1. NAME OF THE MEDICINAL PRODUCT

Capsules
IMBRUVICA 140 mg hard capsules.

Tablets
IMBRUVICA 140mg film-coated tablets
IMBRUVICA 280mg film-coated tablets
IMBRUVICA 420mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IMBRUVICA 140mg hard capsules
Each hard capsule contains 140 mg of ibrutinib.

IMBRUVICA 140mg film-coated tablets
Each film-coated tablet contains 140 mg of ibrutinib.

Excipients with known effect
Each 140mg film-coated tablet contains 28mg of lactose monohydrate.

IMBRUVICA 280mg film-coated tablets
Each film-coated tablet contains 280mg of ibrutinib.

Excipients with known effect
Each 280mg film-coated tablet contains 56mg of lactose monohydrate.

IMBRUVICA 420mg film-coated tablets
Each film-coated tablet contains 420mg of ibrutinib.

Excipients with known effect
Each 420mg film-coated tablet contains 84mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules
IMBRUVICA 140mg hard capsules

Hard capsule (capsule).
White opaque, hard capsule of 22 mm in length, marked with “ibr 140 mg” in black ink.

Tablets
IMBRUVICA 140mg film-coated tablets
Yellow-green to green round tablets (9mm), debossed with “ibr” on one side and "140" on the other side.

IMBRUVICA 280mg film-coated tablets
Purple oblong tablets (15mm in length and 7mm in width), debossed with "ibr" on one side and "280" on the other side.

IMBRUVICA 420mg film-coated tablets

Yellow-green to green oblong tablets (17.5mm in length and 7.4mm in width), debossed with "ibr" on one side and "420" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMBRUVICA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL).

IMBRUVICA as a single agent or in combination with rituximab or obinutuzumab or venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

IMBRUVICA as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

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, or in first line treatment for patients unsuitable for chemo-immunotherapy. IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with WM.

IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

4.2 Posology and method of administration

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

MCL

The recommended dose for the treatment of MCL is 560 mg once daily until disease progression or no longer tolerated by the patient. For MCL, IMBRUVICA can be administered in combination with bendamustine and rituximab (BR) for patients with previously untreated MCL or as a single agent for patients with relapsed or refractory MCL. For additional information concerning BR see the corresponding rituximab or bendamustine prescribing information. .

CLL and WM

The recommended dose for the treatment of CLL and WM, either as a single agent or in combination, is 420 mg once daily (for details of the combination regimen, see section 5.1).

Treatment with IMBRUVICA should continue until disease progression or no longer tolerated by the patient. In combination with venetoclax for the treatment of CLL, IMBRUVICA should be administered as a single agent for 3 cycles (1 cycle is 28 days), followed by 12 cycles of IMBRUVICA plus venetoclax. See the venetoclax Prescribing Information for full venetoclax dosing information.

When administering IMBRUVICA in combination with anti-CD20 therapy, it is recommended to administer IMBRUVICA prior to anti-CD20 therapy when given on the same day.

Chronic graft versus host disease (cGVHD)
The recommended dose of IMBRUVICA for cGVHD is 420 mg orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity. When a patient no longer requires therapy for the treatment of cGVHD, IMBRUVICA should be discontinued considering the medical assessment of the individual patient.

Dose adjustments
Moderate and strong CYP3A4 inhibitors increase the exposure of ibrutinib (see sections 4.4 and 4.5).

The dose of ibrutinib should be reduced to 280 mg once daily when used concomitantly with moderate CYP3A4 inhibitors.

The dose of ibrutinib should be reduced to 140 mg once daily or withheld for up to 7 days when it is used concomitantly with strong CYP3A4 inhibitors.

IMBRUVICA therapy should be withheld for any new onset or worsening grade 2 cardiac failure, grade 3 cardiac arrhythmias, grade ≥ 3 non-haematological toxicity, grade 3 or greater neutropenia with infection or fever, or grade 4 haematological 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/cGVHD dose modification after recovery**
Grade 3 or 4 non-haematological toxicities Grade 3 or 4 neutropenia with infection or fever Grade 4 haematological 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	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/SLL.
* 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/cGVHD 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 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
Elderly
No specific dose adjustment is required for elderly patients (aged ≥ 65 years).

Renal impairment
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. Administer IMBRUVICA to patients with severe renal impairment (< 30 mL/min creatinine clearance) only if the benefit outweighs the risk and monitor patients closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis (see section 5.2).

Hepatic impairment
Ibrutinib is metabolised in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure (see section 5.2). 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).

Severe cardiac disease
Patients with severe cardiovascular disease were excluded from IMBRUVICA clinical studies.

Paediatric population
IMBRUVICA is not recommended for use in children and adolescents aged 0 to 18 years as efficacy has not been established.

Method of administration
IMBRUVICA should be administered orally once daily with a glass of water approximately at the same time each day. The capsules should be swallowed whole with water and should not be opened, broken or chewed. The tablets should be swallowed whole with water and should not be broken or chewed. IMBRUVICA must not be taken with grapefruit juice or Seville oranges (see section 4.5).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

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 haemorrhage, and haematuria.

Warfarin or other vitamin K antagonists should not be administered concomitantly with IMBRUVICA. Use of either anticoagulants or medicinal products that inhibit platelet function (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

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

Splenic rupture

Cases of splenic rupture have been reported following discontinuation of IMBRUVICA treatment. Disease status and spleen size should be carefully monitored (e.g. clinical examination, ultrasound) when IMBRUVICA treatment is interrupted or ceased. Patients who develop left upper abdominal or shoulder tip pain should be evaluated and a diagnosis of splenic rupture should be considered.

Infections

Infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) were observed in patients treated with IMBRUVICA. Some of these infections have been associated with hospitalisation and death. Most patients with fatal infections also had neutropenia. Patients should be monitored for fever, abnormal liver function tests, neutropenia and infections and appropriate anti-infective therapy should be instituted as indicated. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Cases of invasive fungal infections, including cases of Aspergillosis, Cryptococcosis and Pneumocystis jiroveci infections have been reported following the use of ibrutinib. Reported cases of invasive fungal infections have been associated with fatal outcomes.

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 (see section 4.8). Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural 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.

Data from one study in elderly patients (≥65 years of age) with previously untreated MCL suggest an increased risk of serious or fatal infections, including pneumonia, when IMBRUVICA is used in combination with bendamustine and rituximab, including during rituximab maintenance and ibrutinib monotherapy phase (for details of the combination regimen, see section 5.1 Pharmacodynamic Properties). Patients with diabetes mellitus, COPD/asthma, and/or lymphopenia may be at greater risk for these events, and benefit/risk should be carefully evaluated in these patients. Patients should be closely monitored for infections, including respiratory signs and symptoms throughout treatment, and appropriate anti-infective therapy should be initiated promptly.

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 and viral hepatitis status should be assessed before initiating treatment with IMBRUVICA. Patients should be periodically monitored 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 anaemia) were reported in patients treated with IMBRUVICA. Monitor complete blood counts monthly.

Interstitial Lung Disease (ILD)

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

Cardiac arrhythmias and cardiac failure

Fatal and serious cardiac arrhythmias and cardiac failure have occurred in patients treated with IMBRUVICA. Patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or 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.

For patients with relevant risk factors for cardiac events, carefully assess benefit/risk before initiating treatment with IMBRUVICA; alternative treatment may be considered.

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.

Patients should be monitored for signs and symptoms of cardiac failure during IMBRUVICA treatment. In some of these cases cardiac failure resolved or improved after IMBRUVICA withdrawal or dose reduction.

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 (please see section 4.4 Cardiac arrhythmia and Hypertension and section 4.8).

Tumour lysis syndrome
Tumour lysis syndrome (TLS) has been reported with IMBRUVICA therapy. Patients at risk of tumour lysis syndrome are those with high tumour 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 (see section 4.8). Regularly monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust antihypertensive medication throughout treatment with IMBRUVICA as appropriate.

Haemophagocytic lymphohistiocytosis (HLH)
Cases of HLH (including fatal cases) have been reported in patients treated with IMBRUVICA. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of extreme systemic inflammation. HLH is characterised by fever, hepatosplenomegaly, hypertriglyceridaemia, high serum ferritin and cytopenias. Patients should be informed about symptoms of HLH. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered.

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 (see sections 4.2 and

4.5). If a CYP3A4 inducer 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 (see section 4.6).

Excipients with known effect
Capsules
Each capsule contains less than 1 mmol sodium (23 mg), and is essentially sodium-free.

Tablets
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Each film-coated tablet contains less than 1 mmol sodium (23 mg), and is essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction
Ibrutinib is primarily metabolised by cytochrome P450 enzyme 3A4 (CYP3A4).

Agents that may increase ibrutinib plasma concentrations
Concomitant use of IMBRUVICA and medicinal products that strongly or moderately inhibit CYP3A4 can increase ibrutinib exposure and strong CYP3A4 inhibitors 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 *Section 4.2 and 5.2*).

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.
Chronic Graft versus Host Disease	• Mild CYP3A inhibitors	420 mg once daily. No dose adjustment required.
	• Moderate CYP3A inhibitors	420 mg once daily. No dose adjustment required.
	• Voriconazole • Posaconazole at doses less than or equal to suspension 200 mg BID	280 mg once daily.
	• Posaconazole at higher doses[b]	140 mg once daily.
	• Other strong CYP3A inhibitors	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 *Section 4.2*).

Agents that may decrease ibrutinib plasma concentrations
Administration of IMBRUVICA with inducers of CYP3A4 can decrease ibrutinib plasma concentrations.

Co-administration of rifampicin, a strong CYP3A4 inducer, in 18 fasted healthy subjects, decreased exposure (C_{max} and AUC) of ibrutinib by 92 and 90%, respectively. Avoid concomitant use of strong or moderate CYP3A4 inducers (e.g., carbamazepine, rifampicin, phenytoin). Preparations containing St. John's Wort are contraindicated during treatment with IMBRUVICA, as efficacy may be reduced. Consider alternative agents with less CYP3A4 induction. If the benefit outweighs the risk and a strong or moderate CYP3A4 inducer must be used, monitor patient closely for lack of efficacy (see sections 4.3 and 4.4). Mild inducers may be used concomitantly with IMBRUVICA, however, patients should be monitored for potential lack of efficacy.

Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. A lower C_{max} was observed in fasted healthy subjects administered a single 560 mg dose of ibrutinib after taking omeprazole at 40 mg once daily for 5 days (see section 5.2). There is no evidence that the lower C_{max} would have clinical significance, and medicinal products that increase stomach pH (e.g., proton pump inhibitors) have been used without restrictions in the pivotal clinical studies.

Agents that may have their plasma concentrations altered by ibrutinib
Ibrutinib is a P-gp and breast cancer resistance protein (BCRP) inhibitor *in vitro*. As no clinical data are available on this interaction, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. To minimise the potential for an interaction in the GI tract, oral 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 in the liver and increase the exposure of medicinal products that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

In studies of ibrutinib (420 mg) in combination with venetoclax (400 mg) in CLL patients, an increase in venetoclax exposure (approximately 1.8-fold based on AUC) was observed compared with monotherapy data for venetoclax.

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 (ethinylestradiol and levonorgestrel), the CYP3A4 substrate midazolam, nor the CYP2B6 substrate bupropion.

4.6 Fertility, pregnancy and lactation
Women of child-bearing potential/Contraception in females
Based on findings in animals, IMBRUVICA may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking IMBRUVICA and for three months after stopping treatment.

Pregnancy
IMBRUVICA should not be used during pregnancy. There are no data from the use of IMBRUVICA in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding
It is not known whether ibrutinib or its metabolites are excreted in human milk. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with IMBRUVICA.

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 (Human Equivalent Dose [HED] 16 mg/kg/day) (see section 5.3). No human data on the effects of ibrutinib on fertility are available.

4.7 Effects on ability to drive and use machines
IMBRUVICA has minor influence on the 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.

4.8 Undesirable effects
Summary of the safety profile
B-cell malignancies
The most commonly occurring adverse reactions (≥ 20%) were diarrhoea, neutropenia, musculoskeletal pain, haemorrhage (e.g., bruising), rash, nausea, thrombocytopenia, arthralgia, and upper respiratory tract infection. The most common grade 3/4 adverse reactions (≥ 5%) were neutropenia, lymphocytosis, thrombocytopenia, hypertension and pneumonia.

Tabulated list of adverse reactions
The safety profile is based on pooled data from 1,981 patients treated with IMBRUVICA in four phase 2 clinical studies and eight randomised phase 3 studies and from post-marketing experience. Patients treated for MCL in clinical studies received IMBRUVICA at 560 mg once daily and patients treated for CLL or WM in clinical studies received IMBRUVICA at 420 mg once daily. All patients in clinical studies received IMBRUVICA until disease progression or no longer tolerated, except for studies with IMBRUVICA in combination with venetoclax where patients received fixed duration treatment (Studies CLL3011 and PCYC-1142-CA). The median duration of IMBRUVICA treatment across the pooled dataset was 14.7 months. The median duration of treatment for CLL/SLL was 14.7months (up to 52 months); MCL was 11.7 months (up to 28 months); WM was 21.6 months (up to 37 months).

Adverse reactions in patients treated with ibrutinib for B-cell malignancies and post-marketing adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported in clinical studies or during post marketing surveillance in patients with B-cell malignancies[†]

System organ class	Frequency (All grades)	Adverse reactions	All Grades (%)	Grade ≥3 (%)
Infections and infestations	Very common	Pneumonia*[#]	12	7
		Upper respiratory tract infection	21	1
		Skin infection*	15	2
	Common	Sepsis*[#]	3	3
		Urinary tract infection	9	1
		Sinusitis*	9	1
	Uncommon	Cryptococcal infections*	<1	0
		Pneumocystis infections*[#]	<1	<1
		Aspergillus infections*	<1	<1
		Hepatitis B reactivation[@ #]	<1	<1
	Rare	Progressive multifocal leukoencephalopathy[#]	<1	<1
Neoplasms benign and malignant (incl cysts and polyps)	Common	Non-melanoma skin cancer*	5	1
		Basal cell carcinoma	3	<1
		Squamous cell carcinoma	1	<1
Blood and lymphatic system disorders	Very common	Neutropenia*	39	31
		Thrombocytopenia*	29	8
		Lymphocytosis[*]	15	11
	Common	Febrile neutropenia	4	4
		Leukocytosis	4	4
	Rare	Leukostasis syndrome	<1	<1
Immune system disorders	Common	Interstitial lung disease[*,#]	2	<1
Metabolism and nutrition disorders	Common	Hyperuricaemia	9	1
	Uncommon	Tumour lysis syndrome	1	1
Nervous system disorders	Very common	Dizziness	12	<1
		Headache	19	1
	Common	Peripheral neuropathy[*]	7	<1
	Uncommon	Cerebrovascular accident[#]	<1	<1
		Transient ischaemic attack	<1	<1
		Ischaemic stroke[#]	<1	<1
Eye disorders	Common	Vision blurred	6	0
	Uncommon	Eye haemorrhage[‡]	<1	0
		Uveitis*	<1	0
Cardiac disorders	Common	Cardiac failure [*, #]	2	1
		Atrial fibrillation	8	4

	Uncommon	Ventricular tachyarrhythmia[*, #] Cardiac arrest[#]	1 <1	<1 <1
Vascular disorders	Very common	Haemorrhage*[#] Bruising* Hypertension*	35 27 18	1 <1 8
	Common	Epistaxis Petechiae	9 7	<1 0
	Uncommon	Subdural haematoma[#]	1	<1
Respiratory, thoracic and mediastinal disorders	Very common	Cough[*]	24	<1
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Stomatitis* Nausea Constipation Dyspepsia	47 15 17 31 16 11	4 1 1 1 <1 <1
Hepatobiliary disorders	Uncommon	Hepatic failure*[, #]	<1	<1
Skin and subcutaneous tissue disorders	Very common	Rash*	34	3
	Common	Urticaria Erythema Onychoclasis	1 3 4	<1 <1 0
	Uncommon	Angioedema Panniculitis[*] Neutrophilic dermatoses[*] Pyogenic granuloma Cutaneous vasculitis	<1 <1 <1 <1 <1	<1 <1 <1 0 0
	Rare	Stevens-Johnson syndrome	<1	<1
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Muscle spasms Musculoskeletal pain*	24 15 36	2 <1 3
Renal and urinary disorders	Common	Acute kidney injury[#]	<2	<1
General disorders and administration site conditions	Very common	Pyrexia Oedema peripheral	19 16	1 1
Investigations	Very common	Blood creatinine increased	10	<1

† Frequencies are rounded to the nearest integer.
* Includes multiple adverse reaction terms.
‡ In some cases associated with loss of vision.
# Includes events with fatal outcome.
@ Lower level term (LLT) used for selection.

Description of selected adverse reactions

Discontinuation and dose reduction due to adverse reactions

Of the 1,981 patients treated with IMBRUVICA for B-cell malignancies, 6% discontinued treatment primarily due to adverse reactions. These included pneumonia, atrial fibrillation, neutropenia, rash, thrombocytopenia, and haemorrhage. Adverse reactions leading to dose reduction occurred in approximately 8% of patients.

Elderly
Of the 1,981 patients treated with IMBRUVICA, 50% were 65 years of age or older. Grade 3 or higher pneumonia (11% of patients age ≥65 versus 4% of patients <65 years) and thrombocytopenia (11% of patients age ≥65 years versus 5% of patients <65 years) occurred more frequently among elderly patients treated with IMBRUVICA.

Long-term safety
The safety data from long-term treatment with IMBRUVICA over 5 years from 1284 patients (treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, relapsed/refractory MCL n=370, and WM n=106) were analysed. The median duration of treatment for CLL/SLL 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%.

Patients with previously untreated MCL
Combination therapy
Adverse reactions and laboratory abnormalities described below in Tables 2 and 3 reflect exposure to IMBRUVICA + BR with a median duration of 27 months and exposure to placebo + BR with a median duration of 34 months in Study MCL3002.

Table 2: Adverse reactions reported in patients with previously untreated MCL treated with 560 mg IMBRUVICA in combination with BR in Study MCL3002[a]

	IMBRUVICA+BR (n=259)		Placebo+BR (n=260)	
System Organ Class/ MedDRA Preferred Term	**All Grades (%)**	**Grade 3 or Higher (%)**	**All Grades (%)**	**Grade 3 or Higher (%)**
Blood and lymphatic system disorders				
Thrombocytopenia*	36	13	27	13
Anemia*	34	15	25	9
Gastrointestinal disorders				
Diarrhea	46	7	37	4
Vomiting	22	3	18	0
Abdominal pain*	20	3	17	1
General disorders and administration site conditions				
Pyrexia	37	2	32	2
Edema peripheral	20	1	16	0
Infections and infestations				
Pneumonia*	39	26	27	17

Skin infection*	24	7	9	2
Metabolism and nutrition disorders				
Decreased appetite	22	2	14	1
Hypokalemia	15	7	12	5
Skin and subcutaneous tissue disorders				
Rash*	56	21	37	6
Bruising*	22	0	8	0
Vascular disorders				
Hemorrhage*	31	4	18	2

* Includes multiple adverse reaction terms.

a Occurring at ≥15% incidence and ≥2% greater in the IMBRUVICA + BR arm when compared to the placebo + BR arm

Table 3: Select laboratory abnormalities (≥20% Any Grade) new or worsening from baseline in patients receiving IMBRUVICA in Study MCL3002

System Organ Class Adverse reaction	**IMBRUVICA+BR (N=259)**		**Placebo+BR (N=260)**	
	All Grades (%)	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematology abnormalities[a]				
Neutrophils decreased	81	59	86	57
Platelets decreased	71	15	60	14
Hemoglobin decreased	56	16	61	12
Chemistry abnormalities				
Hypernatremia	24	1	22	0
Hypocalcemia	34	1	20	1
Hypomagnesemia	27	1	25	2
Bilirubin increased	25	2	19	1
Hyperkalemia	22	1	32	4
Hypokalemia	34	8	26	6
Hyperuricemia	44	7	38	7
Hypophosphatemia	30	7	33	7
AST increased	37	5	34	2
ALP increased	32	0	23	<1
ALT increased	34	6	26	1
Creatinine increased	41	3	40	1

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

<1 used for frequency above 0 and below 0.5%

Chronic graft versus host disease

The data described below reflect exposure to IMBRUVICA in an open-label clinical study that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD study (≥ 20%) were fatigue, bruising, diarrhea, stomatitis, muscle spasms, nausea, hemorrhage, and pneumonia. Atrial fibrillation occurred in one patient (2%), which was Grade 3.

Discontinuation and dose reduction due to ARs
Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions described below in Table 4 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD study.

Table 4: Adverse reactions reported in ≥10% of patients with cGVHD treated with 420 mg IMBRUVICA - Study 1129 (N=42)

System Organ Class	Adverse Reaction	All Grades (%)	Grades 3 4 (%)
Infections and infestations	Pneumonia*	21	10
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Metabolism and nutrition disorders	Hypokalemia	12	7
Nervous system disorders	Headache	17	5
Vascular disorders	Hemorrhage*	26	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Skin and subcutaneous tissue disorders	Bruising*	41	0
	Rash*	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Injury, poisoning and procedural complications	Fall	17	0

* Includes multiple adverse reaction terms.

4.9 Overdose
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 (1,400 mg/day). In a separate study, one healthy subject who received a dose of 1,680 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 dose should be closely monitored and given appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 signalling 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 CLL. BTK's pivotal role in signalling 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 effectively inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.
In preclinical tumour models, the combination of ibrutinib and venetoclax resulted in increased cellular apoptosis and anti-tumor activity compared to either agent alone. BTK inhibition by ibrutinib increases CLL cell dependence on BCL-2, a cell survival pathway, while venetoclax inhibits BCL-2 leading to apoptosis.

Lymphocytosis
Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and an absolute count > 5,000/mcL), often associated with reduction of lymphadenopathy, has been observed in about three fourths of patients with CLL treated with IMBRUVICA. This effect has also been observed in about one third of patients with relapsed or refractory 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 8.0 weeks in patients with MCL and 14 weeks in patients with CLL. A large increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in some patients.

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. Ibrutinib did not show meaningful inhibition of platelet aggregation using other agonists of platelet aggregation.

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 randomised, double-blind thorough QT study with placebo and positive controls. At a supratherapeutic dose of 1,680 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 1,680 mg).

Clinical efficacy and safety
MCL

Patient previously untreated for MCL
Combination therapy

The safety and efficacy of IMBRUVICA in elderly patients 65 years of age or older with previously untreated MCL were evaluated in a randomised, double-blind, placebo-controlled phase 3 study of IMBRUVICA in combination with bendamustine and rituximab (BR) versus placebo + BR (Study MCL3002). Patients (n=523) were randomized 1:1 to receive either IMBRUVICA 560 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles. Bendamustine was administered at a dose of 90 mg/m^2 infused IV over 30

minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 in the first cycle, Day 1, and 500 mg/m^2 Cycles 2 through 6, Day 1. Patients with a CR or PR continued to receive rituximab maintenance every second cycle for a maximum of 12 additional doses.

The median age was 71 years (range, 65 to 87 years), 70% were male, and 77% were Caucasian. At baseline, 99% of patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 37% of subjects had at least one tumor ≥5 cm, 76% had bone marrow involvement, and 88% had extranodal involvement at screening. At baseline, blastoid histology was noted in 7% of patients and pleomorphic histology was noted in 1% of patients. The simplified MIPI score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was low in 17%, intermediate in 48% and high in 34% of patients. Baseline TP53 mutation status was evaluated in 269 of 523 patients and present in 19% of evaluated patients.

With a median follow-up time on study of 84 months, efficacy results for MCL3002 are shown in Table 5 and the Kaplan-Meier curves for PFS are shown in Figure 1. The results were assessed by investigator according to the revised International Working Group (IWG) for non Hodgkin's lymphoma (NHL) criteria (2007).

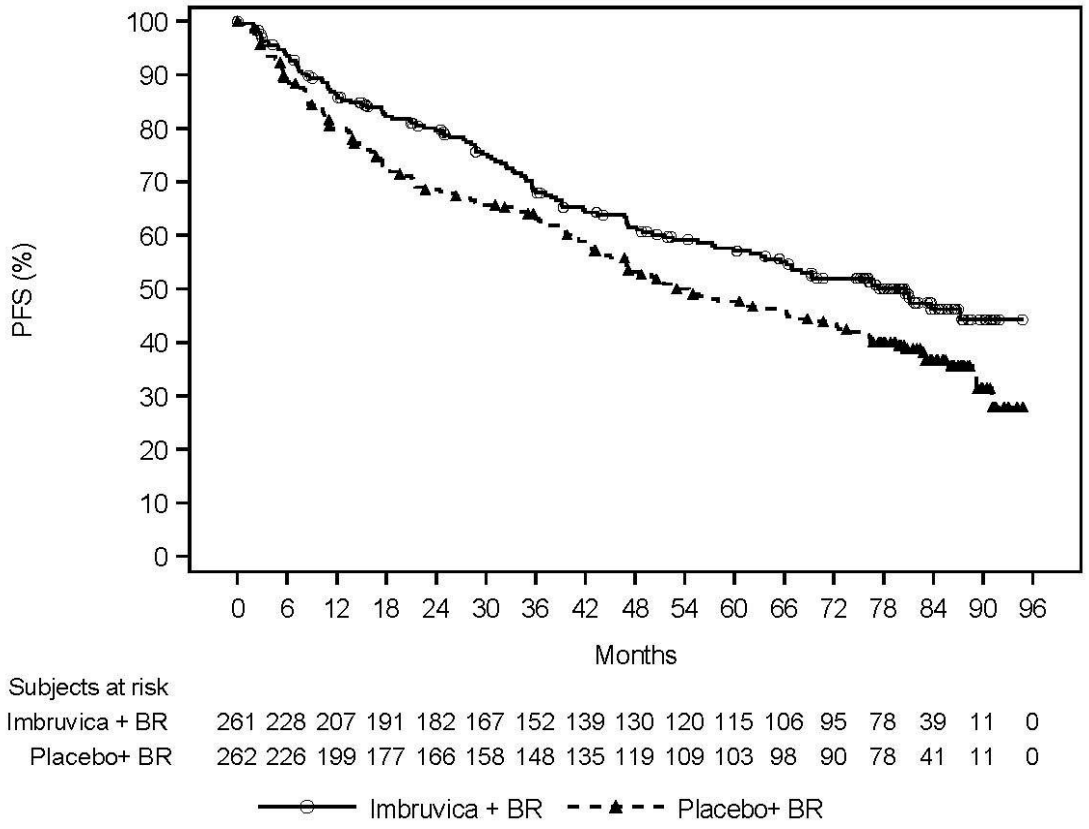
Table 5: Efficacy results in patients with MCL in Study MCL3002

Endpoint	**IMBRUVICA + BR N=261**	**Placebo + BR N=262**
Progression Free Survival[a]		
Number of events (%)	116 (44.4%)	152 (58.0%)
Disease Progression	49 (18.8%)	119 (45.4%)
Deaths	67 (25.7%)	33 (12.6%)
Median (95% CI), months	80.6 (61.9, NE)	52.9 (43.7, 71.0)
HR (95% CI)	0.75 (0.59, 0.96)	
P-value[b]	0.011	
Time to Next Treatment		
Median (95% CI), months	Not reached	92.0 (71.5, NE)
HR (95% CI)	0.48 (0.34, 0.66)	
P-value[c]	<0.001	
Complete Response Rate[a]	**171 (65.5%)**	**151 (57.6%)**
Relative Risk (95% CI)	1.14 (1.00, 1.30)	
P-value[d]	0.0567	
Overall Response Rate (CR+PR)[a]	**234 (89.7%)**	**262 (88.5%)**
Relative Risk (95% CI)	1.01 (0.95, 1.07)	
P-value[d]	0.6752	
Median duration of overall response, months (range)	81 (0.0+, 92.1+)	63.5 (0.0+, 92.1+)
Overall Survival[e]		
Number of deaths (%)	104 (39.8%)	107 (40.8%)
HR (95% CI)	1.07 (0.81, 1.40)	
P-value[c]	0.648	

CI=confidence interval; HR=hazard ratio; CR=complete response; PR=partial response; NE = not estimable
Except the p-values for PFS and CR, all other p-values are nominal.

[a] Investigator evaluated
[b] One-sided p-value is from stratified log-rank test
[c] Two-sided p-value is from a stratified log-rank test
[d] Two-sided p-value is from CMH test
[e] Median OS not reached for both arms

Figure 1: Kaplan Meier curve of PFS (ITT Population) in Study MCL3002



1-year additional follow-up OS Analysis

With a median follow-up of 94.5 months, the overall survival hazard ratio was 1.00 [95% CI (0.77, 1.30)] for MCL3002. There were 110 (42.1%) deaths in the I+BR arm and 119 (45.4%) in the placebo + BR arm, and the median overall survival was 100.6 and 94.2 months, respectively.

Patients with MCL who received at least one prior therapy

Single agent

The safety and efficacy of IMBRUVICA in patients with relapsed or refractory MCL 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 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 autologous or allogeneic 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. Tumour response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Responses to IMBRUVICA are shown in Table 6.

Table 6: ORR and DOR in patients with relapsed or refractory MCL (Study PCYC-1104-CA)

	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; DOR = duration of response; ORR = overall response rate; 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% complete response (CR) rate and a 48% partial response (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/prognostic factors, bulky disease, gender or age.

The safety and efficacy of IMBRUVICA were demonstrated in a randomised phase 3, open-label, multicenter study including 280 patients with MCL who received at least one prior therapy (Study MCL3001). Patients were randomised 1:1 to receive either IMBRUVICA orally at 560 mg once daily for 21 days 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; 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) was assessed by IRC according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. Efficacy results for Study MCL3001 are shown in Table 7 and the Kaplan-Meier curve for PFS in Figure 2.

Table 7: Efficacy Results in patients with relapsed or refractory MCL (Study MCL3001)

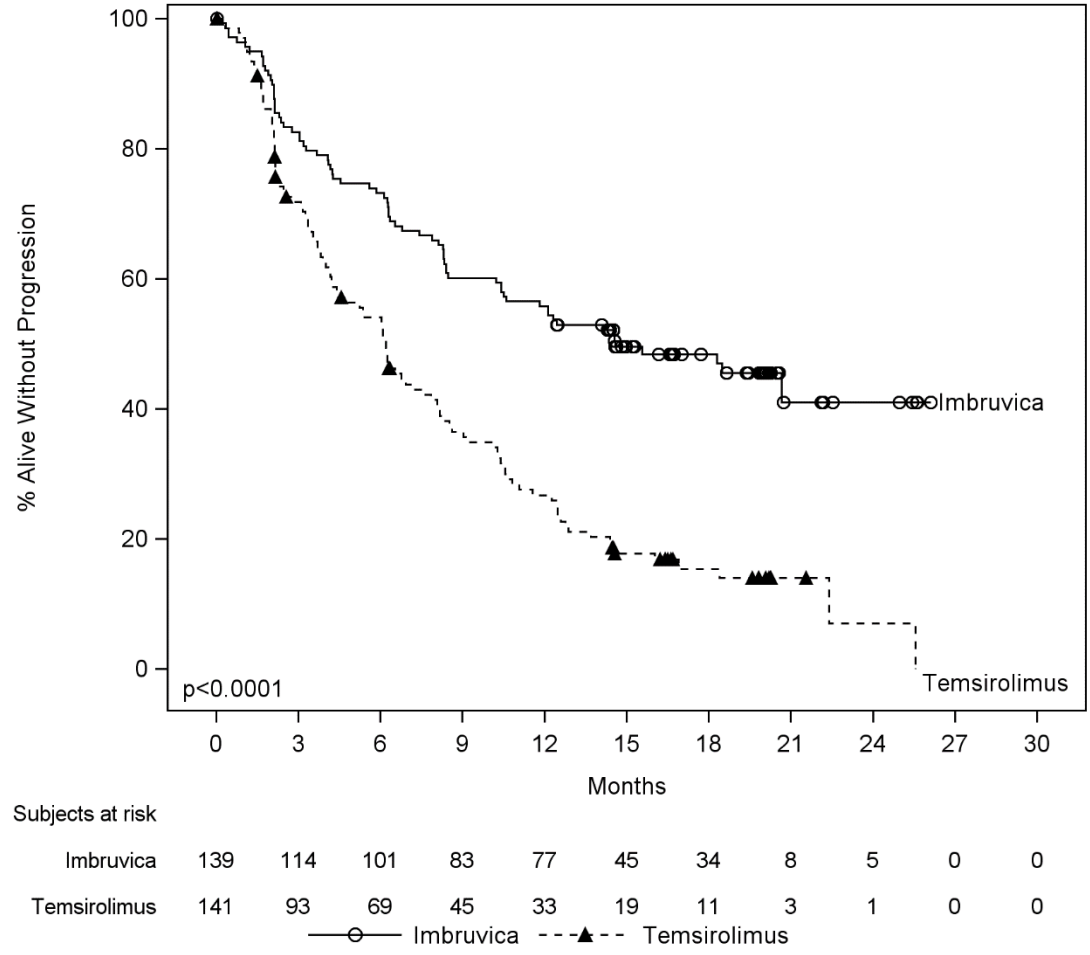
Endpoint	IMBRUVICA N = 139	Temsirolimus N = 141
PFS[a]		
Median PFS (95% CI), (months)	14.6 (10.4, NE)	6.2 (4.2, 7.9)
	HR = 0.43 [95% CI: 0.32, 0.58]	
ORR (%)	71.9	40.4
p-value	p < 0.0001	

NE = not estimable; HR = hazard ratio; CI = confidence interval; ORR = overall response rate; PFS = progression-free survival

[a] IRC evaluated.

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

Figure 2: Kaplan-Meier curve of PFS (ITT Population) in Study MCL3001



CLL

Patients previously untreated for CLL

Single agent

A randomised, multicenter, open-label phase 3 study (PCYC-1115-CA) of IMBRUVICA versus chlorambucil was conducted in patients with treatment-naïve CLL who were 65 years of age or older. Patients between 65 and 70 years of age were required to have at least one comorbidity that precluded the use of frontline chemo-immunotherapy with fludarabine, cyclophosphamide, and rituximab. Patients (n = 269) were randomised 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 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 anaemia, 23% with baseline thrombocytopenia, 65% had elevated β2 microglobulin > 3,500 mcg/L, 47% had a CrCL < 60 mL/min, 20% of patients presented with del11q, 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 International Workshop on CLL (IWCLL) criteria indicated an 84% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm. Efficacy results for Study PCYC-1115-CA are shown in Table 8 and the Kaplan-Meier curves for PFS and OS are shown in Figures 3 and 4, respectively.

There was a statistically significant sustained platelet or haemoglobin improvement in the ITT population in favour of ibrutinib versus chlorambucil. In patients with baseline cytopenias, sustained haematologic improvement was: platelets 77.1% versus 42.9%; haemoglobin 84.3% versus 45.5% for ibrutinib and chlorambucil, respectively.

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

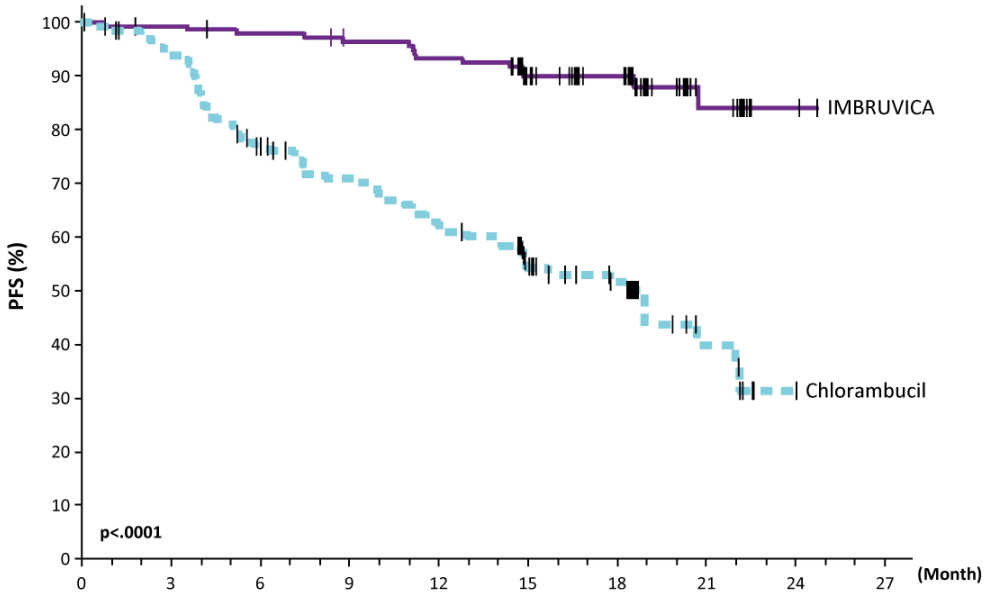
Endpoint	**IMBRUVICA N = 136**	**Chlorambucil N = 133**
PFS[a]		
Number of events (%)	15 (11.0)	64 (48.1)
Median (95% CI), months	Not reached	18.9 (14.1, 22.0)
HR (95% CI)	0.161 (0.091, 0.283)	
ORR[a] **(CR +PR)**	82.4%	35.3%
P-value	< 0.0001	
OS[b]		
Number of deaths (%)	3 (2.2)	17 (12.8)
HR (95% CI)	0.163 (0.048, 0.558)	

CI = confidence interval; HR = hazard ratio; CR = complete response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response

[a] IRC evaluated, median follow--up 18.4 months.

[b] Median OS not reached for both arms. p < 0.005 for OS

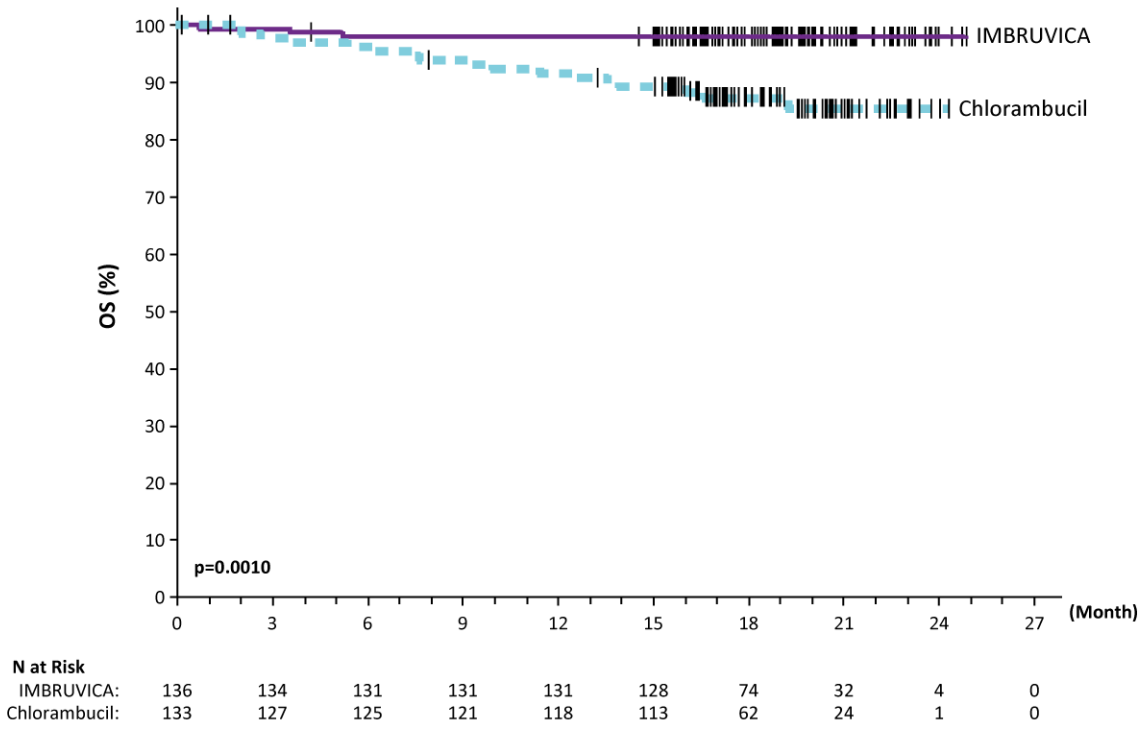
Figure 3: Kaplan-Meier curve of PFS (ITT Population) in Study PCYC-1115-CA



N at Risk

IMBRUVICA:	136	133	130	126	122	98	66	21	2	0
Chlorambucil:	133	121	95	85	74	49	34	10	0	0

Figure 4: Kaplan-Meier curve of OS (ITT Population) in Study PCYC-1115-CA

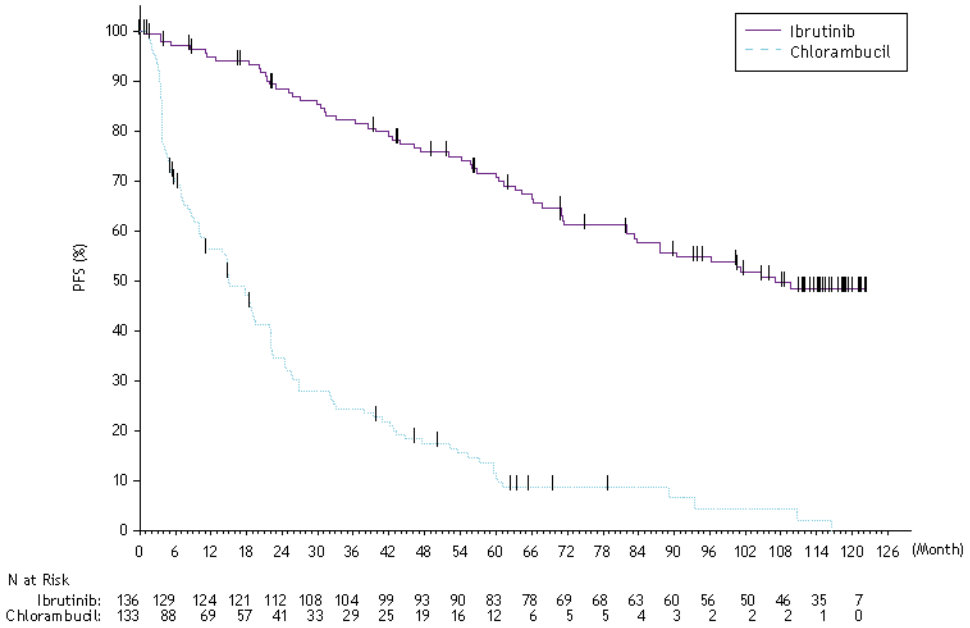


The treatment effect of ibrutinib in Study PCYC-1115-CA was consistent across high-risk patients with del17p/TP53 mutation, del11q, and/or unmutated IGHV.

Final analysis at median follow-up of > 9 years (115 months)
With median follow-up time on study of 115 months in Study PCYC-1115-CA and its extension study, 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 in the IMBRUVICA arm was 107 months and 15 months in the chlorambucil arm; (HR = 0.155 [95% CI (0.110, 0.220)]. The updated Kaplan-Meier

curve for PFS is shown in Figure 5. An improvement in ORR was maintained for the ibrutinib arm (91.2%) compared to the chlorambucil arm (36.8%). The complete response rate (CR and CRi) in the IMBRUVICA arm increased from 11% to 36% between the primary analysis and study closure. The Kaplan-Meier landmark estimate for OS at 108 months was 68.0% in the IMBRUVICA arm.

Figure 5: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1115-CA with 115 Months Follow-up



Combination therapy

The safety and efficacy of IMBRUVICA in patients with previously untreated CLL/SLL were further evaluated in a randomised, multi-center, open-label, phase 3 study (PCYC-1130-CA) of IMBRUVICA in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab. 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 del17p/TP53 mutation. Patients (n=229) were randomised 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 1,000 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 anaemia, 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/SLL with high risk factors (del17p/TP53 mutation [18%], del11q [15%], or unmutated IGHV [54%]).

Progression-free survival (PFS) was 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. Efficacy results for Study PCYC-1130-CA are shown in Table 9 and the Kaplan-Meier curve for PFS is shown in Figure 6.

Table 9: 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

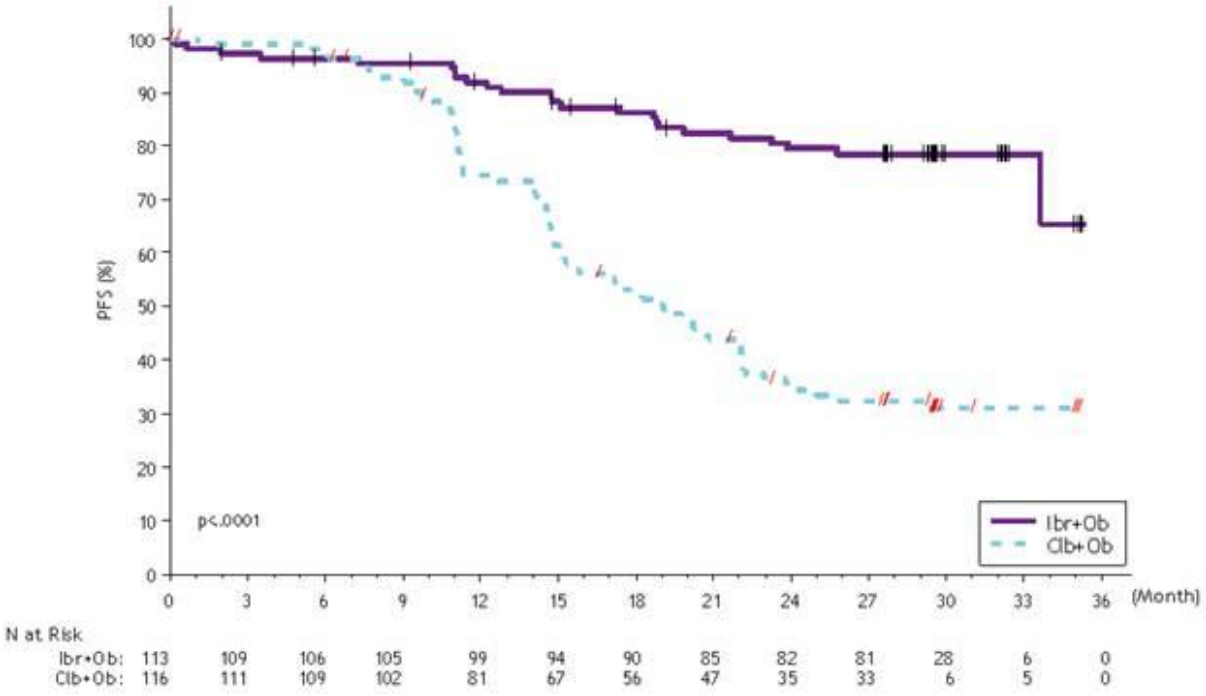
CI=confidence interval; HR=hazard ratio; CR=complete response; PR=partial response.

[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 PFS (ITT Population) in Study PCYC-1130-CA



The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (del17p/TP53 mutation, del11q, or unmutated IGHV), with a PFS HR of 0.15 [95% CI (0.09, 0.27)], as shown in Table 10. The 2-year PFS rate estimates for the high-risk CLL/SLL 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 10: 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.

The safety and efficacy of IMBRUVICA in patients with previously untreated CLL or SLL were further evaluated in a randomised, multi-center, open-label, phase 3 study (E1912) of IMBRUVICA in combination with rituximab (IR) versus standard fludarabine, cyclophosphamide, and rituximab (FCR) chemo-immunotherapy. The study enrolled previously untreated patients with CLL or SLL who were 70 years or younger. Patients with del17p were excluded from the study. Patients (n=529) were randomised 2:1 to receive either IR or FCR. IMBRUVICA was administered at a dose of 420 mg daily until disease progression or unacceptable toxicity. Fludarabine was administered at a dose of 25 mg/m2, and cyclophosphamide was administered at a dose of 250 mg/m2, 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

a dose of 50 mg/m2 on Day 1 of the first cycle, 325 mg/m2 on Day 2 of the first cycle, and 500 mg/m2 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 or 1 (98%) or 2 (2%). At baseline, 43% of patients presented with Rai Stage III or IV, and 59% of patients presented with CLL/SLL 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 11. The Kaplan-Meier curves for PFS, assessed according to IWCLL criteria, and OS are shown in Figures 7 and 8, respectively.

Table 11: Efficacy results in Study E1912

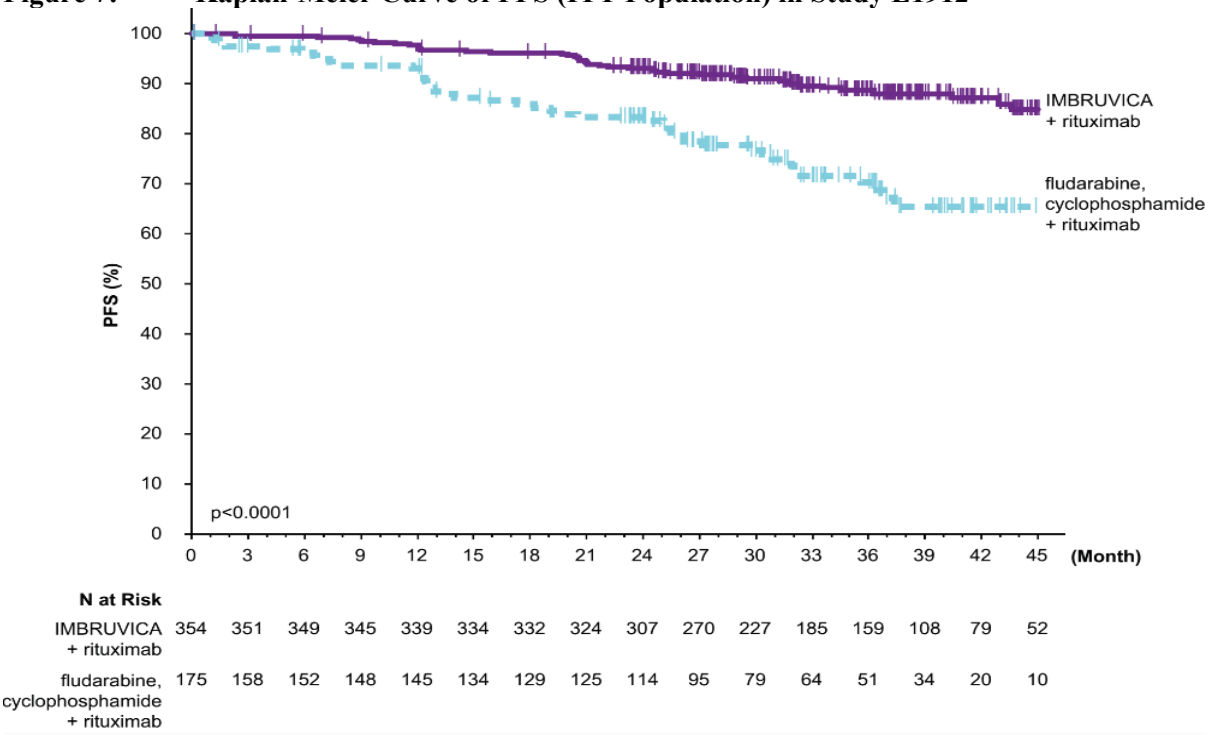
Endpoint	**Ibrutinib+ rituximab (IR) N=354**	**Fludarabine, Cyclophosphamide, and Rituximab (FCR) N=175**
Progression Free Survival		
Number of events (%)	41 (12)	44 (25)
Disease progression	39	38
Death events	2	6
Median (95% CI), months	NE (49.4, NE)	NE (47.1, NE)
HR (95% CI)	0.34 (0.22, 0.52)	
P-value[a]	<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 PFS (ITT Population) in Study E1912



The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (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 12. The 3-year PFS rate estimates for the high-risk CLL/SLL 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.

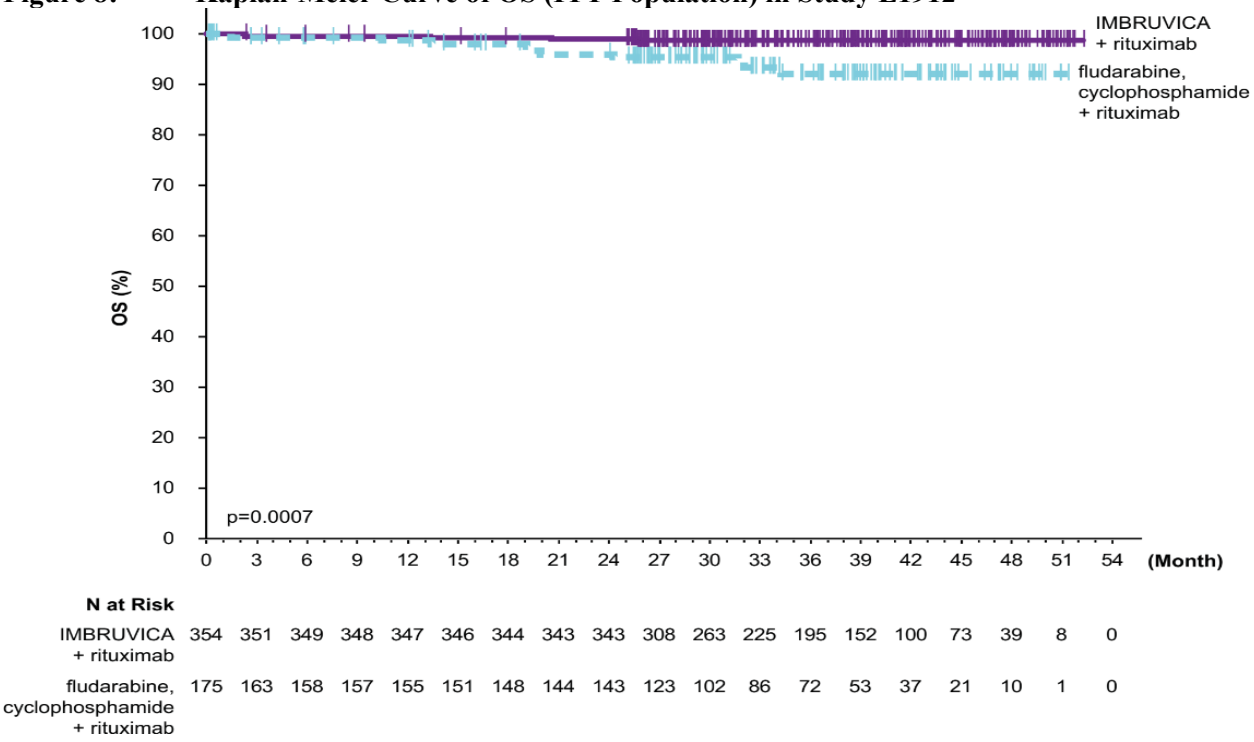
Table 12: Subgroup Analysis of PFS (Study E1912)

	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 OS (ITT Population) in Study E1912



Fixed duration combination therapy

The safety and efficacy of fixed duration therapy with IMBRUVICA in combination with venetoclax versus chlorambucil in combination with obinutuzumab in patients with previously untreated CLL were evaluated in a randomised, open-label, phase 3 (CLL3011) study. The study enrolled patients with previously untreated CLL who were 65 years or older, and adult patients <65 years of age with a CIRS score >6 or CrCL ≥30 to <70 mL/min. Patients with del 17p or known TP53 mutations were excluded. Patients (n=211) were randomised 1:1 to receive either IMBRUVICA in combination with venetoclax or chlorambucil in combination with obinutuzumab. Patients in the IMBRUVICA plus venetoclax arm received single agent IMBRUVICA for 3 cycles followed by IMBRUVICA in combination with venetoclax for 12 cycles (including 5-week dose-titration schedule). Each cycle was 28 days. IMBRUVICA was administered at a dose of 420 mg daily. Venetoclax was administered daily, starting with 20 mg for 1 week, followed by 1 week at each dose level of 50 mg, 100 mg, and 200 mg, then the recommended daily dose of 400 mg. Patients randomised to the chlorambucil plus obinutuzumab arm received treatment for 6 cycles. Obinutuzumab was administered at a dose of 1,000 mg on

Days 1, 8 and 15 in Cycle 1. In Cycles 2 to 6, 1,000 mg obinutuzumab was given on Day 1. Chlorambucil was administered at a dose of 0.5 mg/kg body weight on Days 1 and 15 of Cycles 1 to 6. Patients with confirmed progression by IWCLL criteria after completion of either fixed duration regimen could be treated with single-agent IMBRUVICA.

The median age was 71 years (range, 47 to 93 years), 58% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (35%), 1 (53%), or 2 (12%). At baseline, 18% of patients presented with CLL with del 11q and 52% with unmutated IGHV.
At baseline assessment for risk of tumor lysis syndrome, 25% of patients had high tumor burden. After 3 cycles of single-agent IMBRUVICA lead-in therapy, 2% of patients had high tumor burden. High tumor burden was defined as any lymph node ≥10 cm; or any lymph node ≥5 cm and absolute lymphocyte count ≥25×109/L.
With a median follow-up time on study of 28 months, efficacy results for Study CLL3011 assessed by an IRC according to IWCLL criteria are shown in Table 13, the Kaplan-Meier curve for PFS is shown in Figure 9, and rates of minimal residual disease (MRD) negativity are shown in Table 14.

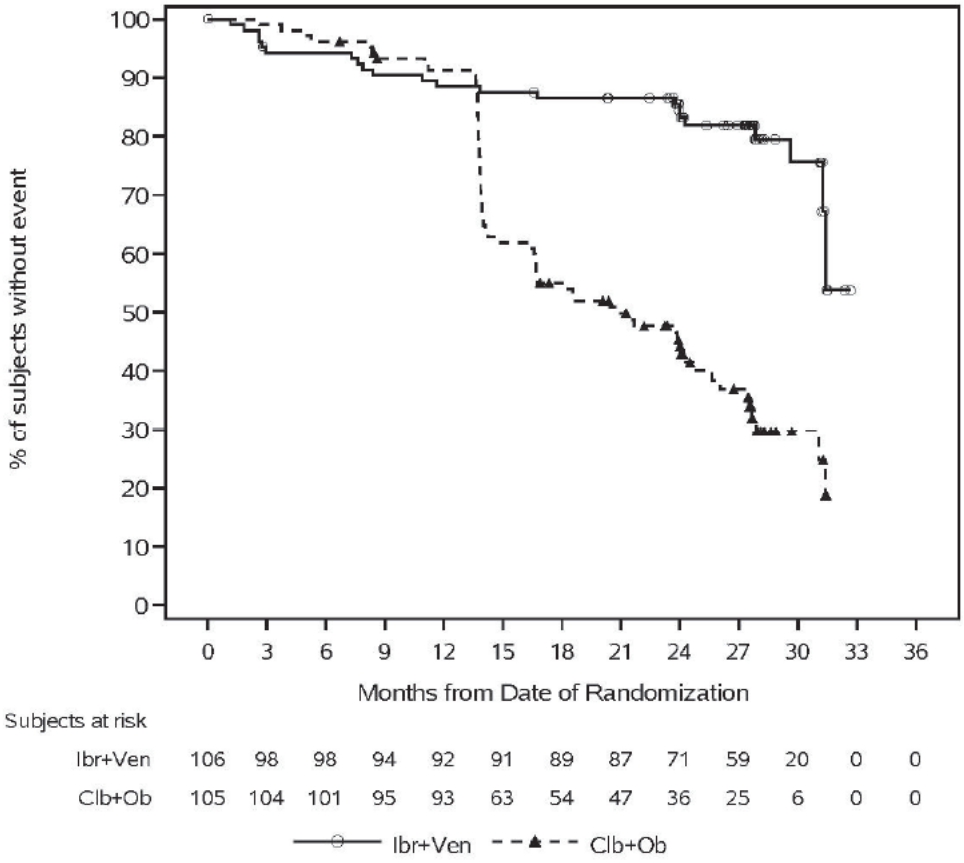
Table 13: Efficacy Results in Study CLL3011

Endpoint[a]	**IMBRUVICA + Venetoclax N=106**	**Chlorambucil + Obinutuzumab N=105**
Progression Free Survival		
Number of events (%)	22 (20.8)	67 (63.8)
Median (95% CI), months	NE (31.2, NE)	21.0 (16.6, 24.7)
HR (95% CI)	0.22 (0.13, 0.36)	
P-value[b]	<0.0001	
Complete Response Rate (%)[c]	38.7	11.4
95% CI	(29.4, 48.0)	(5.3, 17.5)
P-value[d]	<0.0001	
Overall Response Rate (%)[e]	86.8	84.8
95% CI	(80.3, 93.2)	(77.9, 91.6)

[a] Based on IRC assessment
[b] P-value is from stratified log-rank test
[c] Includes 3 patients in the IMBRUVICA + venetoclax arm with a complete response with incomplete marrow recovery (CRi)
[d] P-value is from Cochran-Mantel-Haenszel chi-square test
[e] Overall response = CR+CRi+nPR+PR

CR = complete response; CRi = complete response with incomplete marrow recovery; HR = hazard ratio; NE = not evaluable; nPR = nodular partial response; PR = partial response

Figure 9: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL in Study CLL3011



The treatment effect of IMBRUVICA plus venetoclax was consistent across the high-risk CLL population (TP53 mutation, del 11q, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.41)].

Overall survival data were not mature. With a median follow-up of 28 months, there was no significant difference between treatment arms with a total of 23 deaths: 11 (10.4%) in the IMBRUVICA plus venetoclax arm and 12 (11.4%) in the chlorambucil plus obinutuzumab arm with a OS HR of 1.048 [95% CI (0.454, 2.419)]. After 6 months additional follow-up, 11 (10.4%) and 16 (15.2%) deaths were reported in the IMBRUVICA plus venetoclax arm and the chlorambucil plus obinutuzumab arm, respectively with OS HR estimated at 0.760 [95% CI (0.352, 1.642]).

Table 14: Minimal Residual Disease Negativity Rates in Study CLL3011

	NGS Assay[a]		**Flow cytometry[b]**	
	IMBRUVICA + Venetoclax	**Chlorambucil + Obinutuzumab**	**IMBRUVICA + Venetoclax**	**Chlorambucil + Obinutuzumab**

	N=106	N=105	N=106	N=105
MRD Negativity Rate				
Bone marrow, n (%)	59 (55.7)	22 (21.0)	72 (67.9)	24 (22.9)
95% CI	(46.2, 65.1)	(13.2, 28.7)	(59.0, 76.8)	(14.8, 30.9)
P-value	<0.0001			
Peripheral Blood, n (%)	63 (59.4)	42 (40.0)	85 (80.2)	49 (46.7)
95% CI	(50.1, 68.8)	(30.6, 49.4)	(72.6, 87.8)	(37.1, 56.2)
MRD Negativity Rate at Three Months After Completion of Treatment				
Bone marrow, n (%)	55 (51.9)	18 (17.1)	60 (56.6)	17 (16.2)
95% CI	(42.4, 61.4)	(9.9, 24.4)	(47.2, 66.0)	(9.1, 23.2)
Peripheral Blood, n (%)	58 (54.7)	41 (39.0)	65 (61.3)	43 (41.0)
95% CI	(45.2, 64.2)	(29.7, 48.4)	(52.0, 70.6)	(31.5, 50.4)

P-values are from Cochran-Mantel-Haenszel chi-square test. P-value for MRD negativity rate in bone marrow by NGS was the primary MRD analysis.
a Based on threshold of 10-4 using a next-generation sequencing assay (clonoSEQ)
b MRD was evaluated by flow cytometry of peripheral blood or bone marrow per central laboratory. The definition of negative status was <1 CLL cell per 10,000 leukocytes (<1×104).
CI = confidence interval; NGS = next-generation sequencing

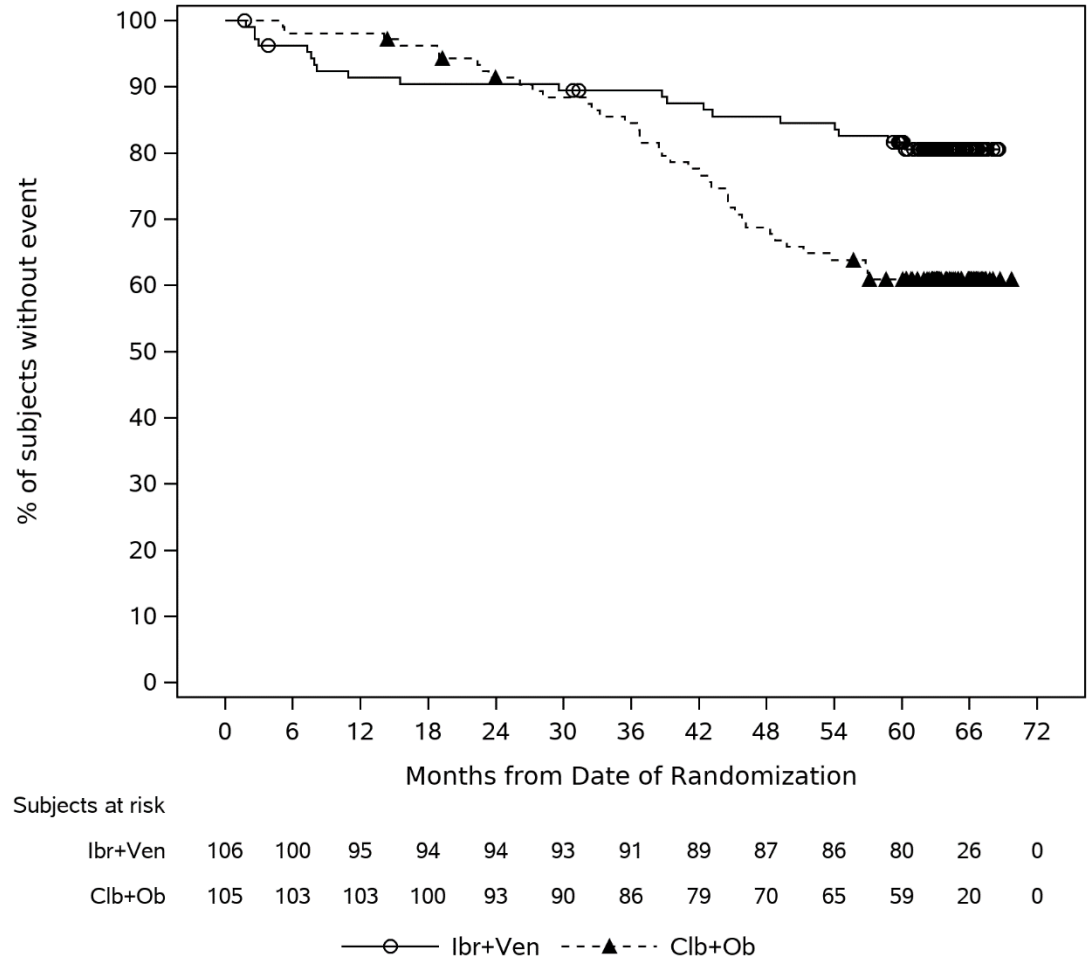
Twelve months after the completion of treatment, MRD negativity rates in peripheral blood were 49.1% (52/106) by NGS assay and 54.7% (58/106) by flow cytometry in patients treated with IMBRUVICA plus venetoclax and, at the corresponding time point, was 12.4% (13/105) by NGS assay and 16.2% (17/105) by flow cytometry in patients treated with chlorambucil plus obinutuzumab.

TLS was reported in 6 patients treated with chlorambucil plus obinutuzumab and no TLS was reported in IMBRUVICA in combination with venetoclax.

Median follow-up of 64-months
With a median follow-up time on study of 64.0 months in Study CLL3011, a 73% reduction in the risk of death or progression by investigator assessment was observed for patients in the IMBRUVICA arm. The PFS hazard ratio was 0.267 [95% CI (0.182, 0.393), nominal p<0.0001, not type 1 error controlled]. There were 20 (18.9%) deaths in the IMBRUVICA plus venetoclax arm and 40 (38.1%) in the chlorambucil plus obinutuzumab arm corresponding to a HR of 0.462 (95% CI:0.269, 0.791, nominal p=0.0039, not type 1 error controlled). Median time to next treatment was not reached for IMBRUVICA plus venetoclax arm and was 65months for chlorambucil plus obinutuzumab arm (HR=0.233; 95% CI: 0.130, 0.416) with 15.1% of subjects in the IMBRUVICA plus venetoclax arm and 43.8% of subjects in the chlorambucil plus obinutuzumab arm having initiated subsequent anticancer therapy.

Kaplan-Meier curve for OS is shown in Figure 10.

Figure 10: Kaplan-Meier Curve of Overall Survival (ITT Population) in Patients with CLL/SLL in Study CLL3011 at 64 Months Follow-up



The safety and efficacy of fixed duration therapy with IMBRUVICA in combination with venetoclax in patients with previously untreated CLL were further evaluated in a cohort of the phase 2, multi center, 2-cohort study (PCYC-1142-CA). The study enrolled previously untreated patients with CLL who were 70 years or younger. The study enrolled 323 patients, of these, 159 patients were enrolled to fixed duration therapy consisting of 3 cycles of single agent IMBRUVICA followed by IMBRUVICA in combination with venetoclax for 12 cycles (including 5-week dose titration schedule). Each cycle was 28 days. IMBRUVICA was administered at a dose of 420 mg daily. Venetoclax was administered daily, starting with 20 mg for 1 week, followed by 1 week at each dose level of 50 mg, 100 mg, and 200 mg, then the recommended daily dose of 400 mg. Patients with confirmed progression by IWCLL criteria after completion of the fixed duration regimen could be retreated with single-agent IMBRUVICA.

The median age was 60 years (range, 33 to 71 years), 67% were male, and 92% were Caucasian. All patients had a baseline ECOG performance status of 0 (69%) or 1 (31%). At baseline, 13% of patients had del 17p, 18% with del 11q, 17% with del 17p/TP53 mutation, 56% with unmutated IGHV and 19% with complex karyotype. At baseline assessment for risk of tumor lysis syndrome, 21% of patients had high tumor burden.

After 3 cycles of single-agent IMBRUVICA lead-in therapy, 1% of patients had high tumor burden. High tumor burden was defined as any lymph node ≥10 cm, or any lymph node ≥5 cm and absolute lymphocyte count ≥25×109/L.

With a median follow-up time on study of 28 months, efficacy results for PCYC 1142-CA assessed by an IRC according to IWCLL criteria are shown in Table 15, and rates of minimal residual disease (MRD) negativity are shown in Table 16.

Table 15: Efficacy Results in Study PCYC-1142-CA (Fixed Duration Cohort)

Endpoint[a]	**IMBRUVICA + Venetoclax**	
	Without Del 17p (N=136)	**All (N=159)**
Overall Response Rate, n (%)[b]	130 (95.6)	153 (96.2)
95% CI (%)	(92.1, 99.0)	(93.3, 99.2)
Complete Response Rate, n (%)[c]	83 (61.0)	95 (59.7)
95% CI (%)	(52.8, 69.2)	(52.1, 67.4)
Median duration of CR, months (range)[d]	NE (0.03+, 24.9+)	NE (0.03+, 24.9+)

[a] Based on IRC assessment
[b] Overall response = CR + CRi + nPR + PR
[c] Includes 3 patients with a complete response with incomplete marrow recovery (CRi)
[d] A '+' sign indicates a censored observation
CR = complete response; CRi = complete response with incomplete marrow recovery; nPR = nodular partial response; PR = partial response; NE = not evaluable

Table 16: Minimal Residual Disease Negativity Rates in Study PCYC-1142-CA (Fixed Duration Cohort)

Endpoint	**IMBRUVICA + Venetoclax**	
	Without Del 17p (N=136)	**All (N=159)**
MRD Negativity Rate		
Bone marrow, n (%)	84 (61.8)	95 (59.7)
95% CI	(53.6, 69.9)	(52.1, 67.4)
Peripheral Blood, n (%)	104 (76.5)	122 (76.7)
95% CI	(69.3, 83.6)	(70.2, 83.3)
MRD Negativity Rate at Three Months After Completion of Treatment		
Bone marrow, n (%)	74 (54.4)	83 (52.2)
95% CI	(46.0, 62.8)	(44.4, 60.0)
Peripheral Blood, n (%)	78 (57.4)	90 (56.6)
95% CI	(49.0, 65.7)	(48.9, 64.3)

MRD was evaluated by flow cytometry of peripheral blood or bone marrow per central laboratory. The definition of negative status was <1 CLL cell per 10,000 leukocytes ($<1\times10^4$).
CI = confidence interval

In patients with del 17p/TP53 mutation (n=27) in PCYC-1142-CA the overall response rate based on IRC assessment was 96.3%; complete response rate was 55.6% and the median duration of complete response was not reached (range, 4.3 to 22.6 months). The MRD negativity rate in patients with del 17p/TP53 mutation 3 months after completion of treatment in bone marrow and peripheral blood was 40.7% and 59.3%, respectively.

No TLS was reported in patients treated with IMBRUVICA in combination with venetoclax.

Patients with CLL who received at least one prior therapy

Single agent

The safety and efficacy of IMBRUVICA in patients with CLL were demonstrated in one uncontrolled study and one randomised, controlled study. The open-label, multi-center study (PCYC-1102-CA) included 51 patients with relapsed or refractory CLL, who received 420 mg once daily. IMBRUVICA was administered until disease progression or unacceptable toxicity. The median age was 68 years (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 92.2% with a prior nucleoside analogue, 98.0% with prior rituximab, 86.3% with a prior alkylator, 39.2% with prior bendamustine and 19.6% with prior ofatumumab. At baseline, 39.2% of patients had Rai Stage IV, 45.1% had bulky disease (≥ 5 cm), 35.3% had deletion 17p and 31.4% had deletion 11q.

ORR was assessed according to the 2008 IWCLL criteria by investigators and IRC. At a median duration follow-up of 16.4 months, the ORR by IRC for the 51 relapsed or refractory patients was 64.7% (95% CI: 50.1%; 77.6%), all PRs. The ORR including PR with lymphocytosis was 70.6%. Median time to response was 1.9 months. The DOR ranged from 3.9 to 24.2+ months. The median DOR was not reached.

A randomised, multi-center, open-label phase 3 study of IMBRUVICA versus ofatumumab (PCYC-1112-CA) was conducted in patients with relapsed or refractory CLL. Patients (n = 391) were randomised 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or ofatumumab for up to 12 doses (300/2,000 mg). Fifty-seven patients randomised 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 tumour ≥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. 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 17.

Table 17: Efficacy results in patients with CLL (Study PCYC-1112-CA)

Endpoint	IMBRUVICA N = 195	Ofatumumab N = 196
Median PFS	Not reached	8.1 months
	HR = 0.215 [95% CI: 0.146; 0.317]	
OS[a]	HR = 0.434 [95% CI: 0.238; 0.789][b] HR = 0.387 [95% CI: 0.216; 0.695][c]	
ORR[d,e] (%)	42.6	4.1
ORR including PR with lymphocytosis[d] (%)	62.6	4.1

HR = hazard ratio; CI = confidence interval; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response

[a] Median OS not reached for both arms. $p < 0.005$ for OS.

[b] Patients randomised to ofatumumab were censored when starting IMBRUVICA 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

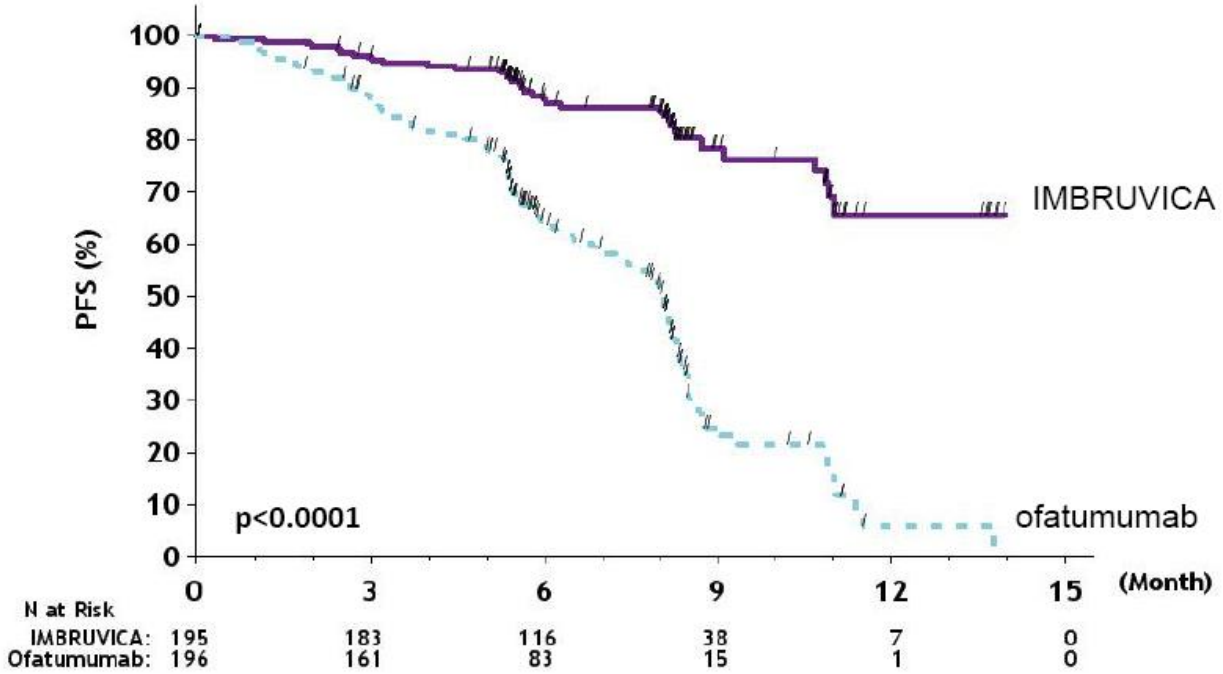
The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (Table 18).

Table 18: Subgroup analysis of PFS (Study PCYC-1112-CA)

	N	Hazard Ratio	95% CI
All subjects	391	0.210	(0.143; 0.308)
Del17P			
Yes	127	0.247	(0.136; 0.450)
No	264	0.194	(0.117; 0.323)
Refractory disease to purine analogue			
Yes	175	0.178	(0.100; 0.320)
No	216	0.242	(0.145; 0.404)
Age			
<65	152	0.166	(0.088; 0.315)
≥65	239	0.243	(0.149; 0.395)
Number of prior lines			
<3	198	0.189	(0.100; 0.358)
≥3	193	0.212	(0.130; 0.344)
Bulky disease			
<5 cm	163	0.237	(0.127; 0.442)
≥5 cm	225	0.191	(0.117; 0.311)
Hazard ratio based on non-stratified analysis			

The Kaplan-Meier curve for PFS is shown in Figure 11.

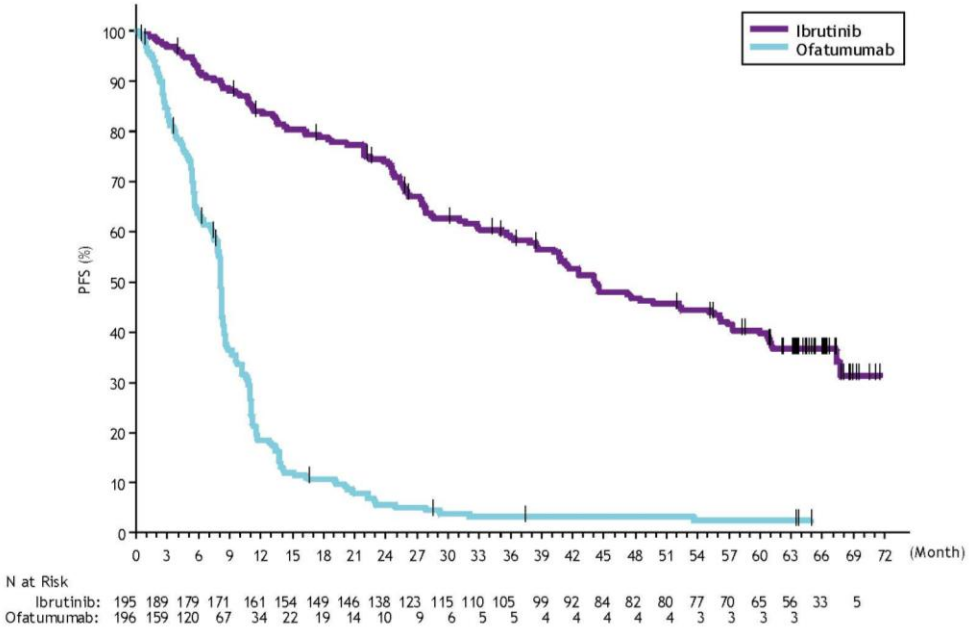
Figure 11: Kaplan-Meier curve of PFS (ITT Population) in Study PCYC-1112-CA



Final Analysis at 65-month follow-up
With a 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 randomised to the ofatumumab treatment arm had crossed over to ibrutinib treatment. The median investigator-assessed PFS2 (time from randomisation 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 deletion 17p/TP53 mutation, deletion 11q, and/or unmutated IGHV.

Figure 12: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1112-CA at Final Analysis with 65 Months Follow-up



Combination therapy
The safety and efficacy of IMBRUVICA in patients previously treated for CLL were further evaluated in a randomised, multicenter, double-blinded phase 3 study of IMBRUVICA in combination with BR versus placebo+BR (Study CLL3001). Patients (n=578) were randomised 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles. Bendamustine was dosed at 70 mg/m^2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 in the first cycle, Day 1, and 500 mg/m^2 Cycles 2 through 6, Day 1. Ninety patients randomised to placebo+BR crossed over to receive IMBRUVICA following IRC confirmed progression. The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since

diagnosis was 6 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumour ≥5 cm, 26% had del11q.

Progression free survival (PFS) was assessed by IRC according to IWCLL criteria. Efficacy results for Study CLL3001 are shown in Table 19.

Table 19: Efficacy Results in patients with CLL (Study CLL3001)

Endpoint	IMBRUVICA+BR N=289	Placebo+BR N=289
PFSa		
Median (95% CI), months	Not reached	13.3 (11.3, 13.9)
	HR=0.203 [95% CI: 0.150, 0.276]	
ORRb %	82.7	67.8
OSc	HR=0.628 [95% CI: 0.385, 1.024]	

CI=confidence interval; HR=hazard ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival

[a] IRC evaluated.

[b] IRC evaluated, ORR (complete response, complete response with incomplete marrow recovery, nodular partial response, partial response).

[c] Median OS not reached for both arms.

WM

Single agent

The safety and efficacy of IMBRUVICA in WM (IgM-excreting lymphoplasmacytic lymphoma) were evaluated in an open-label, multi-center, single-arm trial of 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, and 60% of patients were anaemic (haemoglobin ≤11 g/dL or 6.8 mmol/L).

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 WM. Responses to IMBRUVICA are shown in Table 20.

Table 20: ORR and DOR in patients with WM

	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; DOR=duration of response; 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: 0.7-13.4 months).

Efficacy results were also assessed by an IRC demonstrating an ORR of 83%, with a 11% VGPR rate and a 51% PR rate.

Combination therapy

The safety and efficacy of IMBRUVICA in WM were further evaluated in patients with treatment-naïve or previously treated WM in a randomised, multicenter, double-blinded phase 3 study of IMBRUVICA in combination with rituximab versus placebo in combination with rituximab (PCYC-1127-CA). Patients (n=150) were randomised 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/m2 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 anaemic (haemoglobin ≤11 g/dL or 6.8 mmol/L) 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.

At the primary analysis, with a median follow-up of 26.5 months, the IRC-assessed PFS hazard ratio was 0.20 [95% CI (0.11, 0.38)]. 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.

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.

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.

Final Analysis at 63-month follow-up

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 21 and the Kaplan-Meier curve for PFS is shown in Figure 13. 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 21: 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	
Time to next treatment		
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 Haemoglobin Improvement[c, e] (%)	77.3	42.7

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

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

[a] IRC evaluated.

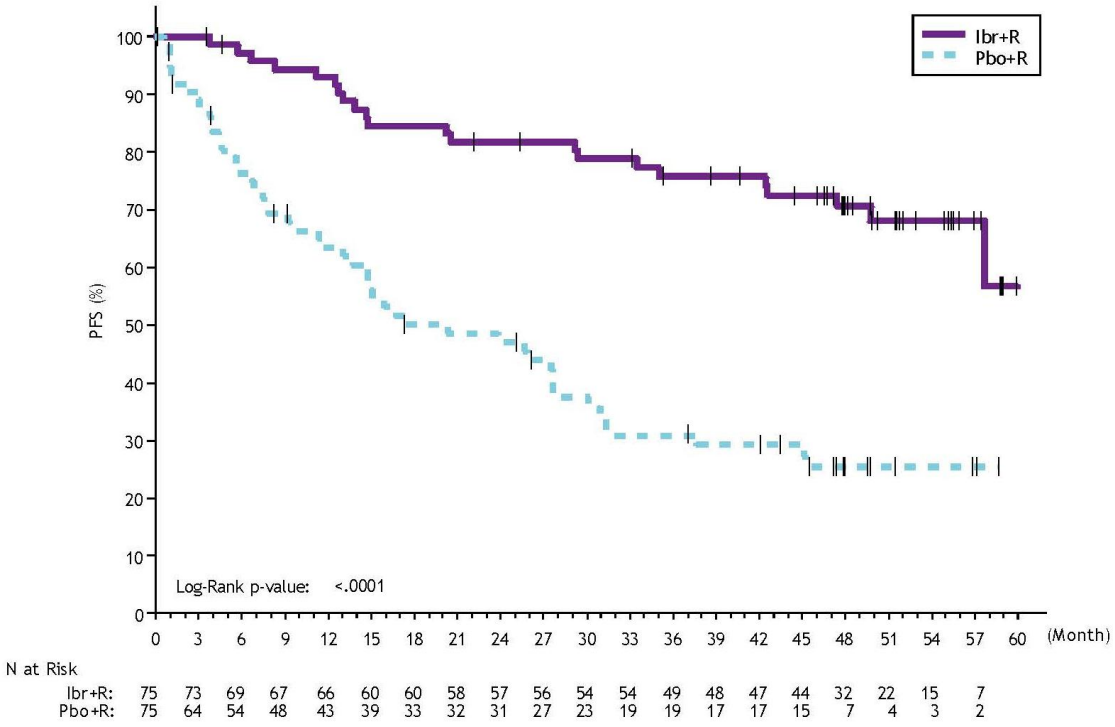
[b] 4-year PFS estimates were 70.6% [95% CI (58.1, 80.0)] in the IMBRUVICA + R arm versus 25.3% [95% CI (15.3, 36.6)] in the placebo + R arm.

[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.

Figure 13: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1127-CA (Final Analysis)



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). 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).

Chronic graft versus host disease (cGVHD)
The safety and efficacy of IMBRUVICA in cGVHD were evaluated in an open-label, multi-center, single-arm trial of 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy. The median age was 56 years (range, 19 to 74 years), 52% were male, and 93% were Caucasian. The most common underlying malignancies leading to transplant were acute lymphocytic leukemia, acute myeloid leukemia, and CLL. The median time since diagnosis was 14 months and the median number of prior cGVHD treatments was 2 (range, 1 to 3 treatments). The majority of patients (88%) had at least 2 organs involved at baseline, with the most commonly involved organs being mouth (86%), skin (81%), and gastrointestinal tract (33%). The median daily steroid dose per body weight at baseline was 0.3 mg/kg/day.

IMBRUVICA was administered orally at 420 mg once daily until disease progression, unacceptable toxicity or recurrence of underlying malignancy. The primary endpoint in this study was best ORR per investigator assessment using the 2005 National Institutes of Health Consensus Panel Response Criteria with modification. Responses were seen across involved organs for cGVHD (skin, mouth, gastrointestinal tract, and liver). Efficacy results are shown in Table 22.

Table 221: Best overall response rate (ORR) and sustained response rate based on investigator assessment in patients with cGVHD

	Total (N=42)
ORR (%)	66.7
95% CI (%)	(50.5, 80.4)
Complete response (CR) (%)	21.4
Partial response (PR) (%)	45.2
Sustained response rate* (%)	71.4

CI = confidence interval
* Sustained response rate is defined as the proportion of patients who achieved a CR or PR (N=28) that was sustained for at least 20 weeks.

ORR results were supported by exploratory analyses of patient-reported symptom burden which showed at least a 7-point decrease in Lee Symptom Scale overall summary score in 24% (10/42) of patients on at least 2 consecutive visits.

5.2 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 420mg with cGVHD is 1159 ± 583 ng·h/mL. 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.

Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. In fasted healthy subjects administered a single 560 mg dose of ibrutinib after taking omeprazole at 40 mg once daily for 5 days, compared to ibrutinib alone, geometric mean ratios (90% CI) were 83% (68-102%), 92% (78-110%), and 38% (26-53%) for AUC_{0-24}, AUC_{last}, and C_{max}, respectively.

Distribution
Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1,000 ng/mL. The apparent volume of distribution at steady state ($V_{d, ss}/F$) was approximately 10,000 L.

Metabolism
Ibrutinib is metabolised primarily by CYP3A4 to produce a dihydrodiol metabolite with an inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. Involvement of CYP2D6 in the metabolism of ibrutinib appears to be minimal.

Therefore, no precautions are necessary in patients with different CYP2D6 genotypes.

Elimination
Apparent clearance (CL/F) is approximately 1,000 L/h. The half-life of ibrutinib is 4 to 13 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 faeces and < 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in faeces and none in urine.

Special populations
Elderly
Population pharmacokinetics indicated that age does not significantly influence ibrutinib clearance from the circulation.

Paediatric population
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.

Race
There are insufficient data to evaluate the potential effect of race on ibrutinib pharmacokinetics.

Body weight
Population pharmacokinetics data indicated that body weight (range: 41-146 kg; mean [SD]: 83 [19 kg]) had a negligible effect on ibrutinib clearance.

Renal impairment
Ibrutinib has minimal renal clearance; urinary excretion of metabolites is < 10% of the dose. No specific studies have been conducted to date in subjects with impaired renal function. There are no data in patients with severe renal impairment or patients on dialysis (see section 4.2).

Hepatic impairment
Ibrutinib is metabolised in the liver. A hepatic impairment trial was performed in non-cancer subjects administered a single dose of 140 mg of medicinal product under fasting conditions. The effect of impaired

liver function varied substantially between individuals, but on average a 2.7-, 8.2-, and 9.8-fold increase in ibrutinib exposure (AUC_{last}) was observed 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 (see section 4.2).

Co-administration with transport substrates/inhibitors
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 an *in vitro* inhibitor of P-gp and BCRP (see section 4.5).

5.3 Preclinical safety data
The following adverse effects were seen in studies of 13-weeks duration in rats and dogs. Ibrutinib was found to induce gastrointestinal effects (soft faeces/diarrhoea and/or inflammation) and lymphoid depletion in rats and dogs with a No Observed Adverse Effect Level (NOAEL) of 30 mg/kg/day in both species. Based on mean exposure (AUC) at the 560 mg/day clinical dose, AUC ratios were 2.6 and 21 at the NOAEL in male and female rats, and 0.4 and 1.8 at the NOAEL in male and female dogs, respectively. Lowest Observed Effect Level (LOEL) (60 mg/kg/day) margins in the dog are 3.6-fold (males) and 2.3-fold (females). In rats, moderate pancreatic acinar cell atrophy (considered adverse) was observed at doses of ≥ 100 mg/kg in male rats (AUC exposure margin of 2.6-fold) and not observed in females at doses up to 300 mg/kg/day (AUC exposure margin of 21.3-fold). Mildly decreased trabecular and cortical bone was seen in female rats administered ≥ 100 mg/kg/day (AUC exposure margin of 20.3-fold). All gastrointestinal, lymphoid and bone findings recovered following recovery periods of 6-13 weeks. Pancreatic findings partially recovered during comparable reversal periods.

Juvenile toxicity studies have not been conducted.

Carcinogenicity/genotoxicity
Ibrutinib was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse at oral doses up to 2000 mg/kg/day with an exposure margin of approximately 23 (males) to 37 (females) times the human AUC of ibrutinib at a dose of 560 mg daily.

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

Reproductive toxicity
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) (see section 4.6).

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) (see section 4.6).

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules

Capsule content
Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose
Sodium lauril sulfate (E487)

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac
Black iron oxide (E172)
Propylene glycol (E1520)

Film-coated tablets

Tablet core
Colloidal anhydrous silica
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Povidone
Sodium lauril sulfate (E487)

Film-coat
IMBRUVICA 140mg film-coated tablet and IMBRUVICA 420mg film-coated tablets
Macrogol
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Black iron oxide (E172)
Yellow iron oxide (E172)

IMBRUVICA 280mg film-coated tablets
Macrogol
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Black iron oxide (E172)

Red iron oxide (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Capsules
3 years.

Film-coated tablets
3 years.

6.4 Special precautions for storage
Store below 30°C.
Keep out of reach of children.

6.5 Nature and contents of container
Capsules
HDPE bottles with a child-resistant polypropylene closure.
Each carton contains one bottle of either 90 or 120 hard capsules.
Not all pack sizes may be marketed.

Film-coated tablets
Two polyvinyl chloride (PVC) laminated with polychlorotrifluoroethylene (PCTFE)/aluminum blisters with 5 film-coated tablets each in one cardboard wallet. Each carton contains (30 film-coated tablets) 3 wallets.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER
Capsules
Catalent CTS, LLC
10245 Hickman Mills Drive
Kansas City, MO
64137 USA

Cilag AG
Hochstrasse 201
Schaffhausen, 8200
Switzerland

Film-coated tablets
Cilag AG
Hochstrasse 201
Schaffhausen, 8200
Switzerland

8. PRODUCT REGISTRATION HOLDER

Johnson & Johnson Sdn Bhd (3718-D)
Level 8, The Pinnacle,
Persiaran Lagoon, Bandar Sunway,
46150, Petaling Jaya, Selangor, Malaysia

9. DATE OF REVISION OF THE TEXT

23 September 2026 (based on EU SmPC v14Sep2026)