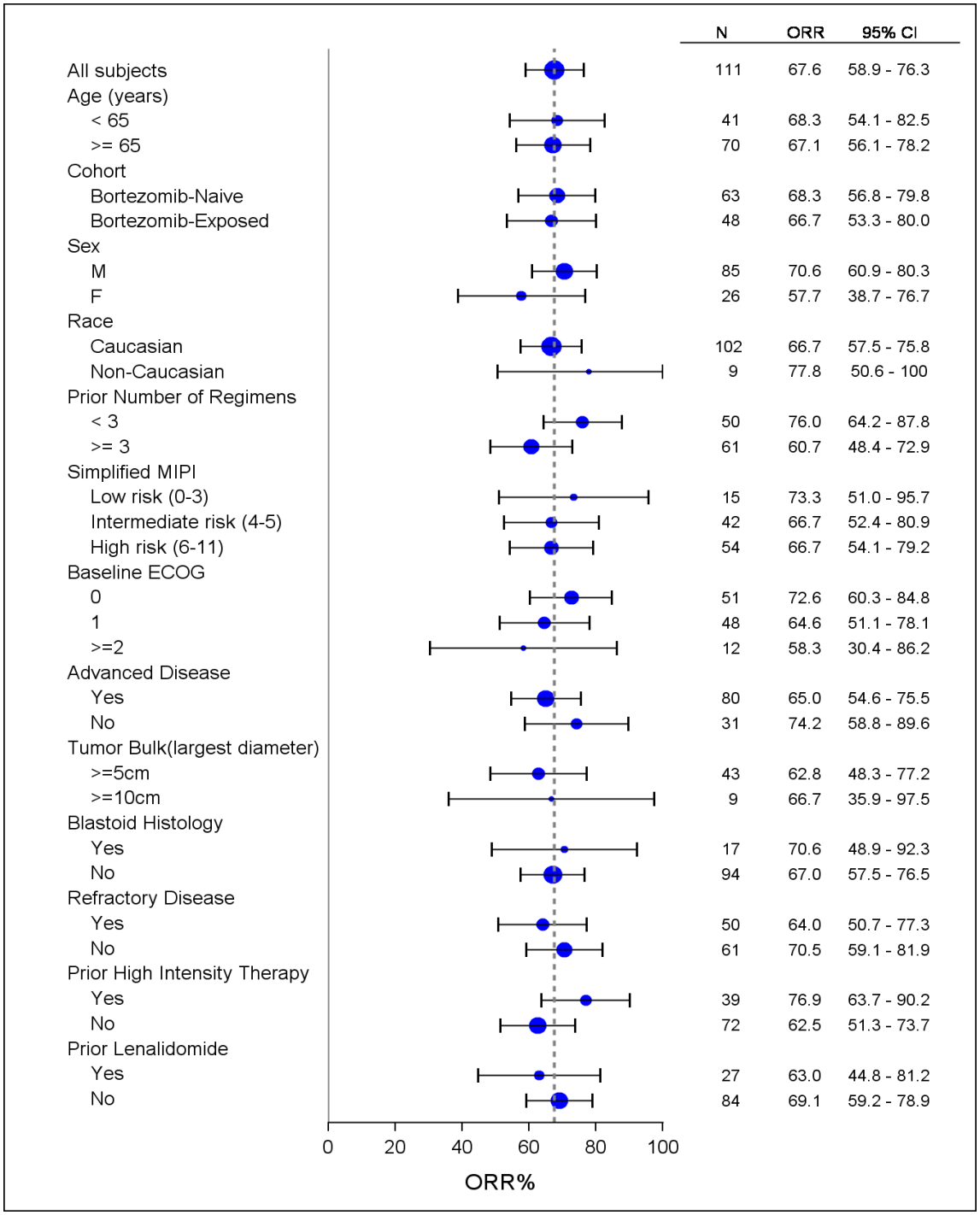
	Total N = 111
ORR (%)	67.6
95% CI (%)	(58.0, 76.1)
CR (%)	20.7
PR (%)	46.8
Median DOR (CR+PR) (months)	17.5 (15.8, NR)
Median Time to Initial Response, months (range)	1.9 (1.4-13.7)
Median Time to CR, months (range)	5.5 (1.7, 11.5)

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 12 and the Kaplan-Meier curve for PFS in Figure 2.

Table 12: Efficacy results in Study MCL3001

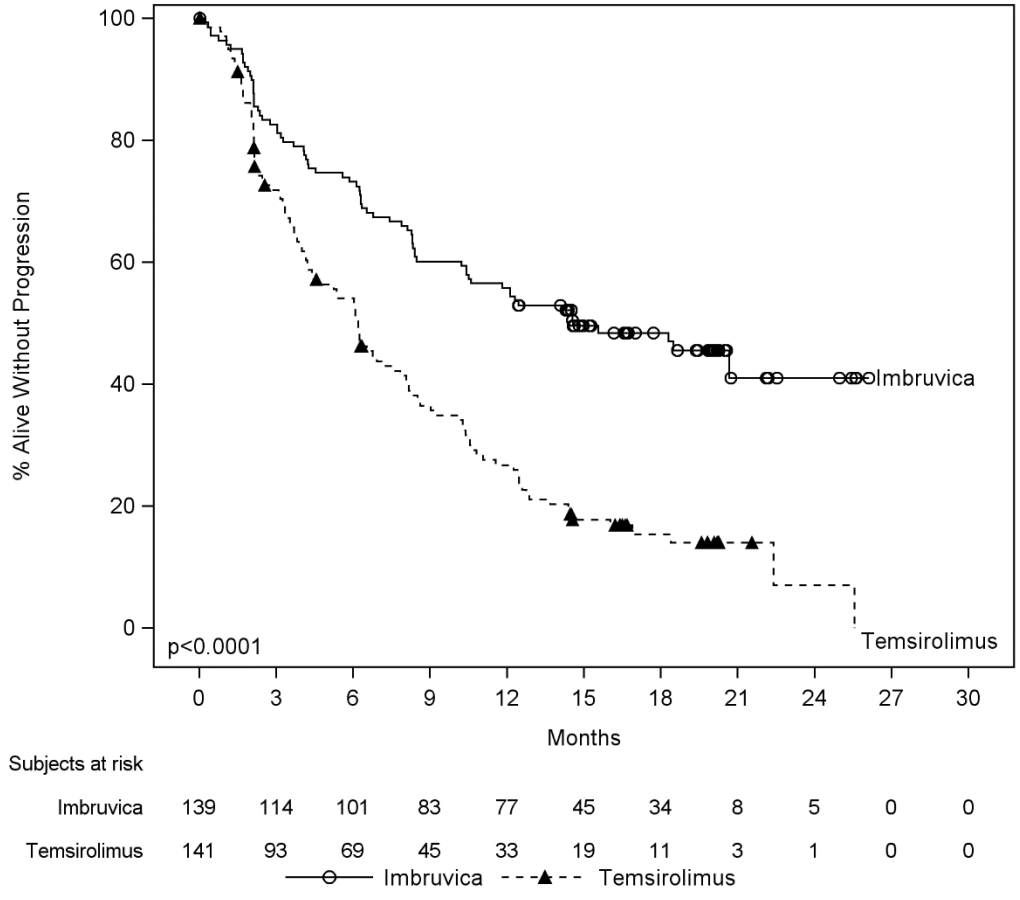
Endpoint	IMBRUVICA N=139	Temsirolimus N=141
Progression-Free Survival[a]		
Number of events (%)	73 (52.5)	111 (78.7)
Median Progression-Free Survival (95% CI), months	14.6 (10.4, NE)	6.2 (4.2, 7.9)
HR (95% CI)	0.43 (0.32, 0.58)	
Overall Response Rate (CR+PR)	71.9%	40.4%
p-value	p<0.0001	

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 five 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 intrapatient 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 β2 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 13 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 13: 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

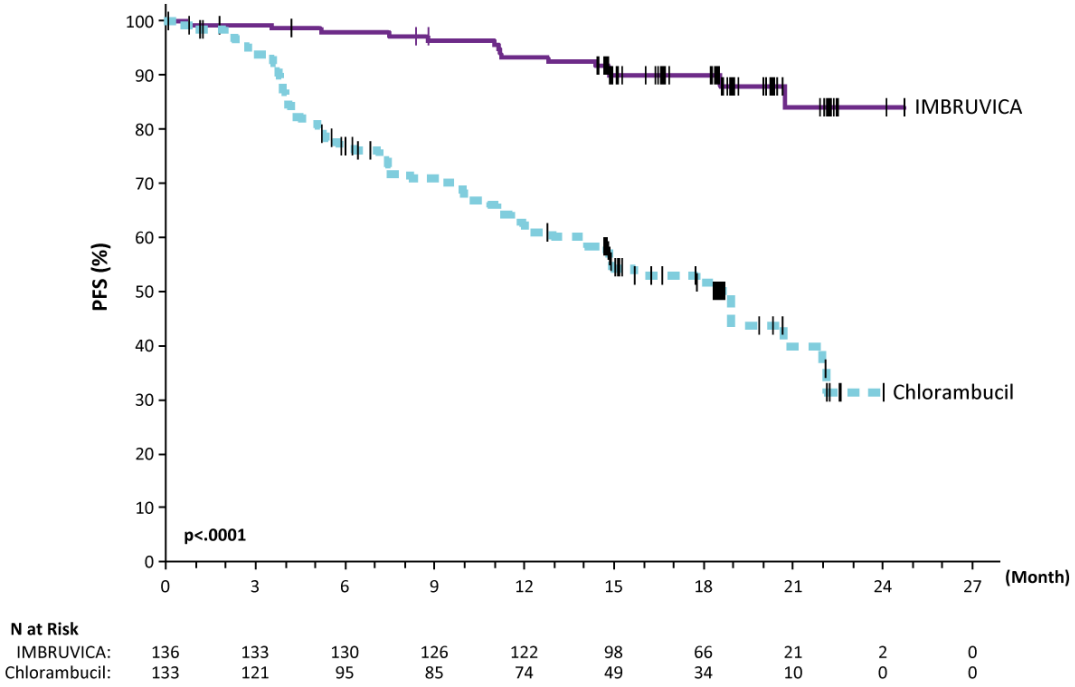
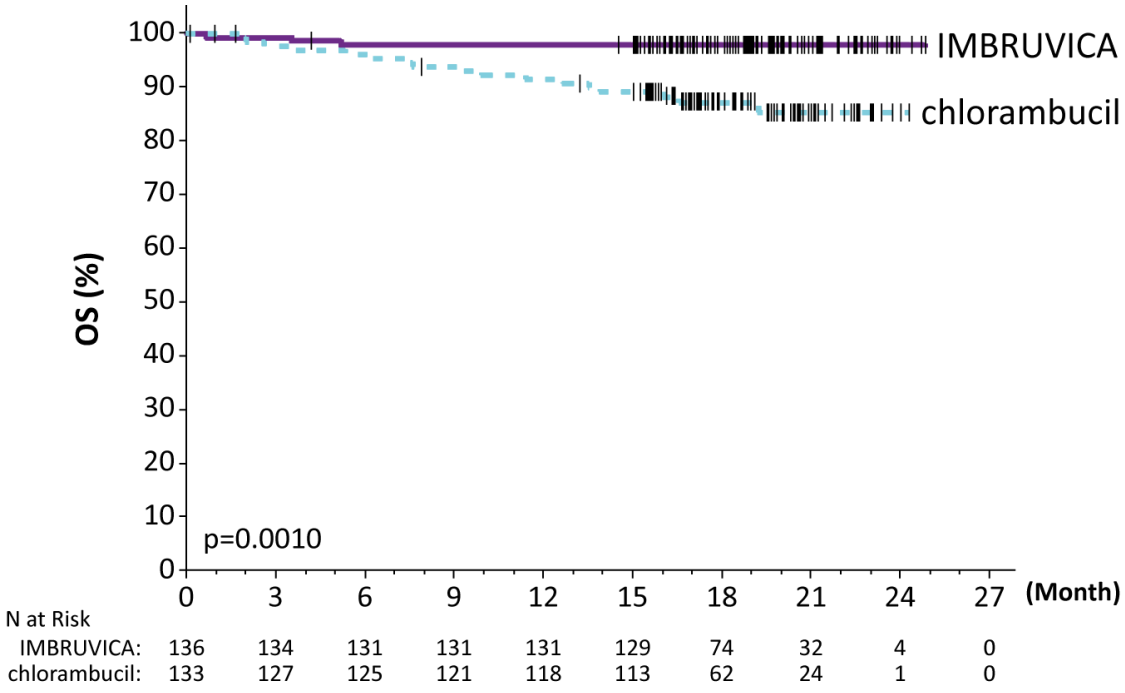


Figure 4:Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1115-CA



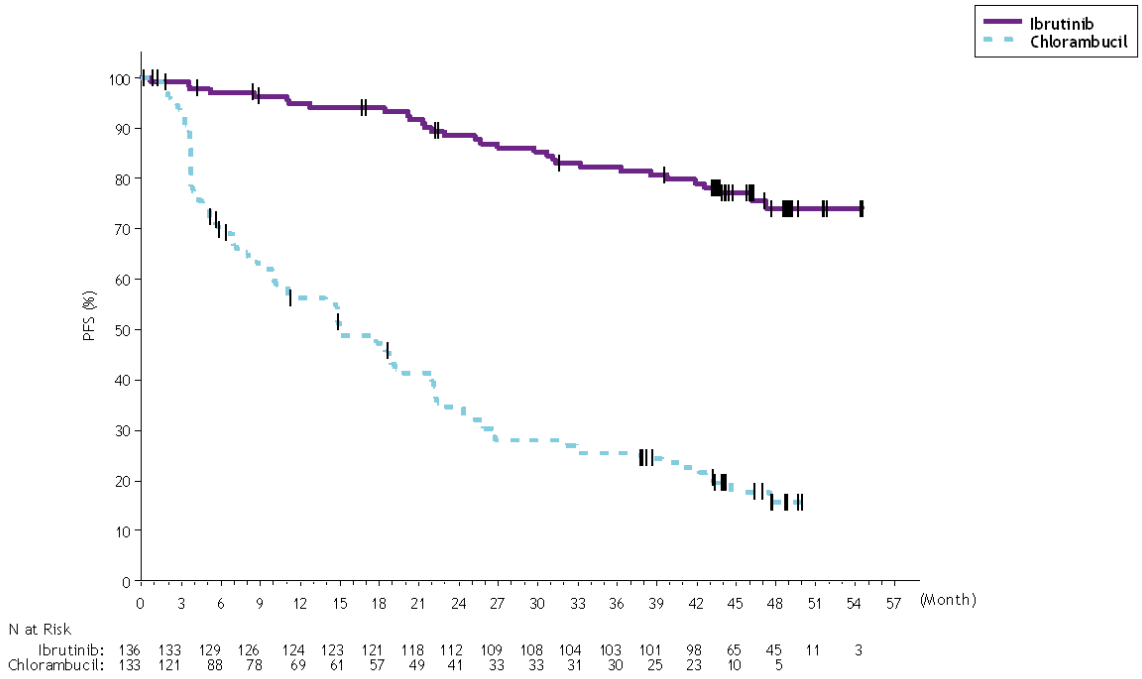
Overall follow-up of 55 months (median of 48 months)

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



Combination therapy
Study PCYC-1130-CA

A randomized, multi-center, open-label, phase 3 study of IMBRUVICA in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab was conducted in patients with treatment naïve CLL. The study enrolled patients who were 65 years of age or older or < 65 years of age with coexisting medical conditions, reduced renal function as measured by creatinine clearance <70 mL/min, or presence of del 17p/TP53 mutation. Patients (n=229) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity or chlorambucil at a dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for 6 cycles. In both arms, patients received 1000 mg of obinutuzumab on Days 1, 8 and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of obinutuzumab was divided between day 1 (100 mg) and day 2 (900 mg).

The median age was 71 years (range, 40 to 87 years), 64% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (48%) or 1-2 (52%). At baseline, 52% had advanced clinical stage (Rai Stage III or IV), 32% of patients had bulky disease (≥ 5 cm), 44% with baseline anemia, 22% with baseline thrombocytopenia, 28% had a CrCL < 60 mL/min, and the median Cumulative Illness Rating Score for Geriatrics (CIRS-G) was 4 (range, 0 to 12). At baseline, 65% of patients presented with CLL with high risk factors (del 17p/TP53 mutation [18%], del 11q [15%], or unmutated IGHV [54%]).

Progression-free survival (PFS) as assessed by IRC according to IWCLL criteria indicated a 77% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm. With a median follow-up time on study of 31 months, the median PFS was not reached in the IMBRUVICA + obinutuzumab arm and was 19 months in the chlorambucil + obinutuzumab arm. The results from investigator and IRC assessments for PFS and ORR were consistent.

Efficacy results for Study PCYC-1130-CA are shown in Table 14 and the Kaplan-Meier curve for PFS is shown in Figure 6.

Table 14: Efficacy results in Study PCYC-1130-CA

Endpoint	IMBRUVICA + Obinutuzumab N=113	Chlorambucil + Obinutuzumab N=116
Progression Free Survival[a]		
Number of events (%)	24 (21.2)	74 (63.8)
Median (95% CI), months	Not reached	19.0 (15.1, 22.1)
HR (95% CI)	0.23 (0.15, 0.37)	
Overall Response Rate[a] (%)	88.5	73.3
CR[b]	19.5	7.8
PR[c]	69.0	65.5

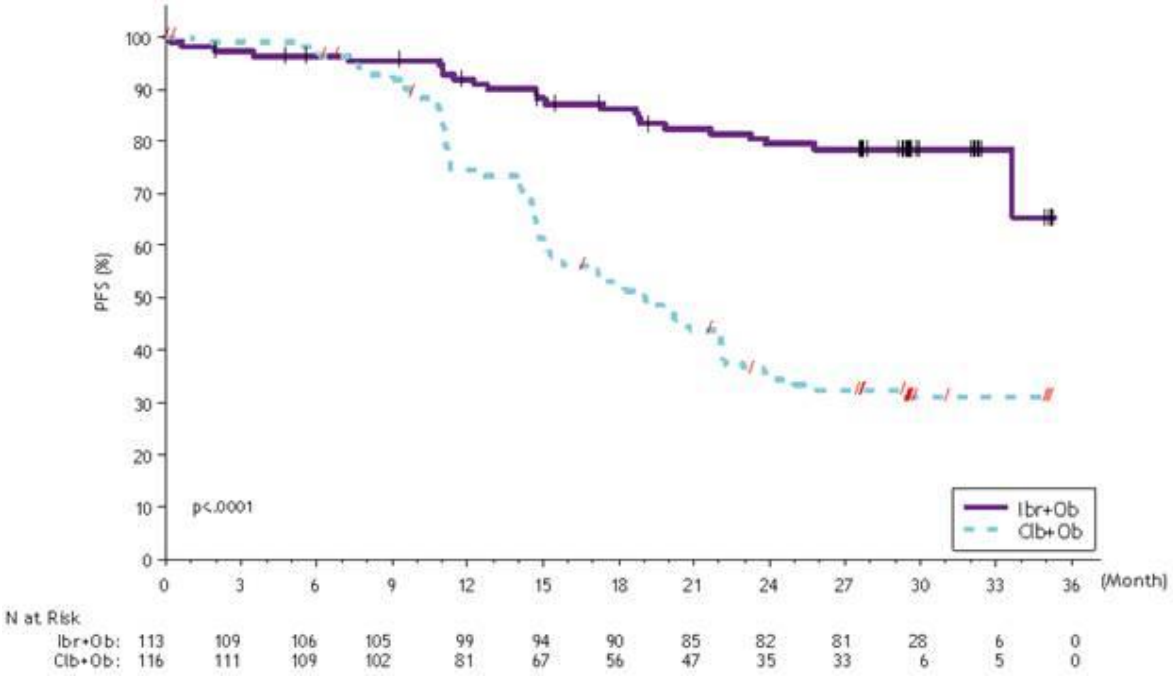
CI = confidence interval; HR = hazard ratio; CR = complete response; PR = partial response.

[a] IRC evaluated.

[b] Includes 1 patient in the IMBRUVICA + obinutuzumab arm with a complete response with incomplete marrow recovery (CRi).

[c] PR = PR + nPR.

Figure 6:Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1130-CA



The treatment effect of ibrutinib was consistent across the high-risk CLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), with a PFS HR of 0.15 [95% CI (0.09, 0.27)], as shown in Table 15. The 2-year PFS rate estimates for the high-risk CLL population were 78.8% [95% CI (67.3, 86.7)] and 15.5% [95% CI (8.1, 25.2)] in the IMBRUVICA + obinutuzumab and chlorambucil + obinutuzumab arms, respectively.

Table 15: Subgroup Analysis of PFS (Study PCYC-1130-CA)

	N	Hazard Ratio	95% CI
All subjects	229	0.231	0.145, 0.367
High risk (del17p/TP53/del11q/unmutated IGHV)			
Yes	148	0.154	0.087, 0.270
No	81	0.521	0.221, 1.231
Del17p/TP53			
Yes	41	0.109	0.031, 0.380
No	188	0.275	0.166, 0.455
FISH			
Del17p	32	0.141	0.039, 0.506
Del11q	35	0.131	0.030, 0.573
Others	162	0.302	0.176, 0.520
Unmutated IGHV			
Yes	123	0.150	0.084, 0.269
No	91	0.300	0.120, 0.749
Age			
< 65	46	0.293	0.122, 0.705
≥ 65	183	0.215	0.125, 0.372
Bulky disease			
< 5 cm	154	0.289	0.161, 0.521
≥ 5 cm	74	0.184	0.085, 0.398
Rai stage			
0/I/II	110	0.221	0.115, 0.424
III/IV	119	0.246	0.127, 0.477
ECOG per CRF			
0	110	0.226	0.110, 0.464
1-2	119	0.239	0.130, 0.438

Hazard ratio based on non-stratified analysis

Any grade infusion-related reactions were observed in 25% of patients treated with IMBRUVICA + obinutuzumab and 58% of patients treated with chlorambucil + obinutuzumab. Grade 3 or higher or serious infusion-related reactions were observed in 3% of patients treated with IMBRUVICA + obinutuzumab and 9% of patients treated with chlorambucil + obinutuzumab.

Study E1912

A randomized, multicenter, open-label, safety and efficacy, phase 3 study of IMBRUVICA in combination with rituximab versus standard fludarabine, cyclophosphamide, and rituximab [FCR] chemoimmunotherapy was conducted in patients with treatment naïve CLL who were 70 years or younger. Patients (n=529) were randomized 2:1 to receive either IR or FCR. IMBRUVICA was administered at 420 mg daily until disease progression or unacceptable toxicity. Fludarabine was administered at a dose of 25 mg/m^2, and cyclophosphamide was administered at a dose of 250 mg/m^2, both on Days 1, 2, and 3 of Cycles 1-6. Rituximab was initiated in Cycle 2 for the IR arm and in Cycle 1 for the FCR arm and was administered at 50 mg/m^2 on Day 1 of the first cycle, 325 mg/m^2 on Day 2 of the first cycle, and 500 mg/m^2 on Day 1 of 5 subsequent cycles, for a total of 6 cycles. Each cycle was 28 days.

The median age was 58 years (range, 28 to 70 years), 67% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0-1 (98%) or 2 (2%). At baseline, 43% of patients presented with Rai stage III or IV, and 59% of patients presented with CLL with high risk factors (TP53 mutation [6%], del11q [22%], or unmutated IGHV [53%]).

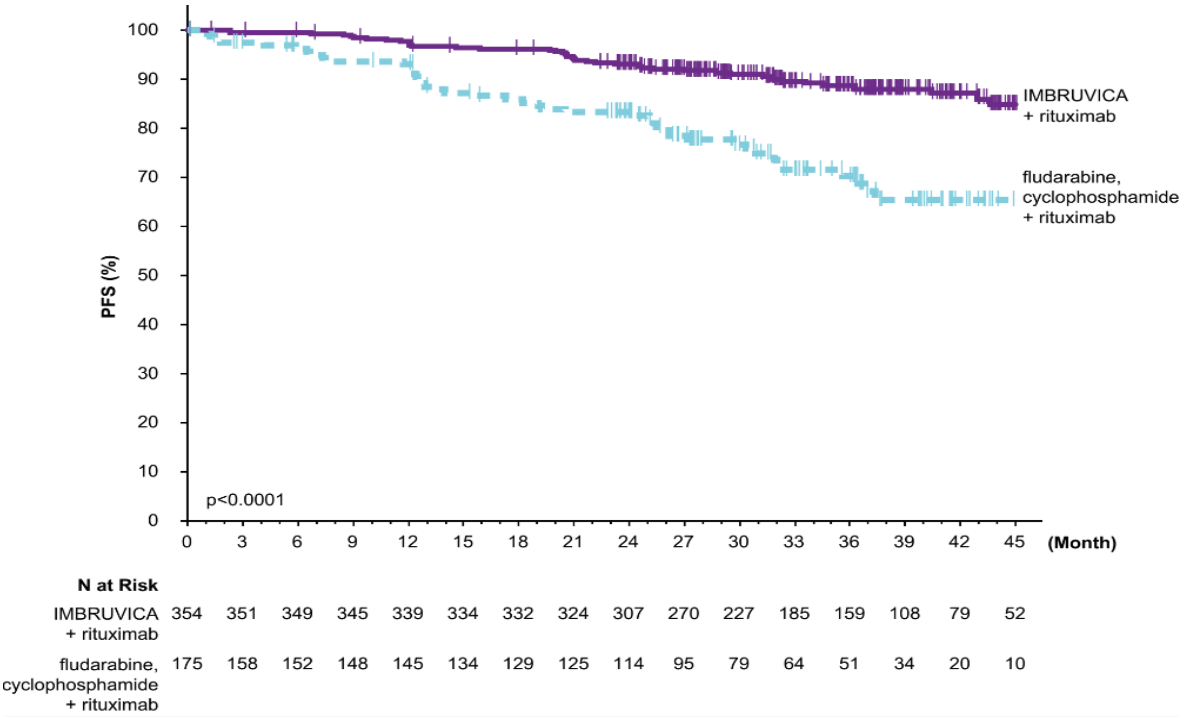
With a median follow-up time on study of 37 months, efficacy results for E1912 are shown in table 16. The Kaplan-Meier curves for PFS, assessed according to IWCLL criteria, and OS are shown in Figures 7 and 8, respectively.

Table 16: Efficacy results in Study E1912

Endpoint	Ibrutinib+ rituximab (IR) N=354	Fludarabine, Cyclophosphamide, and Rituximab (FCR) N=175
Progression Free Survival		
Number of events (%)	41 (12)	44 (25)
Disease progression	39	38
Death events	2	6
Median (95% CI), months	NE (49.4, NE)	NE (47.1, NE)
HR (95% CI)	0.34 (0.22, 0.52)	
P-value[a]	<0.0001	
Overall Survival		
Number of deaths (%)	4 (1)	10 (6)
HR (95% CI)	0.17 (0.05, 0.54)	
P-value[a]	0.0007	
Overall Response Rate[b] (%)	96.9	85.7

[a] P-value is from unstratified log-rank test.
[b] Investigator evaluated.
HR = hazard ratio; NE = not evaluable

Figure 7:Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL in E1912



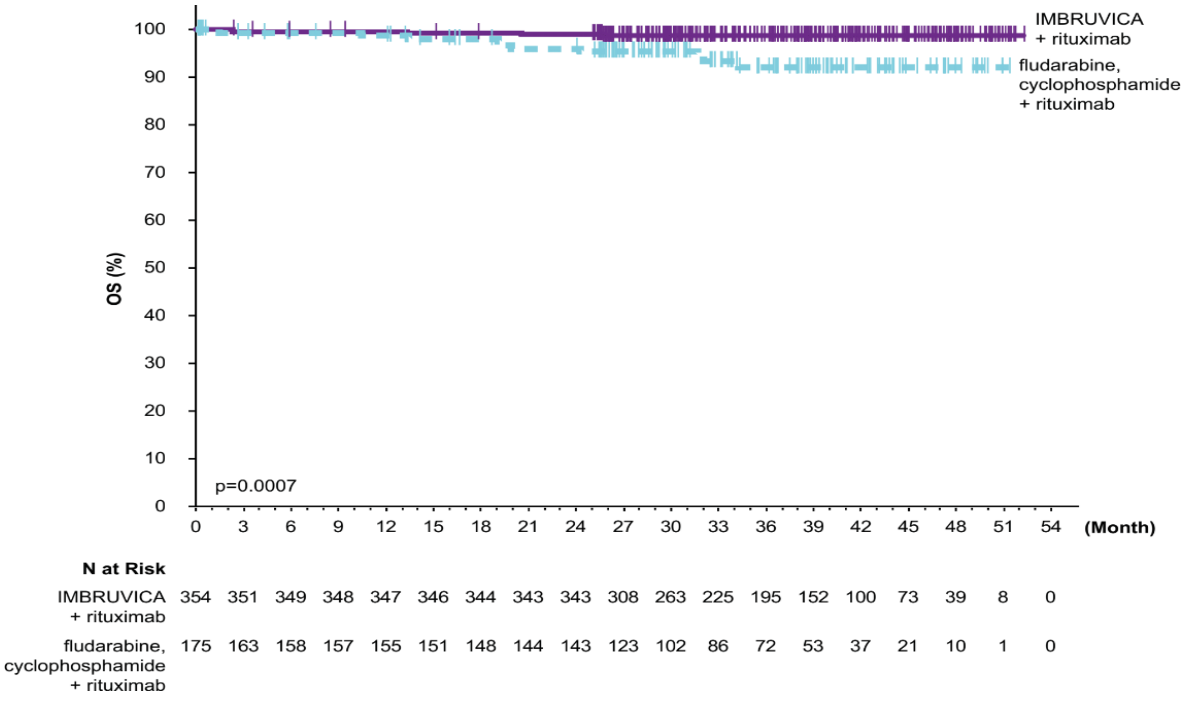
The treatment effect of ibrutinib was consistent across the high-risk CLL population (del17p/TP53 mutation, del11q, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.40)], p <0.0001, as shown in Table 17. The 3-year PFS rate estimates for the high-risk CLL population were 90.4% [95% CI (85.4, 93.7)] and 60.3% [95% CI (46.2, 71.8)] in the IR and FCR arms, respectively.

Table 17: Subgroup Analysis of PFS (Study E1912)

	N	Hazard Ratio	95% CI
All subjects	529	0.340	0.222, 0.522
High risk (TP53/del11q/unmutated IGHV)			
Yes	313	0.231	0.132, 0.404
No	216	0.568	0.292, 1.105
del11q			
Yes	117	0.199	0.088, 0.453
No	410	0.433	0.260, 0.722
Unmutated IGHV			
Yes	281	0.233	0.129, 0.421
No	112	0.741	0.276, 1.993
Bulky disease			
<5 cm	316	0.393	0.217, 0.711
≥5 cm	194	0.257	0.134, 0.494
Rai stage			
0/I/II	301	0.398	0.224, 0.708
III/IV	228	0.281	0.148, 0.534
ECOG			
0	335	0.242	0.138, 0.422
1-2	194	0.551	0.271, 1.118

Hazard ratio based on non-stratified analysis

Figure 8:Kaplan-Meier Curve of Overall Survival (ITT Population) in Patients with CLL in E1912



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 18.

Table 18: 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 19.

Table 19: Efficacy results in patients with chronic lymphocytic leukemia (Study PCYC-1112-CA)

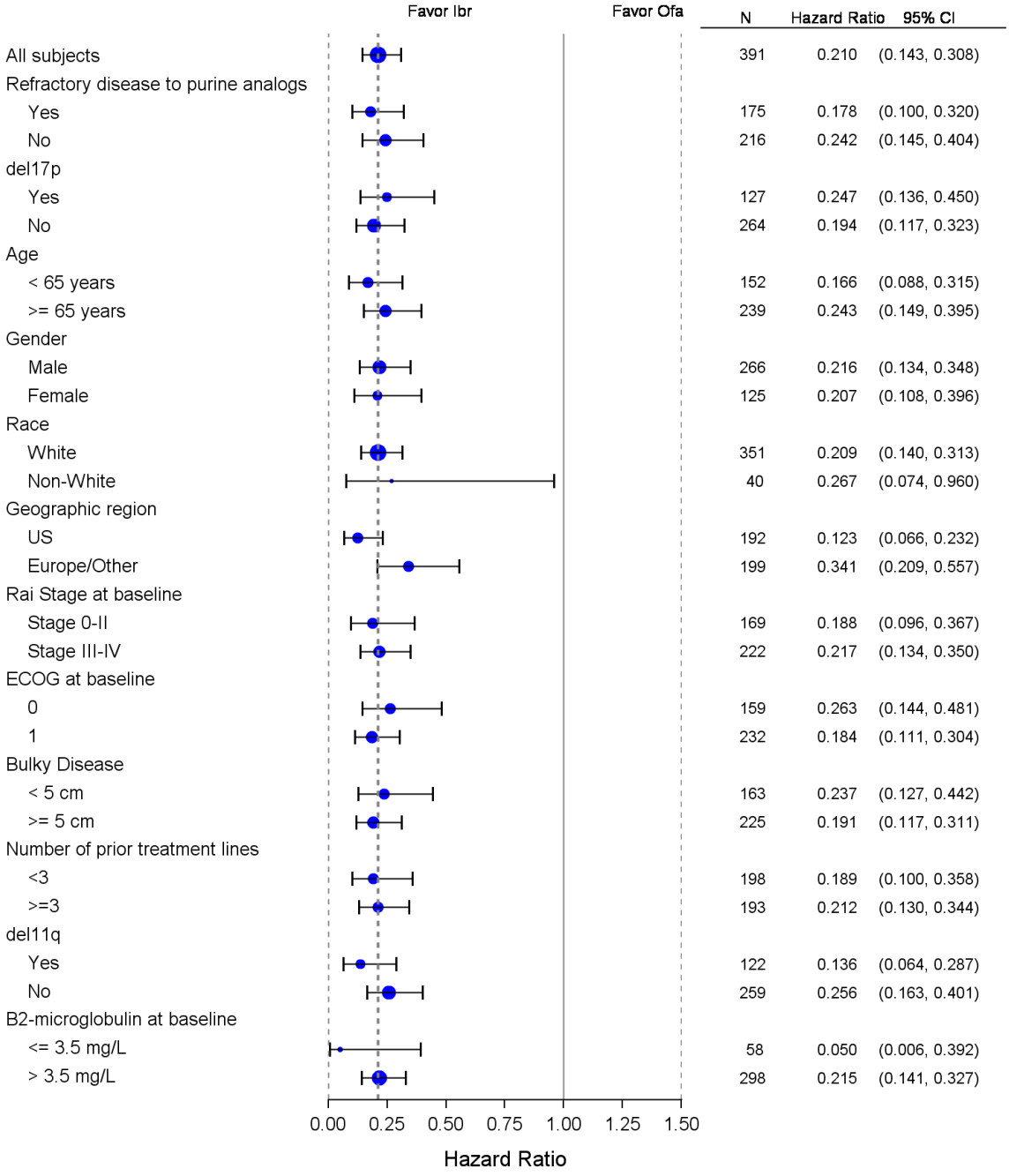
Endpoint	**IMBRUVICA N=195**	**Ofatumumab N=196**
Progression-Free Survival		
Median Progression-Free Survival, months	Not reached	8.1
HR (95% CI)	0.215 (0.146; 0.317)	
Overall Survival[a]		
HR (95% CI)	0.434 (0.238; 0.789)[b]	
HR (95% CI)	0.387 (0.216; 0.695)[c]	
Overall Response Rate[d,e] **(%)**	42.6	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.
Median follow-up time on study = 9 months

The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (Figure 9).

Figure 9: 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 10: Kaplan Meier curve of progression free survival (ITT Population) in study PCYC 1112 CA

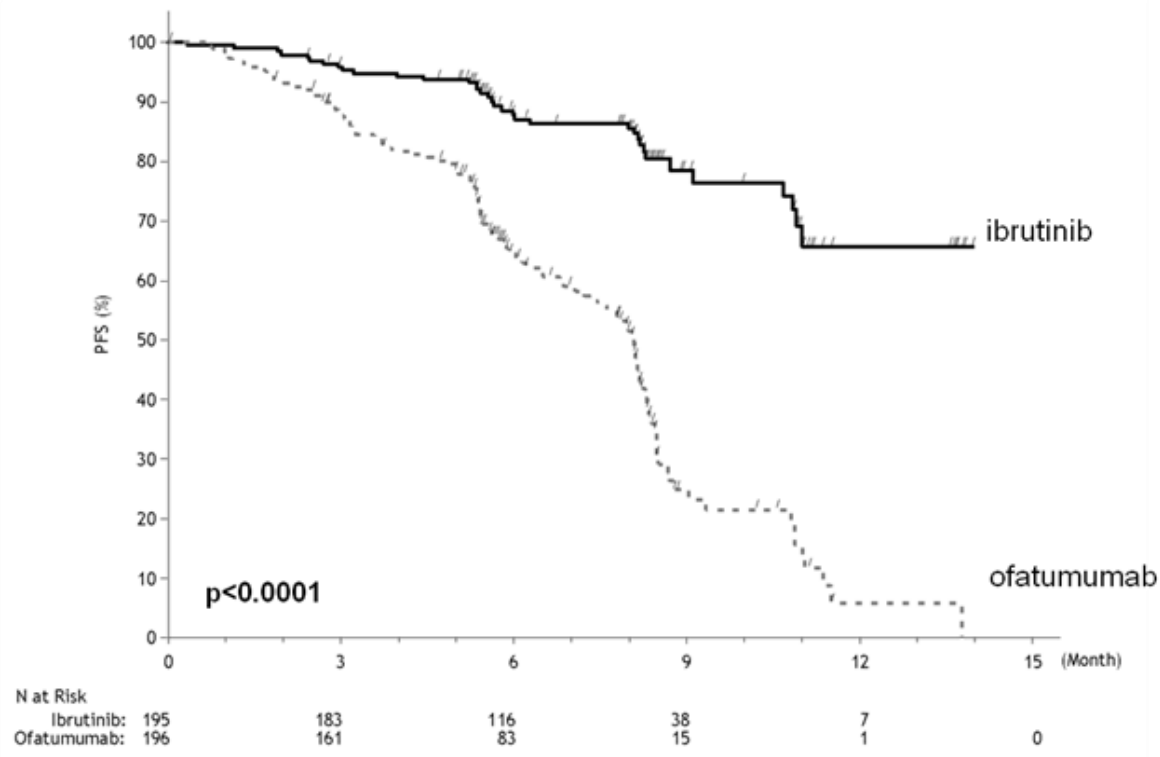
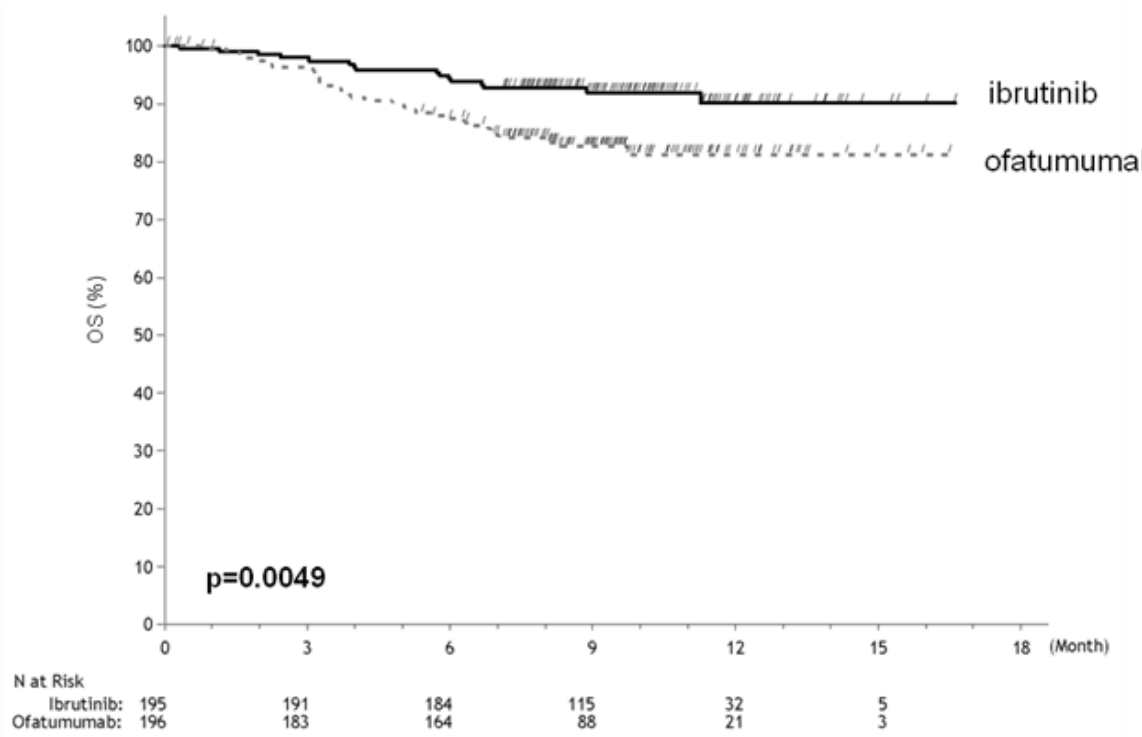


Figure 11: Kaplan-Meier curve of overall survival (ITT Population) in study PCYC-1112-CA

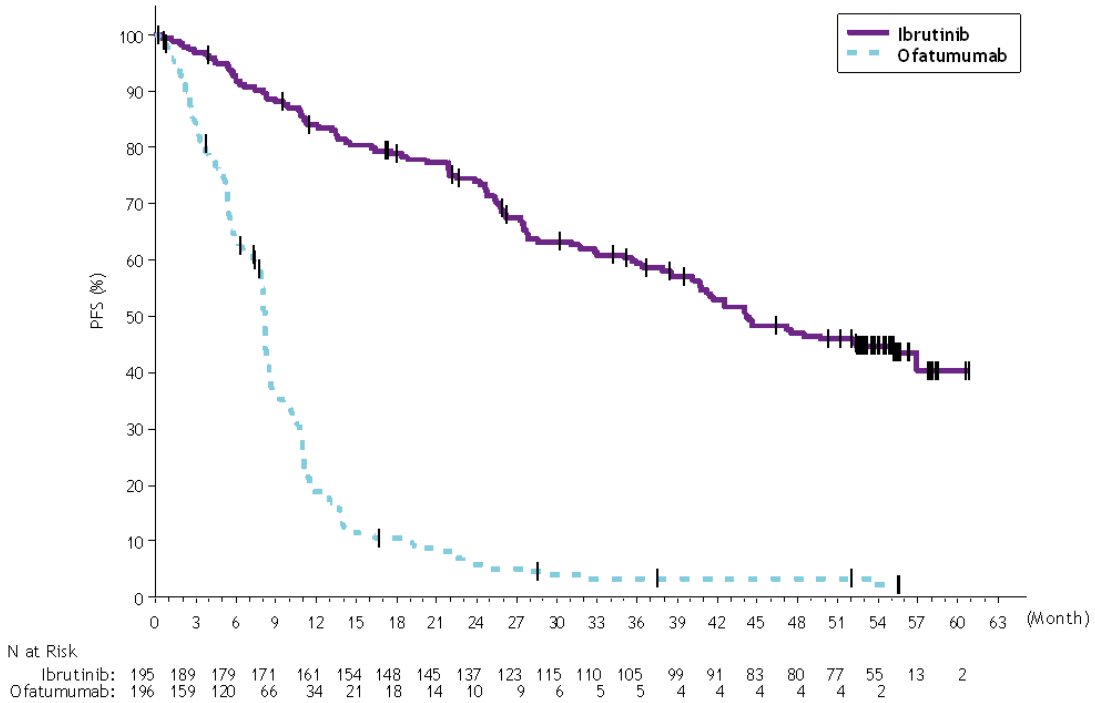


Final Analysis at 65-month Follow-up

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 12. 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 12: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) by Investigator in Study PCYC-1112-CA at Fianl 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 20.

Table 20: 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.

Waldenström's Macroglobulinemia (WM)
The safety and efficacy of IMBRUVICA in WM (IgM-excreting lymphoplasmacytic lymphoma) were evaluated in one single-arm and one randomized, controlled study.

Study PCYC-1118E
An open-label, multi-center, single-arm trial (PCYC-1118E) was conducted in 63 previously-treated patients. The median age was 63 years (range, 44 to 86 years), 76% were male, and 95% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 74 months, and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL (range, 0.7 to 8.4 g/dL), and 60% of patients were anemic (hemoglobin ≤11 g/dL).

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The primary endpoint in this study was ORR per investigator assessment. The ORR and DOR were assessed using criteria adopted from the Third International Workshop of Waldenstrom's Macroglobulinemia. Responses to IMBRUVICA are shown in Table 21.

Table 21: Overall response rate (ORR) and duration of response (DOR) based on investigator assessment in patients with WM in Study PCYC-1118E

	Total (N=63)
ORR (%)	87.3
95% CI (%)	(76.5, 94.4)
VGPR (%)	14.3
PR (%)	55.6
MR (%)	17.5
Median DOR months (range)	NR (0.03+, 18.8+)

CI = confidence interval; NR = not reached; MR = minor response; PR = partial response; VGPR = very good partial response; ORR = MR+PR+VGPR
Median follow-up time on study = 14.8 months

The median time to response was 1.0 month (range, 0.7 to 13.4 months).
Efficacy results were also assessed by an IRC demonstrating an ORR of 82.5%, with a 11% VGPR rate and a 51% PR rate.

Study PCYC-1127-CA
A randomized, multicenter, double-blinded phase 3 study of IMBRUVICA in combination with rituximab versus placebo in combination with rituximab (PCYC-1127-CA) was conducted in patients with treatment-naïve or previously treated WM. Patients (n=150) were randomized 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with rituximab until disease progression or unacceptable toxicity. Rituximab was administered weekly at a dose of 375 mg/m^2 for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 consecutive weeks (weeks 17-20).

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were Caucasian. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were treatment-naïve, and 55% of patients were previously treated. The median time since diagnosis was 52.6 months (treatment-naïve patients = 6.5 months and previously treated patients = 94.3 months). Among previously treated patients, the median number of prior treatments was 2 (range, 1 to 6 treatments). At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), 63% of patients were anemic (hemoglobin ≤11 g/dL) and MYD88 L265P mutations

were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status.

Progression free survival (PFS) as assessed by IRC indicated an 80% statistically significant reduction in the risk of death or progression. Efficacy results for Study PCYC-1127-CA are shown in Table 22 and the Kaplan-Meier curve for PFS is shown in Figure 14. PFS hazard ratios for treatment-naïve patients, previously treated patients, and patients with or without MYD88 L265P mutations were consistent with the PFS hazard ratio for the ITT population.

Table 22: Efficacy results in Study PCYC-1127-CA

Endpoint	IMBRUVICA + R N=75	Placebo + R N=75
Progression Free Survival[a]		
Number of events (%)	14 (18.7)	42 (56.0)
Median (95% CI), months	Not reached	20.3 (13.7, 27.6)
HR (95% CI)	0.20 (0.11, 0.38)	
TTnT		
Median (95% CI), months	Not reached	18.1 (11.1, NE)
HR (95% CI)	0.1 (0.04, 0.23)	
Best Overall Response (%)		
CR	2.7	1.3
VGPR	22.7	4.0
PR	46.7	26.7
MR	20.0	14.7
Overall Response Rate (CR, VGPR, PR, MR)[b] **(%)**	92.0	46.7
Median duration of overall response, months (range)	Not reached (1.9+, 36.4+)	24.8 (1.9, 30.3+)
Response Rate (CR, VGPR, PR)[b] **(%)**	72.0	32.0
Median duration of response, months (range)	Not reached (1.9+, 36.4+)	21.2 (4.6, 25.8)
Rate of Sustained Hemoglobin Improvement[b, c] **(%)**	73.3	41.3

CI = confidence interval; CR = complete response; HR = hazard ratio; MR = minor response; NE = not estimable; PR = partial response; R = Rituximab; TTnT = time to next treatment; VGPR = very good partial response

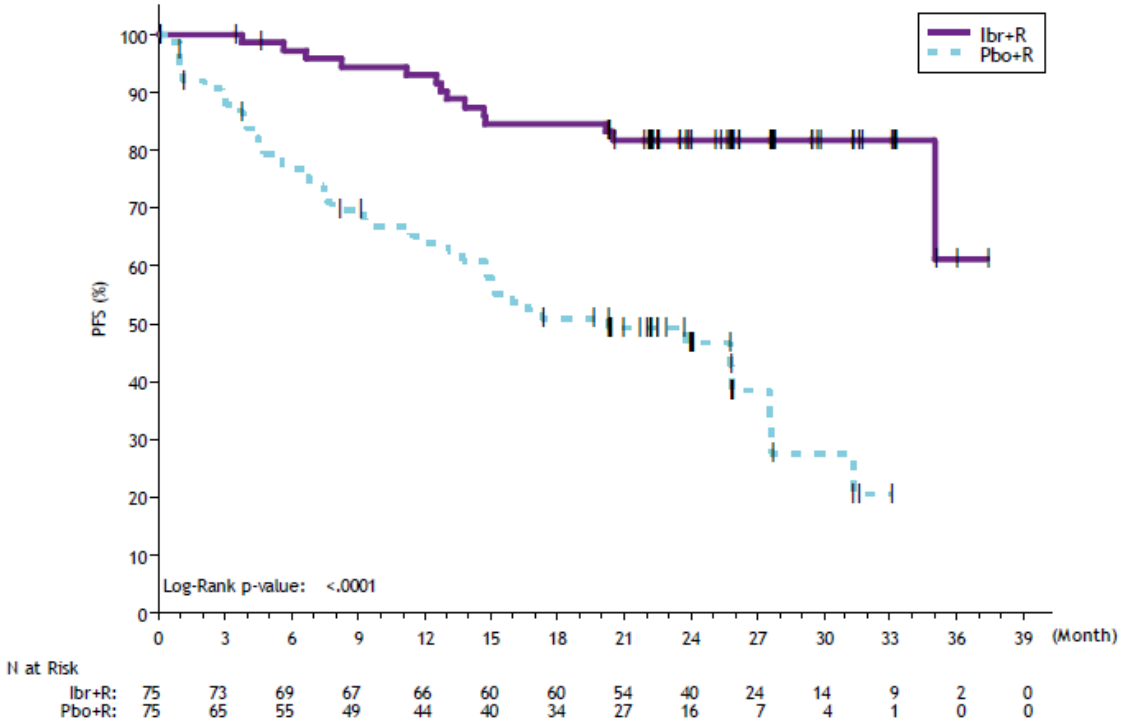
[a] IRC evaluated.

[b] p-value associated with response rate was <0.0001.

[c] Defined as increase of ≥2 g/dL over baseline regardless of baseline value, or an increase to >11 g/dL with a ≥0.5 g/dL improvement if baseline was ≤11 g/dL.

Median follow-up time on study = 26.5 months.

Figure 13: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1127-CA



Tumor flare in the form of IgM increase occurred in 8.0% of subjects in the IMBRUVICA + rituximab arm and 46.7% of subjects in the placebo + rituximab arm.

63-Month Follow-Up (Final Analysis)

With an overall follow-up of 63 months, efficacy results as assessed by an IRC at the time of the final analysis for PCYC-1127-CA are shown in Table 23. PFS hazard ratios for treatment-naïve patients (0.31 [95% CI (0.14, 0.69)]) and previously treated patients (0.22 [95% CI (0.11, 0.43)]) were consistent with the PFS hazard ratio for the ITT population.

Table 23: Efficacy results in Study PCYC-1127-CA (Final Analysis*)

Endpoint	IMBRUVICA + R N=75	Placebo + R N=75
Progression Free Survival[a, b]		
Number of events (%)	22 (29)	50 (67)
Median (95% CI), months	Not reached	20.3 (13.0, 27.6)
HR (95% CI)	0.25 (0.15, 0.42)	
P-value	<0.0001	
TTnT		
Median (95% CI), months	Not reached	18.1 (11.1, 33.1)
HR (95% CI)	0.1 (0.05, 0.21)	
Best Overall Response (%)		
CR	1.3	1.3
VGPR	29.3	4.0
PR	45.3	25.3
MR	16.0	13.3
Overall Response Rate[c] (CR, VGPR, PR, MR) (%)	69 (92.0)	33 (44.0)
Median duration of overall response, months (range)	Not reached (2.7, 58.9+)	27.6 (1.9, 55.9+)
Response Rate (CR, VGPR, PR)[c,d] (%)	57 (76.0)	23 (30.7)

Median duration of response, months (range)	Not reached (1.9+, 58.9+)	Not reached (4.6, 49.7+)
Rate of Sustained Hemoglobin Improvement[c,e] (%)	77.3	42.7

CI = confidence interval; CR = complete response; HR = hazard ratio; MR = minor response; PR = partial response; R = Rituximab; TTnT = time to next treatment; VGPR = very good partial response

* Median follow-up time on study = 49.7 months.

[a] IRC evaluated.

[b] 4-year PFS estimates were 70.6% [95% CI (58.1, 80.0)] in the IMBRUVICA + R arm versus 25.3% [95% CI (15.3, 36.6)] in the placebo + R arm.

[c] p-value associated with response rate was <0.0001.

[d] Response rate was 76% vs 41% in treatment-naïve patients and 76% vs 22% in previously treated patients for the IMBRUVICA + R arm vs the placebo + R arm, respectively.

[e] Defined as increase of ≥2 g/dL over baseline regardless of baseline value, or an increase to >11 g/dL with a ≥0.5 g/dL improvement if baseline was ≤11 g/dL.

Study PCYC-1127-CA had a separate monotherapy arm of 31 patients with previously treated WM who failed prior rituximab-containing therapy and received single agent IMBRUVICA. The median age was 67 years (range, 47 to 90 years). Eighty-one percent of patients had a baseline ECOG performance status of 0 or 1, and 19% had a baseline ECOG performance status of 2. The median number of prior treatments was 4 (range, 1 to 7 treatments). The response rate per IRC observed in the monotherapy arm was 71% (0% CR, 29% VGPR, 42% PR). The overall response rate per IRC observed in the monotherapy arm was 87% (0% CR, 29% VGPR, 42% PR, 16% MR). With a median follow-up time on study of 34 months (range, 8.6+ to 37.7 months), the median duration of response has not been reached.

61-Month Follow-Up (Final Analysis)

With an overall follow-up of 61 months, the response rate observed in Study PCYC-1127-CA monotherapy arm per IRC assessment was 77% (0% CR, 29% VGPR, 48% PR). The median duration of response was 33 months (range, 2.4 to 60.2+ months). The overall response rate per IRC observed in the monotherapy arm was 87% (0% CR, 29% VGPR, 48% PR, 10% MR). The median duration of overall response was 39 months (range, 2.07 to 60.2+ months).

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 ± 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 (Vd) 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
Film-coated tablets
IMBRUVICA tablet core contains the following excipients:
colloidal silicon dioxide
croscarmellose sodium
lactose monohydrate
magnesium stearate
microcrystalline cellulose
povidone
sodium lauryl sulfate

Film-coating
ferrosoferric oxide (140 mg tablets)
polyvinyl alcohol
polyethylene glycol
talc
titanium dioxide
yellow iron oxide (140 mg tablets)

Incompatibilities
Not applicable

Shelf Life
Shelf-life before opening: 24 months.

Storage Conditions
Keep out of the sight and reach of children.
Store below 30^0C.

Nature and Contents of Container

Film-coated tablets
IMBRUVICA film-coated tablets are supplied in a polyvinyl chloride (PVC) laminated with polychlorotrifluoroethylene (PCTFE) / 2 aluminum blister of 10 film-coated tablets in a cardboard wallet.
The pack sizes are cartons of 30 film-coated tablets (3 cardboard wallets @ 2 blisters @ 5 film-coated tablets each).

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

HOW SUPPLIED

Imbruvica tablets 140 mg
Box, 3 cardboard wallets @ 2 blisters @ 5 film-coated tablets
Reg. No.: DKI2310902417A1

FIRST AUTHORISATION DATE: 10 JUNE 2022

Manufactured of the finished product by Cilag AG, Schaffhausen, Switzerland
Primary & Secondary packaged and final batch release by Janssen-Cilag SpA., Latina, Italy
Registered by PT Integrated Healthcare Indonesia, Jakarta - Indonesia
For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or Phone (021) 2935 3935

HARUS DENGAN RESEP DOKTER

Based on CCDS v.39 09Aug2024

Informasi Produk untuk Pasien
IMBRUVICA® 140 mg Tablet salut selaput
Ibrutinib

Baca informasi ini secara lengkap dan seksama sebelum Anda mulai menggunakan obat ini.
- Simpan informasi produk ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau tenaga medis professional Anda.
- Obat ini telah diresepkan untuk Anda saja. Jangan berikan kepada orang lain. Hal tersebut dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka sama seperti Anda.
- Jika Anda menemukan efek samping serius atau jika Anda menemukan efek samping yang tidak tercantum dalam informasi produk ini, laporkan kepada dokter, perawat atau apoketer Anda.

Apa yang ada dalam informasi produk ini

1. Apakah Imbruvica itu dan digunakan untuk apa

Imbruvica adalah obat anti kanker yang mengandung zat aktif ibrutinib. Imbruvica digunakan untuk pengobatan kanker darah berikut pada orang dewasa:
- *Mantle Cell Lymphoma* (MCL), yaitu jenis kanker yang mempengaruhi kelenjar getah bening;
- *Chronic Lymphocytic Leukemia* (CLL), yaitu jenis kanker yang mempengaruhi sel darah putih yaitu limfosit yang juga mempengaruhi kelenjar getah bening. IMBRUVICA digunakan pada pasien yang sebelumnya belum pernah mendapatkan perawatan untuk CLL atau ketika penyakit tersebut kembali atau belum ada respon terhadap pengobatan.
- *Chronic Lymphocytic Leukemia* dengan penghapusan 17p, yaitu jenis CLL di mana sel-sel kanker memiliki perubahan DNA tertentu.
- *Waldenström's Macroglobulinemia* (WM), sejenis kanker yang menyerang sel darah putih yang disebut limfosit.

IMBRUVICA bekerja dengan menghambat protein didalam tubuh yang membantu kehidupan dan pertumbuhan sel kanker. Protein ini disebut *Bruton's tyrosine kinase*. Dengan menghambat protein ini, IMBRUVICA dapat membunuh dan mengurangi jumlah sel kanker dan juga dapat memperlambat penyebaran kanker.

2. Apa saja yang harus Anda ketahui sebelum menggunakan Imbruvica

Jangan gunakan IMBRUVICA
- Jika Anda alergi terhadap ibrutinib atau salah satu bahan lain dari obat ini (lihat bagian **apa isi IMBRUVICA**).
- Jika Anda menggunakan obat-obatan herbal yang bernama St. John's Wort, yang digunakan untuk depresi.

Jika Anda tidak yakin, tanyakan kepada dokter Anda sebelum menggunakan IMBRUVICA. Jika Anda memiliki salah satu dari tanda-tanda reaksi alergi (gatal-gatal, kesulitan bernapas, atau pembengkakan pada wajah, bibir, lidah, atau tenggorokan Anda) ketika menggunakan IMBRUVICA, segera dapatkan bantuan medis.

Peringatan dan Perhatian
Bicaralah dengan dokter atau tenaga medis profesional Anda sebelum atau saat menggunakan Imbruvica:
- jika Anda pernah memiliki memar yang tidak biasa atau perdarahan atau pada setiap obat atau suplemen yang meningkatkan risiko perdarahan (lihat **Obat-obat lain dan IMBRUVICA**)

- jika Anda pernah mengalami masalah dengan irama jantung atau gagal jantung berat, atau jika Anda merasakan hal-hal berikut: denyut jantung Anda cepat dan tidak teratur, pening, pusing, sesak napas, ketidaknyamanan di dada, kaki bengkak, atau Anda pingsan
- jika Anda memiliki masalah pada hati atau ginjal
- jika Anda memiliki tekanan darah tinggi
- jika Anda baru saja menjalani operasi apapun, terutama jika hal ini dapat mempengaruhi bagaimana Anda menyerap makanan atau obat-obatan melalui perut atau usus
- jika Anda berencana untuk menjalani operasi apapun - dokter Anda akan meminta Anda untuk berhenti menggunakan IMBRUVICA untuk waktu yang singkat.

Jika salah satu di atas terjadi pada Anda atau Anda tidak yakin, tanyakan kepada dokter atau tenaga medis profesional Anda sebelum menggunakan IMBRUVICA.

Saat menggunakan IMBRUVICA, beritahu dokter Anda secepatnya jika Anda atau orang lain menyadari Anda mengalami kehilangan ingatan, sulit berpikir, kesulitan berjalan atau kehilangan penglihatan, keadaan-keadaan ini mungkin tapi sangat jarang terjadi yang disebabkan oleh infeksi otak serius yang dapat berakibat fatal (*Progressive Multifocal Leukoencephalopathy* atau PML).

Beritahu dokter Anda segera jika Anda memperhatikan atau seseorang memperhatikan Anda: tiba-tiba mati rasa atau kelemahan pada anggota badan (terutama pada satu sisi tubuh), kebingungan tiba-tiba, kesulitan berbicara atau memahami pembicaraan, kehilangan penglihatan, kesulitan berjalan, kehilangan keseimbangan atau kurang koordinasi, sakit kepala parah tiba-tiba tanpa diketahui penyebabnya. Ini mungkin merupakan tanda dan gejala stroke.

Efek pada jantung
Pengobatan dengan IMBRUVICA dapat mempengaruhi jantung, terutama jika Anda sudah memiliki penyakit jantung seperti masalah irama, gagal jantung, tekanan darah tinggi atau memiliki diabetes. Efeknya mungkin parah dan dapat menyebabkan kematian, termasuk terkadang kematian mendadak. Fungsi jantung Anda akan diperiksa sebelum dan selama perawatan dengan IMBRUVICA. Beri tahu dokter Anda segera jika Anda merasa sesak napas, kesulitan bernapas saat berbaring, pembengkakan pada kaki, pergelangan kaki atau tungkai dan kelemahan/kelelahan selama perawatan dengan IMBRUVICA – ini mungkin merupakan tanda-tanda gagal jantung.

Anda mungkin mengalami infeksi virus, bakteri, atau jamur selama pengobatan dengan IMBRUVICA. Hubungi dokter jika Anda mengalami demam, menggigil, lemas, kebingungan, nyeri badan, gejala pilek atau flu, merasa lelah atau sesak napas, kulit atau mata menguning (penyakit kuning). Ini bisa jadi merupakan tanda-tanda infeksi.

Kejadian yang berhubungan dengan liver
Hubungi dokter Anda jika Anda merasa lelah atau kulit atau mata menguning (penyakit kuning) – hal ini kemungkinan merupakan tanda adanya masalah liver. Dokter Anda akan melakukan beberapa tes darah untuk memeriksa apakah liver Anda berfungsi dengan baik.

Tes dan pemeriksaan sebelum dan selama pengobatan
Tumour lysis syndrome (TLS): konsentrasi bahan kimia pada darah yang tidak lazim yang disebabkan oleh kerusakan sel kanker secara cepat yang terjadi selama pengobatan kanker dan bahkan kadang tanpa pengobatan. Hal ini mungkin menyebabkan perubahan pada fungsi ginjal, detak jantung yang tidak normal atau kejang. Dokter Anda atau ahli kesehatan lain akan melakukan tes darah untuk menguji TLS.
Tes laboratorium menunjukkan bahwa darah Anda mengandung lebih banyak sel darah putih (disebut "*lymphocytes*"), dalam beberapa minggu pertama pengobatan. Hal ini sangat diharapkan dan dapat berlangsung selama beberapa bulan. Ini tidak berarti bahwa kanker darah Anda semakin parah. Dokter Anda akan memeriksa jumlah darah Anda sebelum atau selama pengobatan dan dalam kasus yang jarang mereka harus memberikan obat lain. Bicarakan dengan dokter Anda mengenai hasil tes Anda.

Anak-anak dan remaja

IMBRUVICA tidak digunakan untuk siapapun dengan usia kurang dari 18 tahun karena belum ada penelitian pada usia tersebut.

Obat-obat lain dan IMBRUVICA
Beritahu dokter, atau tenaga medis profesional Anda jika Anda sedang atau baru saja menggunakan obat lain. Termasuk obat yang diperoleh tanpa resep dokter dan obat-obat herbal dan supplemen. Karena IMBRUVICA dapat mempengaruhi cara kerja obat lain. Atau, obat-obat lain dapat mempengaruhi cara kerja IMBRUVICA.

IMBRUVICA membuat Anda mudah mengalami pendarahan. Beritahu dokter atau tenaga medis profesional Anda jika Anda sedang atau baru saja menggunakan obat lain yang dapat meningkatkan risiko perdarahan, termasuk menggunakan:
- aspirin dan non-steroidal anti-inflammatori (NSAIDS) seperti ibuprofen atau naproxen
- pengencer darah seperti warfarin, heparin atau obat lain untuk pembekuan darah
- supplement yang dapat meningkatkan risiko perdarahan seperti minyak ikan dan vitamin E.

Efek dari IMBRUVICA atau obat-obatan lain dapat terpengaruh jika Anda menggunakan IMBRUVICA bersama dengan salah satu obat-obatan berikut. **Beritahukan dokter anda jika anda sedang menggunakan**:
- antibiotik untuk pengobatan infeksi bakteri – clarithromisin, telithromisin, ciprofloksasin atau erythromisin dan rifampisin
- obat untuk infeksi jamur – ketokonazol, itrakonazole, fluconazole atau voriconazole
- obat untuk infeksi HIV – ritonavir, cobicistat, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, darunavir/ritonavir atau fosamprenavir
- obat untuk mencegah mual dan muntah yang berhubungan dengan kemoterapi – aprepitant
- obat untuk depresi – nefazodone
- obat-obat kinase inhibitor untuk pengobatan kanker lain – crizotinib, imatinib
- obat-obat calcium channel blockers untuk tekanan darah tinggi atau sesak dada – diltiazem, verapamil
- obat-obat statin untuk pengobatan kolesterol – rosuvastatin
- obat-obat jantung/anti-arrhythmia - amiodarone, dronedarone
- obat-obat untuk mencegah kejang atau pengobatan epilepsi atau obat-obat untuk mengobati kondisi yang menyakitkan pada wajah yang disebut *trigeminal neuralgia* – carbamazepine, phenytoin
- obat herbal, seperti untuk depresi - *St. John's Wort*.

Jika Anda sedang menggunakan digoxin, obat yang digunakan untuk penyakit jantung, atau metotreksat, obat yang digunakan untuk mengobati kanker lain dan untuk mengurangi aktivitas sistem kekebalan tubuh (misalnya, untuk rheumatoid arthritis atau psoriasis), harus diminum minimal 6 jam sebelum atau setelah menggunakan IMBRUVICA.

Tanyakan kepada dokter Anda jika Anda tidak yakin apakah obat Anda adalah salah satu yang tercantum di atas. Cari tahu obat yang Anda gunakan. Simpan daftar obat-obat Anda dan tunjukkan ke dokter atau tenaga medis profesional Anda ketika Anda mendapatkan obat baru.

IMBRUVICA dengan makanan
Jangan menggunakan IMBRUVICA dengan jeruk bali atau jeruk Seville - termasuk memakannya, meminum jusnya, atau menggunakan suplemen yang mungkin mengandung buah tersebut. Hal ini dapat meningkatkan jumlah IMBRUVICA dalam darah Anda.

Kehamilan, menyusui dan kesuburan
Jangan hamil saat Anda menggunakan IMBRUVICA.

Jika Anda sedang hamil, atau berpikir mungkin saya hamil atau berencana untuk hamil, tanyakan kepada dokter atau tenaga medis profesional Anda untuk sarannya sebelum menggunakan IMBRUVICA.

- Jangan menggunakan IMBRUVICA selama hamil.

Tidak ada informasi keamanan IMBRUVICA pada wanita hamil.

Wanita usia subur harus menggunakan metode yang efektif dalam pengendalian kehamilan selama dan sampai satu bulan setelah menerima IMBRUVICA untuk menghindari hamil saat pengobatan dengan IMBRUVICA. Periode waktu setelah pengobatan dengan IMBRUVICA dimana apakah aman untuk kehamilan belum diketahui.

- Segera beritahu Dokter Anda jika Anda sedang hamil.
- Jangan menyusui jika Anda sedang menggunakan IMBRUVICA.

Jangan melakukan hubungan seksual atau menyumbangkan sperma selama menggunakan IMBRUVICA dan selama 3 bulan setelah pengobatan dihentikan. Gunakan kondom dan jangan menyumbangkan sperma selama pengobatan dan selama 3 bulan setelah pengobatan selesai. Jika Anda berencana untuk melakukan hubungan seksual, bicaralah dengan dokter atau tenaga medis profesional Anda sebelum menggunakan IMBRUVICA.

Mengemudi dan menggunakan mesin
Anda mungkin akan merasa letih atau lemah setelah menggunakan IMBRUVICA, yang dapat mempengaruhi kemampuan Anda untuk mengemudi atau menggunakan peralatan atau mengoperasikan mesin.

3. Bagaimana cara menggunakan Imbruvica

- Gunakan IMBRUVICA seperti yang diresepkan oleh dokter atau tenaga medis professional Anda. Jangan merubah dosis atau berhenti menggunakan IMBRUVICA sampai dokter Anda memberitahukan kepada Anda.
- Telan tablet IMBRUVICA dengan segelas air. Jangan mematahkan atau mengunyah tablet.
- Gunakan IMBRUVICA pada waktu yang sama setiap hari**.**

Minum banyak cairan untuk menjaga Anda tetap terhidrasi saat menggunakan IMBRUVICA. Ini akan membantu ginjal Anda terus berfungsi dengan baik.

Jangan pernah memberikan IMBRUVICA kepada orang lain, bahkan jika mereka memiliki pengobatan yang sama dengan Anda

Berapa banyak digunakan
Mantle Cell Lymphoma (MCL)
Dosis yang dianjurkan dari IMBRUVICA adalah 560 mg sekali sehari.
Chronic Lymphocytic Leukemia (CLL), *Waldenström's Macroglobulinemia* (WM)
Dosis yang dianjurkan dari IMBRUVICA 420 mg sekali sehari.

Dokter Anda mungkin akan menyesuaikan dosis Anda.

Apa yang harus dilakukan jika Anda lupa menggunakan imbruvica
Jika Anda lupa menggunakannya, anda dapat menggunakannya sesegera mungkin pada hari yang sama dengan kembali ke jadwal normal untuk hari berikutnya. Jangan menggunakan dosis ganda untuk menggantikan dosis yang terlewat. Hubungi dokter atau tenaga medis profesional Anda jika Anda tidak yakin apa yang harus dilakukan.

Apa yang harus dilakukan jika Anda menggunakan lebih dari yang seharusnya
Jika Anda menggunakan IMBRUVICA lebih dari yang seharusnya, hubungi dokter atau tenaga medis profesional Anda atau pergi ke rumah sakit segera.

Jika Anda berhenti menggunakan IMBRUVICA
Jangan berhenti meminum Imbruvica kecuali dokter menyuruh Anda. Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan pada dokter, apoteker atau perawat Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, Imbruvica dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.
Efek samping berikut dapat terjadi dengan obat ini:
Hentikan menggunakan Imbruvica dan beritahukan dokter Anda segera jika Anda menyadari efek samping berikut terjadi:
Apabila terjadi gatal-gatal dan ruam, kesulitan bernafas, bengkak pada wajah, bibir, lidah atau tenggorokan – Anda mungkin mengalami reaksi alergi terhadap obat ini.

Beritahukan dokter Anda segera jika Anda menyadari efek samping berikut terjadi:

Sangat sering terjadi (terjadi pada lebih dari pada 1 dari 10 orang)
- Demam, panas dingin, sakit pada area badan, merasa kelelahan, gejala flu, napas pendek – gejala-gejala ini mungkin disebabkan oleh gejala infeksi (bakteri, virus atau fungi). Termasuk gejala infeksi di hidung, sinus atau tenggorokan (infeksi saluran pernapasan atas), atau paru-paru, atau kulit.
- Memar

Sering terjadi (terjadi pada 1 dari 10 orang)
- Infeksi parah di seluruh badan (sepsis)
- Infeksi saluran kemih
- Mimisan, bercak merah atau keunguan yang disebabkan pendarahan di bawah kulit, adanya darah pada feses atau urin, haid yang lebih banyak dari biasanya, pendarahan yang sulit berhenti – gejala ini mungkin tanda-tanda serius adanya pendarahan internal dalam saluran cerna, usus atau otak.
- Denyut jantung yang cepat, denyut jantung yang terlewat, denyut yang lemah atau tidak stabil (gejala atrial fibrilasi)
- Peningkatan jumlah atau proporsi sel darah putih pada tes darah.
- Jumlah sel darah putih yang rendah disertai dengan demam (*febrile neutropenia*)
- Konsentrasi bahan kimia pada darah yang tidak lazim yang disebabkan oleh kerusakan sel kanker secara cepat yang terjadi selama pengobatan kanker dan bahkan kadang tanpa pengobatan (*tumour lysis syndrome*)
- Kenker kulit non-melanoma, paling sering adalah kanker sel squamos dan sel basal.
- Pusing
- Penglihatan kabur
- Tekanan darah tinggi
- Kulit kemerahan
- Konsentrasi “asam urat” yang tinggi pada darah, yang dapat menyebabkan rematik.
- Inflamasi pada paru yang dapat berakibat pada kerusakan permanen.
- Kerusakan pada kuku
- gagal jantung, yang membuat Anda sesak napas dan dapat menyebabkan kaki menjadi bengkak
- Lemah, mati rasa, kesemutan atau nyeri di tangan atau kaki atau bagian tubuh lainnya (*neuropati perifer*).

Jarang terjadi (terjadi pada 1 dari 100 orang)
- Peningkatan jumlah sel darah putih yang mengakibatkan sel saling bergumpal
- Reaksi alergi, kadang berat, termasuk pembengkakan pada wajah, bibir, mulut, lidah atau tenggorokan, sulit menelan atau bernapas, ruam gatal.
- Episode sementara dari gangguan fungsi neurologis yang disebabkan oleh hilangnya alirah darah, stroke.
- Benjolan yang terasa nyeri atau ulkus (luka koreng) pada kulit, kadang-kadang disertai dengan demam (dermatosis neutrofilik).
- pendarahan di mata
- pembuluh darah yang meradang di kulit, yang dapat menyebabkan ruam (vaskulitis kulit)

Efek samping yang sering terjadi lainnya
- Sariawan
- Sakit kepala

- Konstipasi
- Mual atau muntah
- Diare
- Ruam kulit
- Nyeri pada lengan atau kaki
- Nyeri punggung atau nyeri sendi
- Kram otot, nyeri atau kejang pada kram otot, sakit atau kejang
- Jumlah sel yang membantu pembekuan darah yang rendah (trombosit), jumlah sel darah putih yang sangat rendah pada tes darah.
- Bengkak pada tangan, pergelangan kaki, atau telapak kaki.

Belum diketahui frekuensi kejadiannya
- Gagal hati, termasuk kejadian yang berakibat fatal.
- Ruam terus menerus yang disertai dengan kulit melepuh dan mengelupas di sekitar mulut, hidung, mata dan alat kelamin (Steven-Johnson syndrome).

Pelaporan efek samping
Jika Anda mendapat efek samping termasuk efek samping yang tidak tercantum dalam leaflet ini, beritahukan dokter, apoteker, atau perawat Anda. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut keamanan obat ini.

5. Bagaimana cara menyimpan Imbruvica

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan gunakan Imbruvica setelah tanggal kadaluarsa yang tertera pada karton dan label botol setelah kata EXP. Tanggal kadaluarsa mengacu pada hari terakhir dari bulan itu
- Jangan bekukan IMBRUVICA.
- Simpan pada suhu di bawah 30^0C.
- Jangan membuang obat apapun melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana cara membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi produk dan informasi lainnya

Apa isi IMBRUVICA

Tablet salut selaput
- Zat aktif adalah ibrutinib. Tiap tablet mengandung 140 mg ibrutinib.

Bahan lain adalah:
- Tablet inti: koloidal silicon dioksida, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone dan sodium lauryl sulfate
- Penyalut tablet: polivinil alcohol, polyethylene glycol, talk, titanium oksida. 140mg tablet juga mengandung ferrosoferric oksida, dan yellow iron oxide.

Seperti apa IMBRUVICA dan isi kemasan

Tablet salut selaput
IMBRUVICA 140mg tablet salut selaput berwarna kuning-hijau dengan warna hijau di bulatan tablet, dengan "ibr" di satu sisi dan "140" disisi lain.
IMBRUVICA tablet salut selaput tersedia dalam blister di dalam dus amplop. Kemasan berbentuk karton yang berisi 30 tablet salut selaput (Dus @ 3 amplop @ 2 blister @ 5 tablet salut selaput).

- Imbruvica (ibrutinib) 140mg tablet salut selaput
  No. Reg: DKI2310902417A1

Diproduksi oleh:
Cilag AG, Hochstrasse 201, Schaffhausen, 8200, Switzerland

Dikemas dan dirilis oleh:
Janssen-Cilag SpA, Via C. Janssen, Loc. Borgo S. Michele, 04100 Latina, Italy

Pemilik Izin Edar
PT Integrated Healthcare Indonesia, Jakarta – Indonesia

Untuk pelaporan efek samping dan keluhan kualitas produk, dapat menghubungi drugsafety@jacid.jnj.com atau telp. (021) 2935-3935

HARUS DENGAN RESEP DOKTER

Based on CPPI v.28 09Aug2024