ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 140 mg of ibrutinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMBRUVICA in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (IMBRUVICA + R-CHOP) alternating with R-DHAP (or R-DHAOx) without IMBRUVICA, followed by IMBRUVICA monotherapy, is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT).

IMBRUVICA as a single agent is indicated for the treatment of adult patients with relapsed or refractory 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 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.

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
Treatment of adult patients with previously untreated MCL

The recommended dose for the treatment of previously untreated MCL is ibrutinib 560 mg (four capsules) once daily (see Table 1).

Table 1: IMBRUVICA dosing schedule for previously untreated MCL

Treatment	Cycle number	Treatment	IMBRUVICA
Part I[*]	1, 3, 5	IMBRUVICA in combination with R-CHOP[§]	On days 1-19
	2, 4, 6	R-DHAP[#§]	Without IMBRUVICA
Part II[±]		IMBRUVICA	Daily for 24 Months

R-CHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP= rituximab, dexamethasone, cytarabine, cisplatin

[*]6 cycles; each cycle is 21 days.

[§]See the Summary of Product Characteristics (SmPC) for dosing information for each medicinal product.

[#]Interchangeable with R-DHAOx (rituximab, dexamethasone, cytarabine, oxaliplatin)[§].

[±] Treatment should start after recovery of peripheral blood counts. Rituximab may be added as per national treatment guidelines.

Treatment of adult patients with relapsed or refractory MCL

The recommended dose for the treatment of previously treated MCL is ibrutinib 560 mg (four capsules) once daily as a single agent. Treatment with IMBRUVICA as a single agent should continue until disease progression or no longer tolerated by the patient.

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

Treatment with IMBRUVICA as a single agent or in combination with anti-CD20 therapy 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 Summary of Product Characteristics (SmPC) 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.

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 (two capsules) when used concomitantly with moderate CYP3A4 inhibitors.

The dose of ibrutinib should be reduced to 140 mg once daily (one capsule) 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 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 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 capsules 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 (two capsules). For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule). Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with severe hepatic impairment (Child-Pugh class C).

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. Currently available data in patients with mature B-cell non-Hodgkin lymphoma are described in sections 4.8, 5.1 and 5.2.

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. 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. 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.

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
Each capsule 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 CYP3A4 inhibitors
Co-administration of ketoconazole, a very strong CYP3A4 inhibitor, in 18 fasted healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by 29- and 24-fold, respectively. Simulations using fasted conditions suggested that the strong CYP3A4 inhibitor clarithromycin may increase the AUC of ibrutinib by a factor of 14. In patients with B-cell malignancies taking IMBRUVICA with food, co-administration of the strong CYP3A4 inhibitor voriconazole increased C_{max} by 6.7-fold and AUC by 5.7-fold. Strong inhibitors of CYP3A4 (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, cobicistat, voriconazole and posaconazole) should be avoided. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the IMBRUVICA dose to 140 mg (one capsule) for the duration of the inhibitor use or withhold IMBRUVICA temporarily (for 7 days or less). Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

Moderate CYP3A4 inhibitors
In patients with B-cell malignancies taking IMBRUVICA with food, co-administration of the CYP3A4 inhibitor erythromycin increased C_{max} by 3.4-fold and AUC by 3.0-fold. If a moderate CYP3A4 inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone and dronedarone) is indicated, reduce IMBRUVICA dose to 280 mg (two capsules) for the duration of the inhibitor use. Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

Mild CYP3A4 inhibitors
Simulations using fasted conditions suggested that the mild CYP3A4 inhibitors azithromycin and fluvoxamine may increase the AUC of ibrutinib by <2-fold. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed.

Co-administration of grapefruit juice, containing CYP3A4 inhibitors, in eight healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by approximately 4- and 2-fold, respectively. Grapefruit and Seville oranges should be avoided during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A4 (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
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
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.

Summary for B-cell malignancies
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. The TRIANGLE study data is not included in the pooled data and presented separately in Table 3. 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 14.7 months (up to 52 months); MCL was 11.7 months (up to 28 months); WM was 21.6 months (up to 37 months).

Table 2: 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

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Non-melanoma skin cancer[*] Basal cell carcinoma Squamous cell carcinoma	5 3 1	1 <1 <1
Blood and lymphatic system disorders	Very common	Neutropenia[*] Thrombocytopenia[*] Lymphocytosis[*]	39 29 15	31 8 11
	Common	Febrile neutropenia Leukocytosis	4 4	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 Headache	12 19	<1 1
	Common	Peripheral neuropathy[*]	7	<1
	Uncommon	Cerebrovascular accident[#] Transient ischaemic attack Ischaemic stroke[#]	<1 <1 <1	<1 <1 <1
Eye disorders	Common	Vision blurred	6	0
	Uncommon	Eye haemorrhage[‡] Uveitis*	<1 <1	0 0
Cardiac disorders	Common	Cardiac failure[*, #] Atrial fibrillation	2 8	1 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

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.

Summary for patients with previously untreated MCL who were eligible for ASCT

The safety profile is based on data from 265 patients (in the IMBRUVICA arm) treated with IMBRUVICA in the phase 3 TRIANGLE study. Patients received IMBRUVICA at 560 mg once daily according to the TRIANGLE treatment schedule (see section 5.1). The median treatment duration was 28.5 months in the IMBRUVICA arm.

Table 3: Adverse reactions reported in the IMBRUVICA arm of the TRIANGLE Study†

		N=265		
System Organ Class	**Frequency (All Grades)**	**Adverse Reactions**	**All Grades (%)**	**Grade ≥3 (%)**
Infections and infestations	Very common	Pneumonia* #	16	9
		Skin infection*	12	3
	Common	Upper respiratory tract infection	6	<1
		Sepsis*	2	2
		Urinary tract infection	6	<1
		Sinusitis*	6	1
	Uncommon	Aspergillus infections*	1	<1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Non-Melanoma skin cancer*	1	<1
		Basal cell carcinoma	1	<1
	Very common	Thrombocytopenia*	69	61
		Neutropenia*	63	60

Blood and lymphatic system disorders		Febrile neutropenia	14	14
	Common	Leukocytosis	3	1
Immune system disorders	Common	Interstitial lung disease*	5	1
Metabolism and nutrition disorders	Common	Hyperuricaemia	8	3
		Tumour lysis syndrome*	3	3
Nervous system disorders	Very common	Peripheral neuropathy*	35	3
		Headache	11	1
	Common	Dizziness	6	<1
	Uncommon	Transient ischaemic attack	1	0
Eye disorders	Uncommon	Vision blurred	1	0
		Eye haemorrhage	<1	0
Cardiac disorders	Common	Atrial fibrillation	10	4
		Cardiac failure*	2	0
Vascular disorders	Very common	Haemorrhage*	14	2
		Hypertension*	14	5
	Common	Bruising*	8	1
		Epistaxis	6	1
		Petechiae	3	0
Gastrointestinal disorders	Very common	Nausea	32	4
		Diarrhoea	28	5
		Vomiting	18	4
		Stomatitis*	11	2
		Constipation	17	<1
	Common	Dyspepsia	8	0
Skin and subcutaneous tissue disorders	Very common	Rash*	23	2
	Common	Erythema	5	0
		Onychoclasis	2	0
	Uncommon	Urticaria	<1	0
		Angioedema	1	0
		Cutaneous vasculitis	<1	0
		Panniculitis*	1	0
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain*	19	2
	Common	Muscle spasms	9	1
		Arthralgia	8	1
Renal and urinary disorders	Very common	Acute kidney injury	11	5
General disorders and administration site conditions	Very common	Pyrexia	22	2
	Common	Oedema peripheral	5	0
Investigations	Very common	Blood creatinine increased	16	1

† Frequencies are rounded to the nearest integer.

* Terms required grouping.

Includes events with fatal outcome.

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. In the phase 3 TRIANGLE study involving 265 patients with previously untreated MCL who were eligible for ASCT treatment discontinuation due to adverse reactions was observed in 13% in the IMBRUVICA arm. These included neutropenia, pneumonia, atrial fibrillation, acute kidney injury, diarrhoea, rash, and interstitial lung disease. Adverse reactions leading to dose reduction occurred in approximately 12% in the IMBRUVICA arm.

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 1 284 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%.

Paediatric population
The safety assessment is based on data from a phase 3 study of IMBRUVICA in combination with either a rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone (RICE) regimen, or a rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone (RVICI) regimen, as background therapy or background therapy alone in paediatric and young adult patients (aged 3 to 19 years) with relapsed or refractory mature B-cell non-Hodgkin lymphoma (see section 5.1). No new adverse reactions were observed in this study.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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-tumour 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
Combination treatment in patients previously untreated for MCL who were eligible for autologous stem cell transplantation (ASCT)

The safety and efficacy of IMBRUVICA in patients with previously untreated MCL and who were eligible for autologous stem cell transplantation (ASCT) were evaluated in a randomised, phase 3, multi-centre, open-label, three arm study (TRIANGLE). The TRIANGLE study randomised 870 patients in a 1:1:1 ratio to receive either:

- IMBRUVICA Arm: IMBRUVICA 560 mg daily (Days 1-19) in combination with R-CHOP for three 21-day cycles (Cycles 1, 3, 5) alternating with three 21-day cycles of R-DHAP (Cycles 2, 4, 6) as induction therapy followed by 2 years IMBRUVICA 560 mg daily;
- IMBRUVICA + ASCT Arm: IMBRUVICA 560 mg daily (Days 1-19) in combination with R-CHOP for three 21-day cycles (Cycles 1, 3, 5) alternating with three 21-day cycles of R-DHAP (Cycles 2, 4, 6) as induction therapy followed by high-dose chemotherapy and ASCT followed by 2 years IMBRUVICA 560 mg daily;
- ASCT Arm: R-CHOP for three 21-day cycles (Cycles 1, 3, 5) alternating with three 21-day cycles of R-DHAP (Cycles 2, 4, 6) as induction therapy followed by high-dose chemotherapy and ASCT (Control Arm).

The efficacy analyses were conducted based on 809 patients in the full analysis set (FAS) population using 3 pairwise comparisons of the 3 treatment arms: IMBRUVICA + ASCT vs. ASCT; IMBRUVICA vs. ASCT; and IMBRUVICA + ASCT vs. IMBRUVICA. The FAS population included patients that have either provided explicit permission for their data to be included as per EU General Data Protection Regulation or were deceased. The results presented are from the IMBRUVICA (N=265) arm and the ASCT (N=268) arm, only.

Induction with R-CHOP (rituximab 375 mg/m^2 on Day 0 or 1, cyclophosphamide 750 mg/m^2 on Day 1, doxorubicin 50 mg/m^2 on Day 1, vincristine 1.4 mg/m^2 up to maximum of 2 mg on Day 1, and prednisone 100 mg on days 1-5) alternating with R-DHAP (rituximab 375 mg/m^2 on Day 0 or 1, dexamethasone 40 mg on days 1-4, Ara-C 2x 2 g/m^2 every 12 hours on Day 2, cisplatin 100 mg/m^2 (alternatively oxaliplatin 130 mg/m^2) on Day 1, and G-CSF 5 µg/kg from Day 6 until recovery of WBC) was the same in all 3 treatment arms. Rituximab maintenance therapy was allowed in all treatment groups (59.7% in the IMBRUVICA arm; 62.5% in the ASCT arm) according to national treatment guidelines.

The median age was 57 years (range: 27 to 65 years), 78% were male and 99% were Caucasian. Ninety-eight percent of patients had a baseline ECOG performance status of 0 or 1. At baseline, 86% had Ann Arbor Stage IV disease, and 57%, 28%, and 15% of patients had low, intermediate, and high-risk score by MCL International Prognostic Index (MIPI), respectively. Of the patients 11.6% had blastoid or pleomorphic histology. P53 expression was assessed in 64.6% of patients; expression >50% was present in 14.1% of these patients. Ki-67 proliferation index was assessed in 88.3% of patients and 32.9% of these patients had a proliferation index of >30%.

Tumour response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria (2007). The primary endpoint was failure-free survival (FFS), defined as the time from randomisation to stable disease at end of induction chemoimmunotherapy, progressive disease, or death from any cause, whichever was earlier.

With a median follow-up time on study of 54.9 months, efficacy results for TRIANGLE are shown in Table 4. The Kaplan-Meier curves for FFS and OS are shown in Figures 1 and 2, respectively.

Table 4: Efficacy results in patients with previously untreated MCL (TRIANGLE) (FAS population)

Endpoint	IMBRUVICA Arm N=268	ASCT Arm N=269
Failure-free survival[±]		
Number of events (%)	61 (22.8%)	87 (32.3%)
Stable Disease at the end of induction	1 (0.4%)	5 (1.9%)
Disease progression	49 (18.3%)	60 (22.3%)
Death events	11 (4.1%)	22 (8.2%)
Median (95% CI), months	NE (NE, NE)	NE (NE, NE)
IMBRUVICA vs ASCT Arms HR (98.33% CI) (P-value)[*]	0.639 (0.428, 0.953) (0.0068)	
Overall Survival[§]		
Number of deaths (%)	33 (12.3%)	60 (22.3%)
IMBRUVICA vs ASCT Arms HR (95% CI) (P-value)[*]	0.522 (0.341, 0.799) (0.0023)	
Overall Response Rate (%)[§] (95% CI)	258 (96.3%) (93.3%, 98.2%)	248 (92.2%) (88.3%, 95.1%)
CR rate (%)[§] (95% CI)	180 (67.2%) (61.2%, 72.8%)	174 (64.7%) (58.7%, 70.4%)

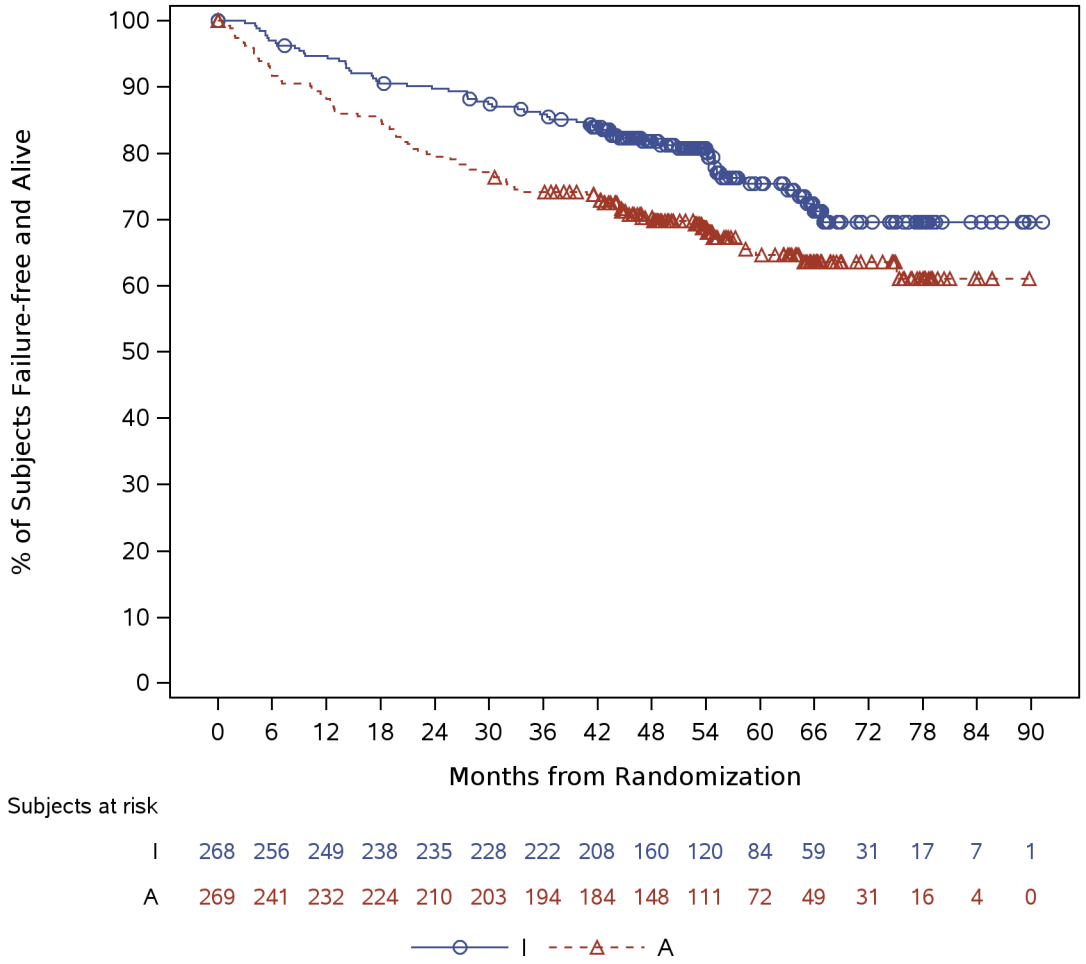
FFS=failure-free survival; NE=not estimable; HR=hazard ratio (based on unstratified Cox-regression model); RR=relative risk; CI=confidence interval; CR=complete response; FAS=full analysis set

[±] The FFS results are not controlled for type 1 error, as these analyses are derived from supplemental analyses conducted for registrational purposes

[*]Two-sided p-values are from unstratified log-rank test; p-values were tested based on $p<0.0167$

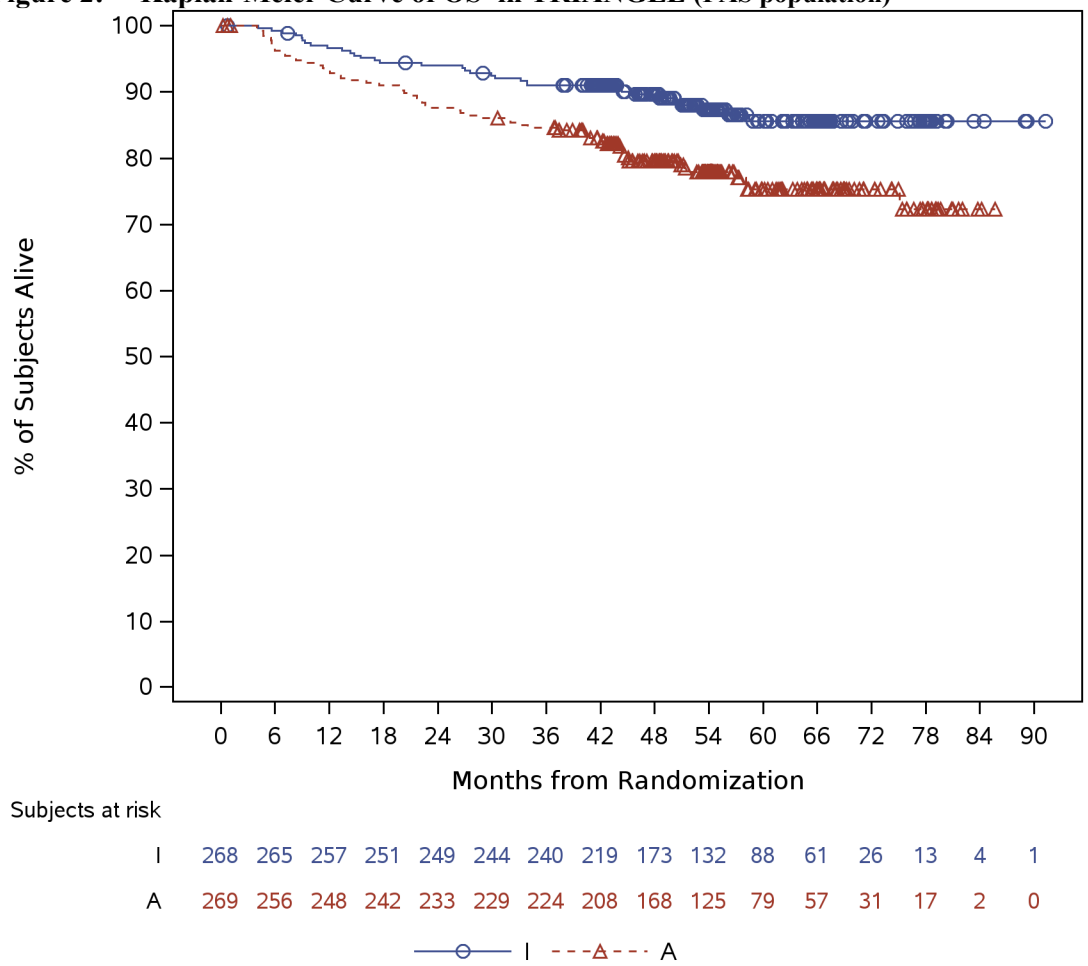
[§]Presented results are derived from descriptive analysis

Figure 1: Kaplan-Meier Curve of European MCL Network Assessed Failure-free Survival in TRIANGLE (FAS population)*



* I=IMBRUVICA; A=ASCT

Figure 2: Kaplan-Meier Curve of OS[§] in TRIANGLE (FAS population)*



*I=IMBRUVICA; A=ASCT

§Presented results are derived from descriptive analysis

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-centre 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 5.

Table 5: 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, multi-centre 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 6 and the Kaplan-Meier curve for PFS in Figure 3.

Table 6: Efficacy Results in patients with relapsed or refractory MCL (Study MCL3001)

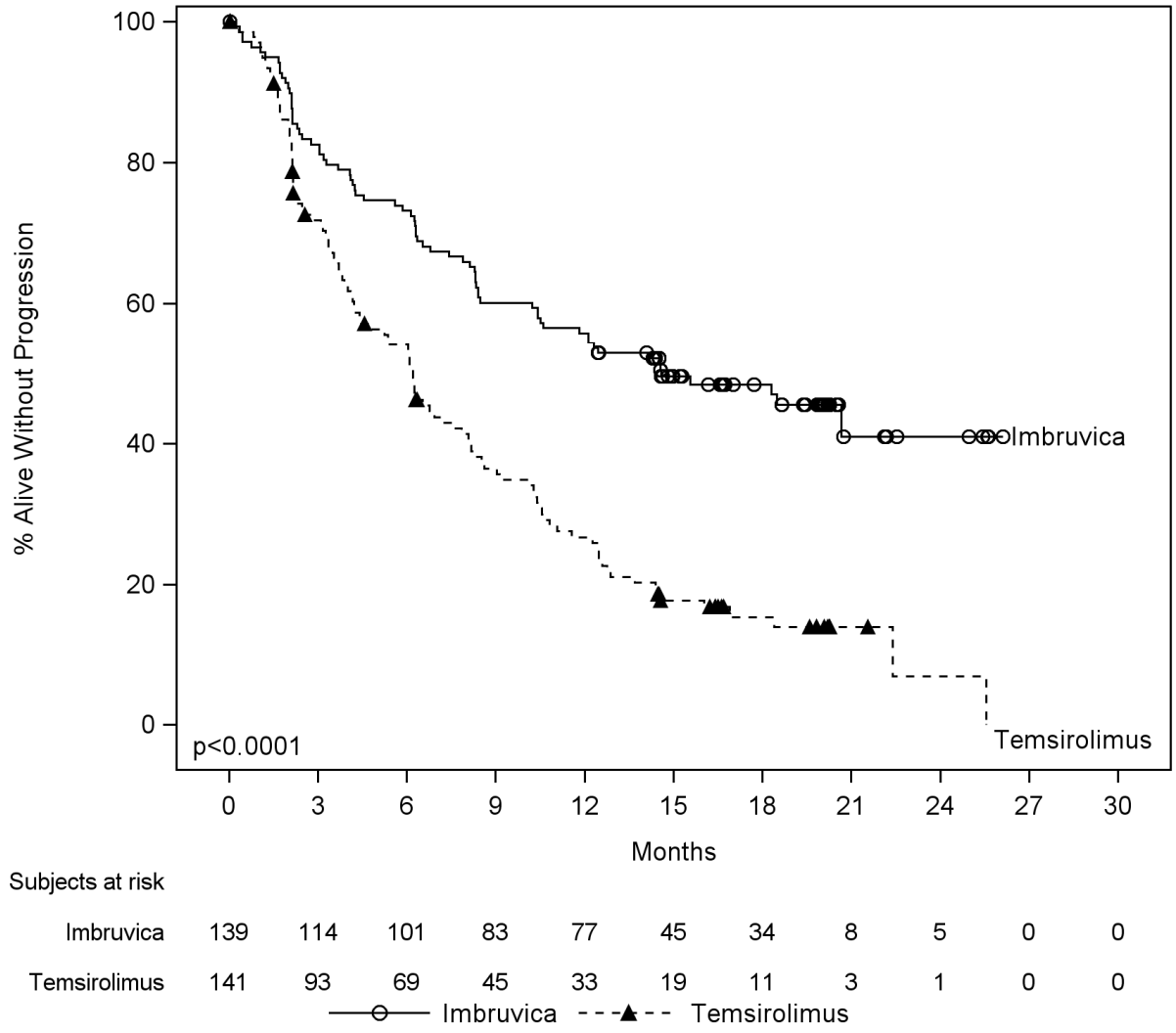
Endpoint	**IMBRUVICA N=139**	**Temsirolimus N=141**
PFS[a]		
Median PFS (95% CI), (months)	14.6 (10.4, NE)	6.2 (4.2, 7.9)
	HR=0.43 [95% CI: 0.32, 0.58]	
ORR (%)	71.9	40.4
p-value	p<0.0001	

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 3: Kaplan-Meier Curve of PFS (ITT Population) in Study MCL3001



CLL

Patients previously untreated for CLL

Single agent

A randomised, multi-centre, 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 tumour ≥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 del17p/tumour 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 7 and the Kaplan-Meier curves for PFS and OS are shown in Figures 4 and 5, 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 7: 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 4: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1115-CA

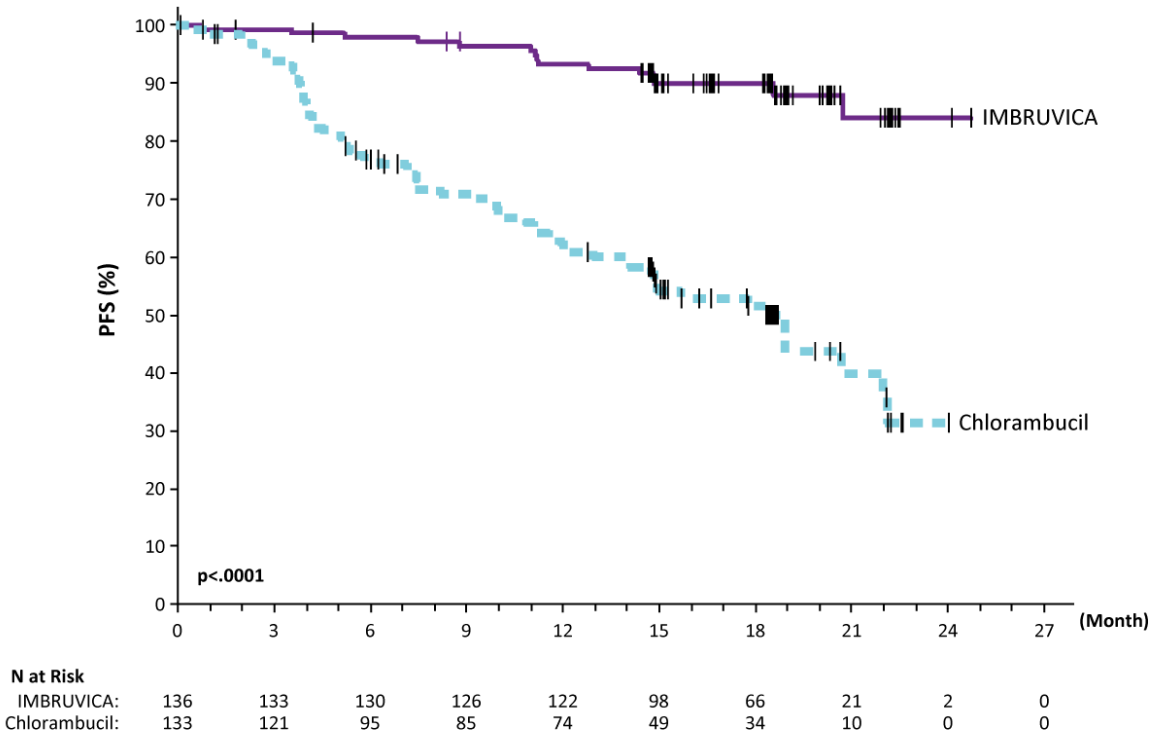
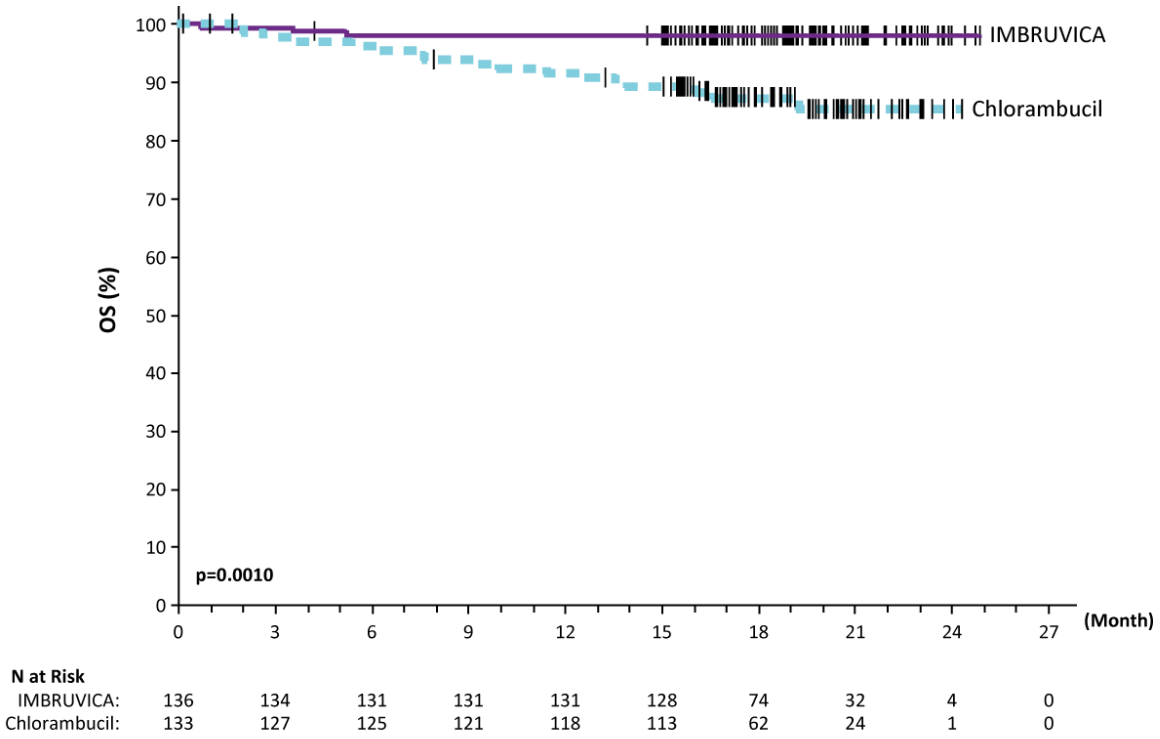


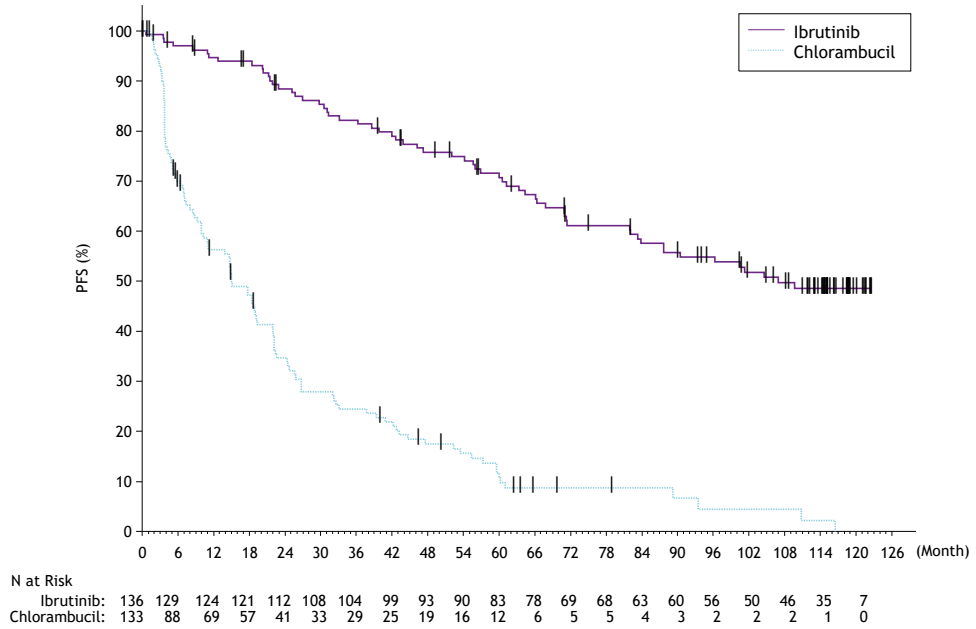
Figure 5: Kaplan-Meier Curve of OS (ITT Population) in Study PCYC-1115-CA



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 6. 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 6: 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-centre, 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 8 and the Kaplan-Meier curve for PFS is shown in Figure 7.

Table 8: 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

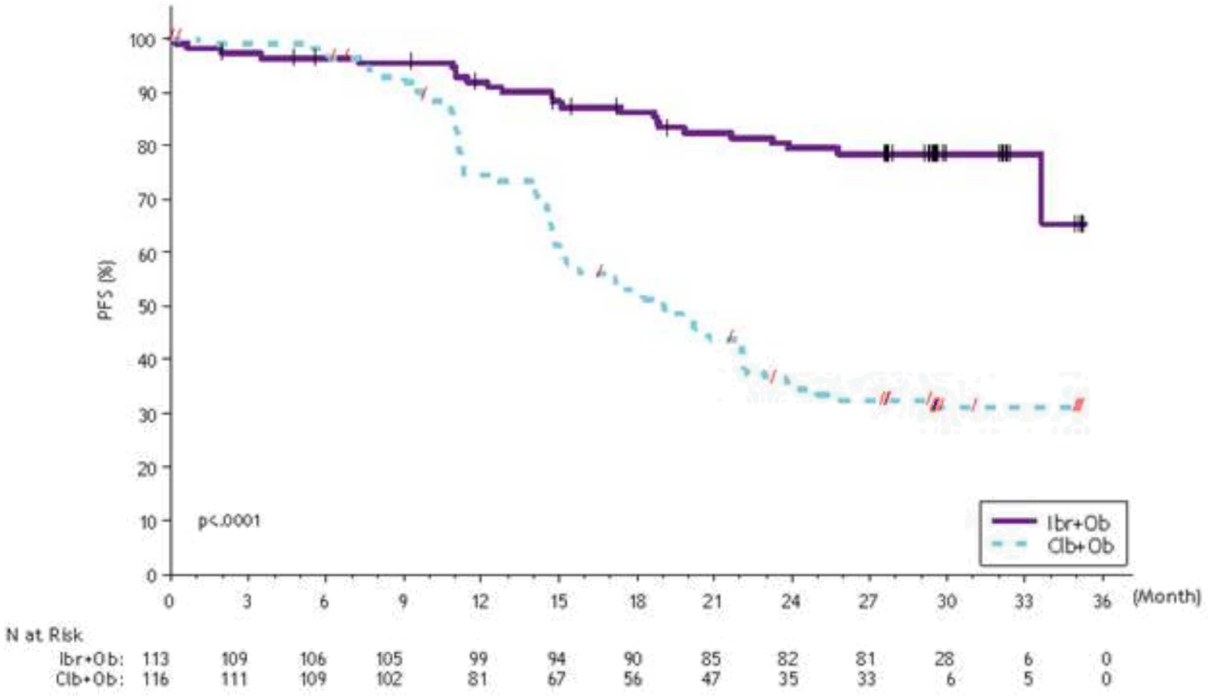
CI=confidence interval; HR=hazard ratio; CR=complete response; PR=partial response.

[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 7: 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 9. 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 9: 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-centre, 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/m^2, and cyclophosphamide was administered at a dose of 250 mg/m^2, both on Days 1, 2, and 3 of Cycles 1-6. Rituximab was initiated in Cycle 2 for the IR arm and in Cycle 1 for the FCR arm and was administered at a dose of 50 mg/m^2 on Day 1 of the first cycle, 325 mg/m^2 on Day 2 of the first cycle, and 500 mg/m^2 on Day 1 of 5 subsequent cycles, for a total of 6 cycles. Each cycle was 28 days.

The median age was 58 years (range, 28 to 70 years), 67% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 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 10. The Kaplan-Meier curves for PFS, assessed according to IWCLL criteria, and OS are shown in Figures 8 and 9, respectively.

Table 10: Efficacy results in Study E1912

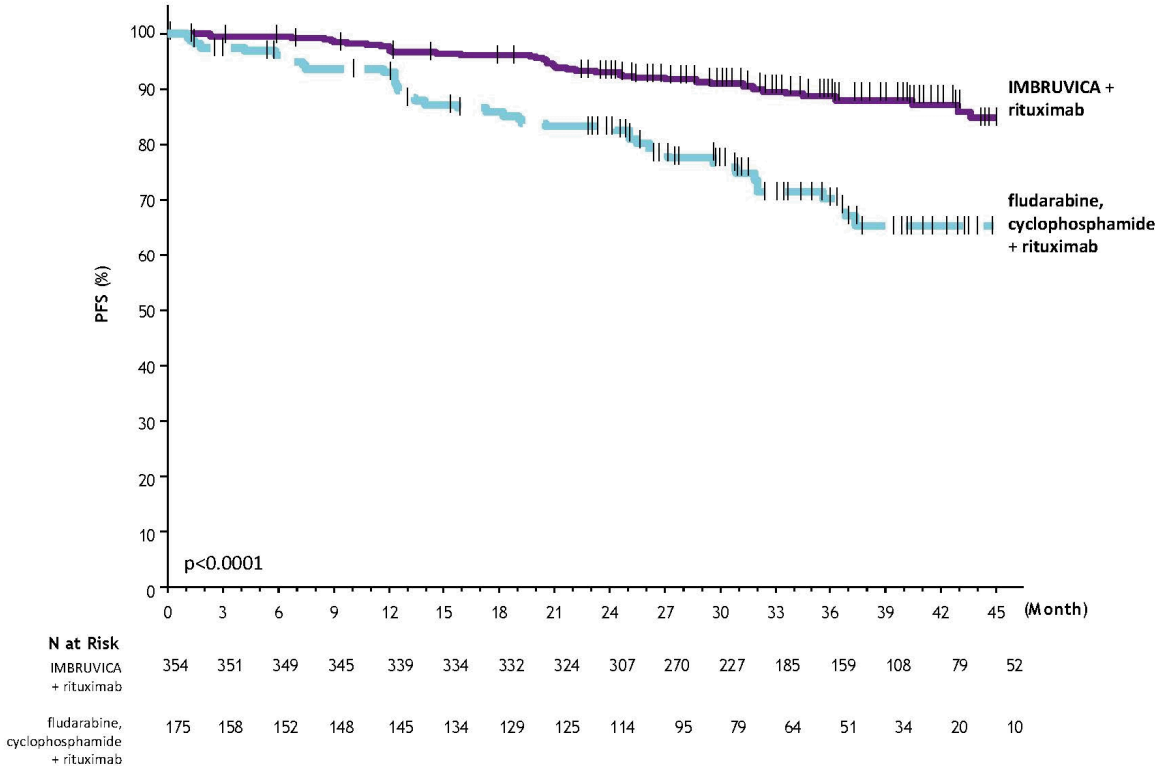
Endpoint	Ibrutinib+rituximab (IR) N=354	Fludarabine, Cyclophosphamide, and Rituximab (FCR) N=175
Progression-Free Survival		
Number of events (%)	41 (12)	44 (25)
Disease progression	39	38
Death events	2	6
Median (95% CI), months	NE (49.4, NE)	NE (47.1, NE)
HR (95% CI)	0.34 (0.22, 0.52)	
P-value[a]	<0.0001	
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 8: Kaplan-Meier Curve of PFS (ITT Population) in Study E1912



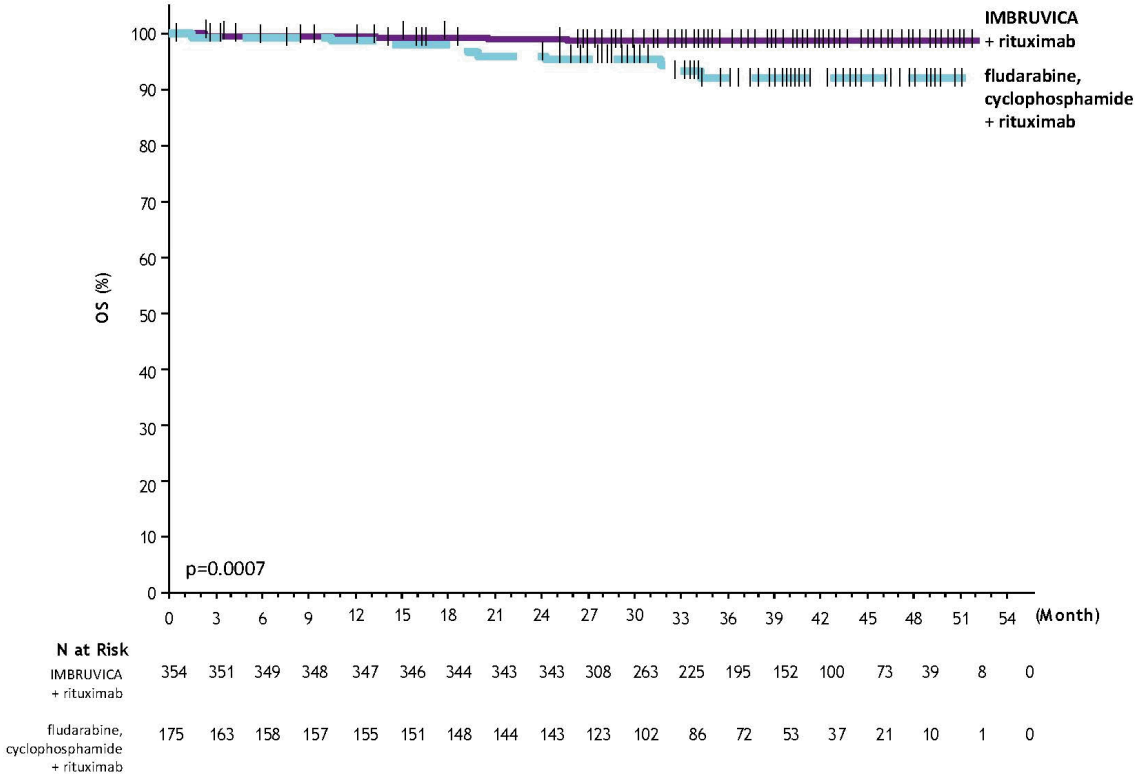
The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (TP53 mutation, del11q, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.40)], p <0.0001, as shown in Table 11. The 3-year PFS rate estimates for the high-risk CLL/SLL population were 90.4% [95% CI (85.4, 93.7)] and 60.3% [95% CI (46.2, 71.8)] in the IR and FCR arms, respectively.

Table 11: 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 9: 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 tumour lysis syndrome, 25% of patients had high tumour burden. After 3 cycles of single-agent IMBRUVICA lead-in therapy, 2% of patients had high tumour burden. High tumour burden was defined as any lymph node ≥10 cm; or any lymph node ≥5 cm and absolute lymphocyte count $\geq 25 \times 10^9$/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 12, the Kaplan-Meier curve for PFS is shown in Figure 10, and rates of minimal residual disease (MRD) negativity are shown in Table 13.

Table 12: 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

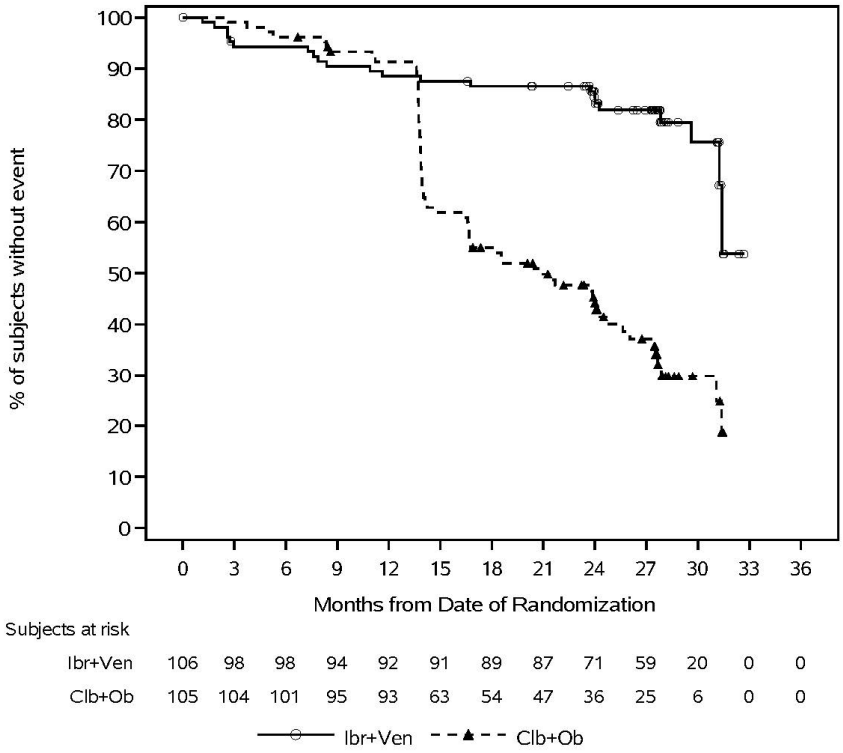
[c] Includes 3 patients in the IMBRUVICA + venetoclax arm with a complete response with incomplete marrow recovery (CRi)

[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 10: 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 13: Minimal residual disease negativity rates in Study CLL3011

	NGS Assay[a]		**Flow cytometry[b]**	
	IMBRUVICA + Venetoclax N=106	**Chlorambucil + Obinutuzumab N=105**	**IMBRUVICA + Venetoclax N=106**	**Chlorambucil + Obinutuzumab 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 ($<1\times10^4$).

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.

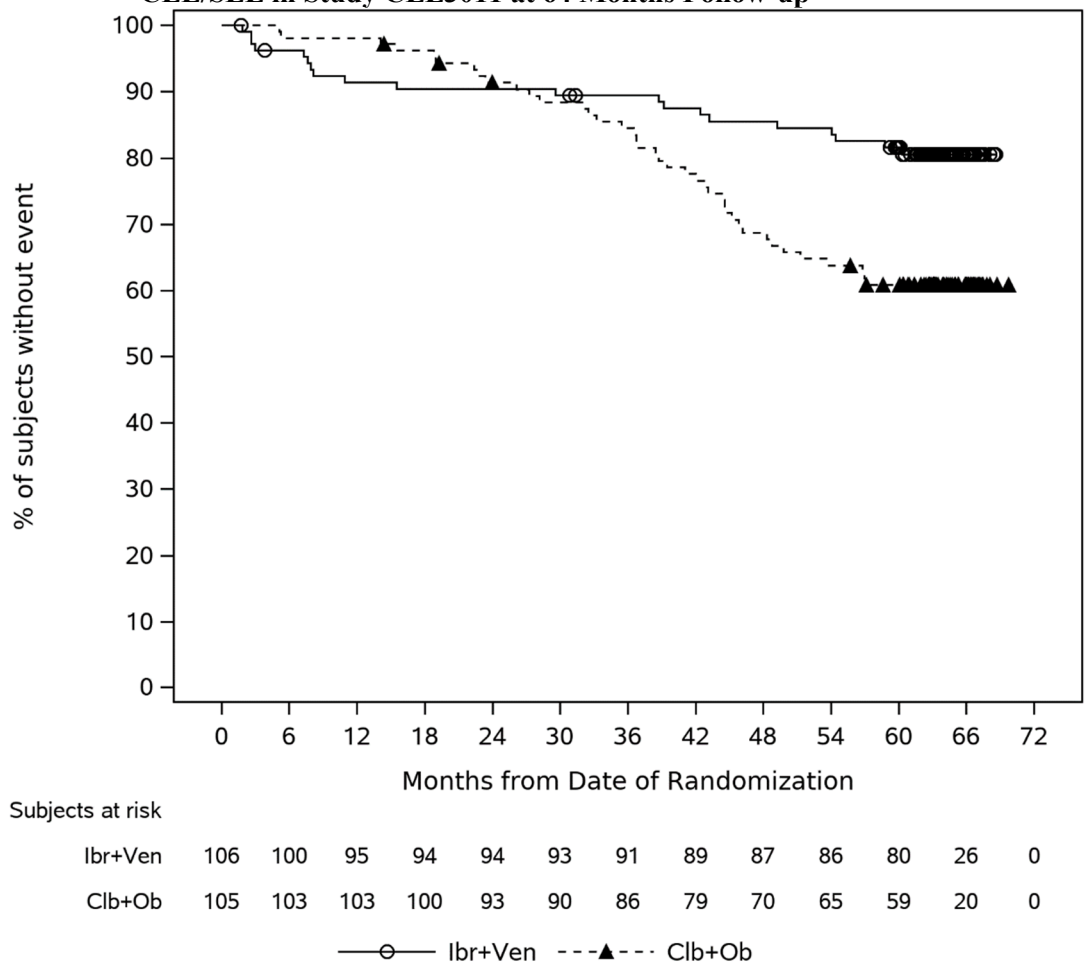
TLS was reported in 6 patients treated with chlorambucil plus obinutuzumab and no TLS was reported in IMBRUVICA in combination with venetoclax.

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 65 months 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 11.

Figure 11: 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-centre, 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 tumour lysis syndrome, 21% of patients had high tumour burden.

After 3 cycles of single-agent IMBRUVICA lead-in therapy, 1% of patients had high tumour burden. High tumour burden was defined as any lymph node ≥10 cm, or any lymph node ≥5 cm and absolute lymphocyte count $\geq 25 \times 10^9$/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 14, and rates of minimal residual disease (MRD) negativity are shown in Table 15.

Table 14: 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 15: 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-centre 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-centre, 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 16.

Table 16: 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 17).

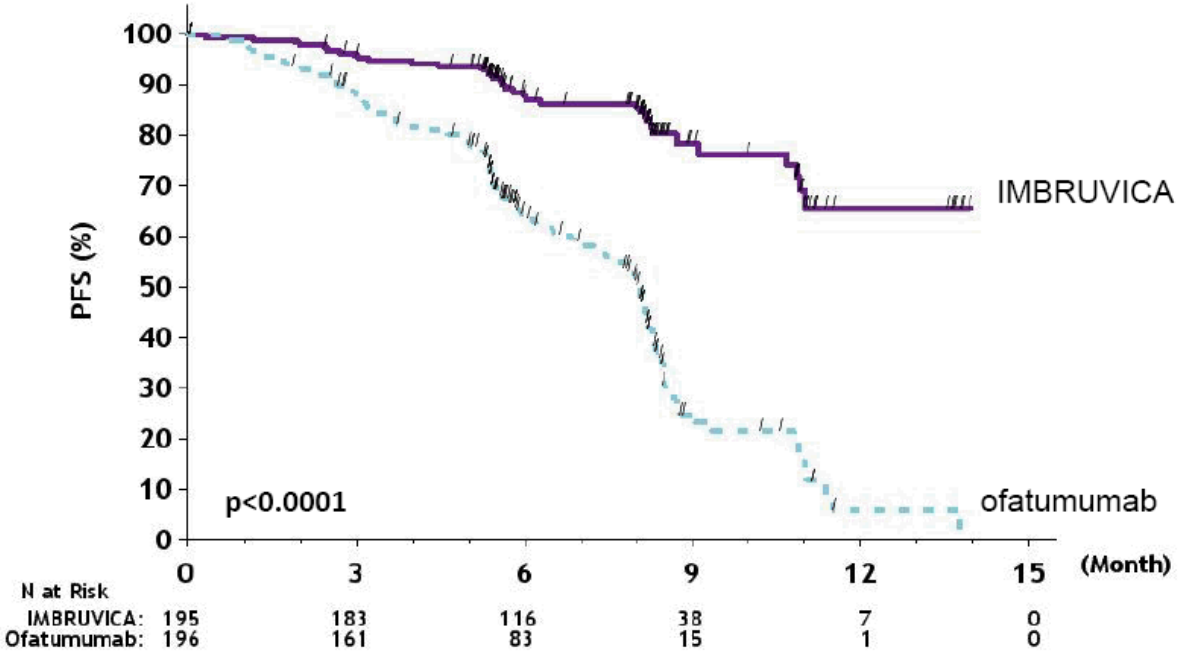
Table 17: Subgroup analysis of PFS (Study PCYC-1112-CA)

	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 12.

Figure 12: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1112-CA



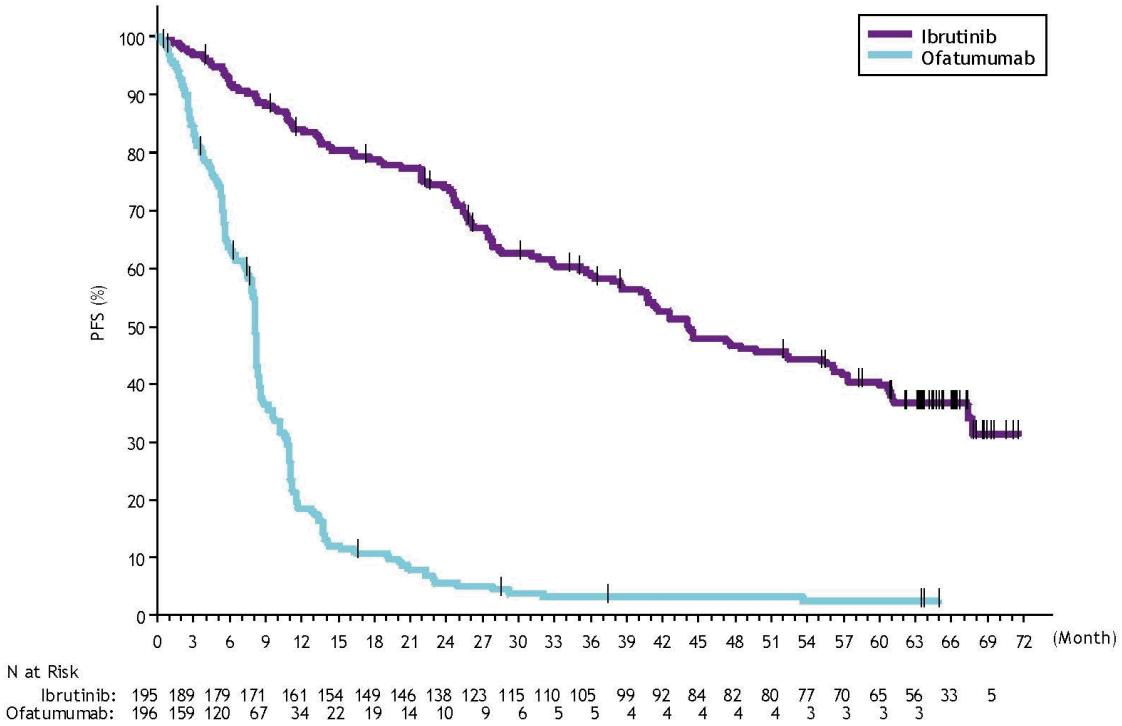
Final Analysis at 65-month follow-up

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 13. 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 13: 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, multi-centre, 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 18.

Table 18: Efficacy results in patients with CLL (Study CLL3001)

Endpoint	IMBRUVICA+BR N=289	Placebo+BR N=289
PFS[a]		
Median (95% CI), months	Not reached	13.3 (11.3, 13.9)
	HR=0.203 [95% CI: 0.150, 0.276]	
ORR[b] %	82.7	67.8
OS[c]	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-centre, 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 19.

Table 19: 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, multi-centre, 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/m^2 for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 consecutive weeks (weeks 17-20).

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were Caucasian. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were treatment-naïve, and 55% of patients were previously treated. The median time since diagnosis was 52.6 months

(treatment-naïve patients=6.5 months and previously treated patients=94.3 months). Among previously treated patients, the median number of prior treatments was 2 (range, 1 to 6 treatments). At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), 63% of patients were 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.

Tumour 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 20 and the Kaplan-Meier curve for PFS is shown in Figure 14. 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 20: 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.

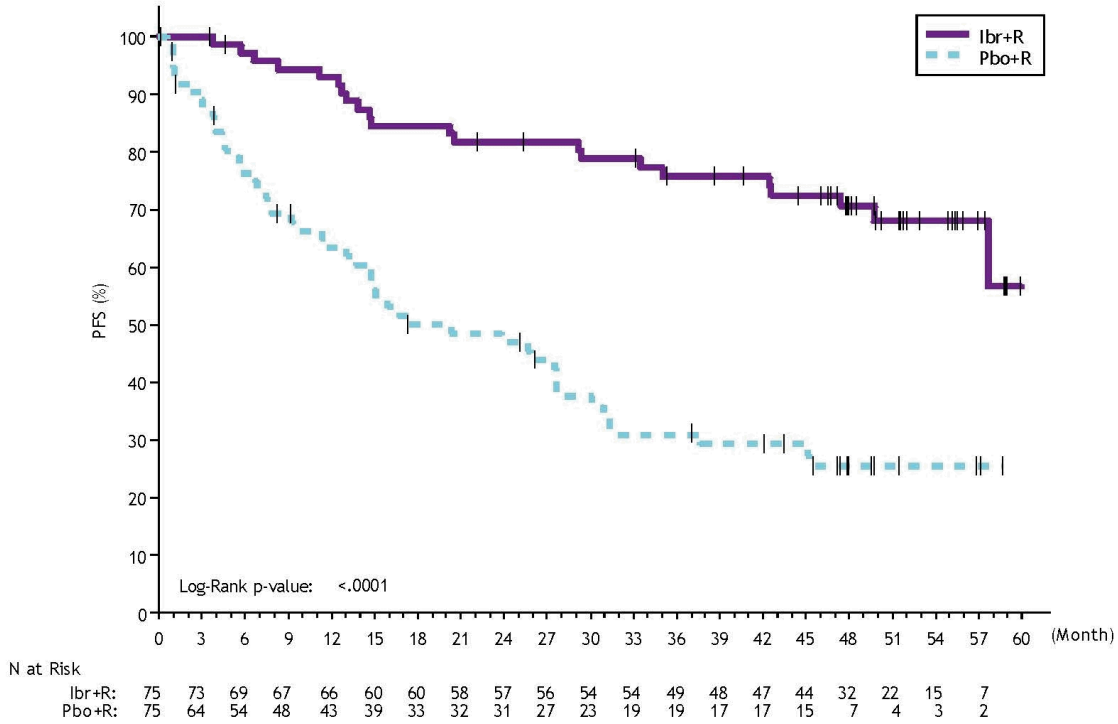
[b] 4-year PFS estimates were 70.6% [95% CI (58.1, 80.0)] in the IMBRUVICA + R arm versus 25.3% [95% CI (15.3, 36.6)] in the placebo + R arm.

[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 14: 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).

Paediatric population

The safety, efficacy, and pharmacokinetics of IMBRUVICA in paediatric and young adult patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma were evaluated in a two-part, multi-centre, open-label Phase 3 study (LYM3003) of IMBRUVICA in combination with either a rituximab, ifosfamide, carboplatin, etoposide and dexamethasone (RICE) regimen or a rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone (RVICI) regimen, as background therapy.

Part 1 of the study (21 patients aged 3 to 17 years) evaluated the dose to be used in part 2 (51 patients aged 3 to 19 years) (see section 5.2).

In part 2, patients were randomised 2:1 to receive either IMBRUVICA as 440 mg/m^2 daily (age below 12 years) or 329 mg/m^2 (age 12 years and older) with background therapy, or background therapy alone until completion of 3 cycles of therapy, transplantation, disease progression or unacceptable toxicity. The primary endpoint of event-free survival (EFS) superiority was not met suggesting no additional benefit from adding ibrutinib to RICE or RVICI (see section 4.2).

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. 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

Pharmacokinetic data show that ibrutinib exposures in children with relapsed or refractory mature B-cell non-Hodgkin lymphoma, aged 12 years and older receiving a daily dose of 329 mg/m^2 and those aged 3 years to below 12 years receiving a daily dose of 440 mg/m^2, were generally within the range of exposures observed in adult patients administered a daily dose of 560 mg.

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 2 000 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

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)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/001 (90 hard capsules)
EU/1/14/945/002 (120 hard capsules)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 October 2014
Date of latest renewal: 25 June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg film-coated tablets
IMBRUVICA 280 mg film-coated tablets
IMBRUVICA 420 mg film-coated tablets
IMBRUVICA 560 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

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

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

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

IMBRUVICA 560 mg film-coated tablets
Each film-coated tablet contains 560 mg of ibrutinib.

Excipients with known effect
Each 560 mg film-coated tablet contains 112 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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

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

IMBRUVICA 420 mg film-coated tablets
Yellow-green to green oblong tablets (17.5 mm in length and 7.4 mm in width), debossed with “ibr” on one side and “420” on the other side.

IMBRUVICA 560 mg film-coated tablets
Yellow to orange oblong tablets (19 mm in length and 8.1 mm in width), debossed with “ibr” on one side and “560” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMBRUVICA in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (IMBRUVICA + R-CHOP) alternating with R-DHAP (or R-DHAOx) without IMBRUVICA, followed by IMBRUVICA monotherapy, is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT).

IMBRUVICA as a single agent is indicated for the treatment of adult patients with relapsed or refractory 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 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.

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
Treatment of adult patients with previously untreated MCL

The recommended dose for the treatment of previously untreated MCL is ibrutinib 560 mg once daily (see Table 1).

Table 1: IMBRUVICA dosing schedule for previously untreated MCL

Treatment	Cycle number	Treatment	IMBRUVICA
Part I[*]	1, 3, 5	IMBRUVICA in combination with R-CHOP[§]	On days 1-19
	2, 4, 6	R-DHAP[#§]	Without IMBRUVICA
Part II[±]		IMBRUVICA	Daily for 24 Months

R-CHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-DHAP= rituximab, dexamethasone, cytarabine, cisplatin.

[*]6 cycles; each cycle is 21 days.

[§]See the Summary of Product Characteristics (SmPC) for dosing information for each medicinal product.

[#]Interchangeable with R-DHAOx (rituximab, dexamethasone, cytarabine, oxaliplatin)[§].

[±] Treatment should start after recovery of peripheral blood counts. Rituximab may be added as per national treatment guidelines.

Treatment of adult patients with relapsed or refractory MCL

The recommended dose for the treatment of previously treated MCL is ibrutinib 560 mg once daily as a single agent.Treatment with IMBRUVICA as a single agent should continue until disease progression or no longer tolerated by the patient.

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 regimens, see section 5.1).

Treatment with IMBRUVICA as a single agent or in combination with anti-CD20 therapy 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 Summary of Product Characteristics (SmPC) 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.

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 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 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 tablets 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. Currently available data in patients with mature B-cell non-Hodgkin lymphoma are described in sections 4.8, 5.1 and 5.2.

Method of administration
IMBRUVICA should be administered orally once daily with a glass of water approximately at the same time each day. 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. 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.

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
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 CYP3A4 inhibitors
Co-administration of ketoconazole, a very strong CYP3A4 inhibitor, in 18 fasted healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by 29- and 24-fold, respectively. Simulations using fasted conditions suggested that the strong CYP3A4 inhibitor clarithromycin may increase the AUC of ibrutinib by a factor of 14. In patients with B-cell malignancies taking IMBRUVICA with food, co-administration of the strong CYP3A4 inhibitor voriconazole increased C_{max} by 6.7-fold and AUC by 5.7-fold. Strong inhibitors of CYP3A4 (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, cobicistat, voriconazole and posaconazole) should be avoided. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the IMBRUVICA dose to 140 mg for the duration of the inhibitor use or withhold IMBRUVICA temporarily (for 7 days or less). Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

Moderate CYP3A4 inhibitors
In patients with B-cell malignancies taking IMBRUVICA with food, co-administration of the CYP3A4 inhibitor erythromycin increased C_{max} by 3.4-fold and AUC by 3.0-fold. If a moderate CYP3A4 inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone and dronedarone) is indicated, reduce IMBRUVICA dose to 280 mg for the duration of the inhibitor use. Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

Mild CYP3A4 inhibitors
Simulations using fasted conditions suggested that the mild CYP3A4 inhibitors azithromycin and fluvoxamine may increase the AUC of ibrutinib by <2-fold. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed.

Co-administration of grapefruit juice, containing CYP3A4 inhibitors, in eight healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by approximately 4- and 2-fold, respectively. Grapefruit and Seville oranges should be avoided during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A4 (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
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

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.

Summary for B-cell malignancies

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. The TRIANGLE study data is not included in the pooled data and presented separately in Table 3. 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 14.7 months (up to 52 months); MCL was 11.7 months (up to 28 months); WM was 21.6 months (up to 37 months).

Table 2: 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
Neoplasms benign, malignant and unspecified (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[*, #] Atrial fibrillation	2 8	1 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
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.

Summary for patients with previously untreated MCL who were eligible for ASCT

The safety profile is based on data from 265 patients (in the IMBRUVICA arm) treated with IMBRUVICA in the phase 3 TRIANGLE study. Patients received IMBRUVICA at 560 mg once daily according to the TRIANGLE treatment schedule (see section 5.1). The median treatment duration was 28.5 months in the IMBRUVICA arm.

Table 3: Adverse reactions reported in the IMBRUVICA arm of the TRIANGLE Study†

		N=265		
System Organ Class	**Frequency (All Grades)**	**Adverse Reactions**	**All Grades (%)**	**Grade ≥3 (%)**
Infections and infestations	Very common	Pneumonia* [#]	16	9
		Skin infection*	12	3
	Common	Upper respiratory tract infection	6	<1
		Sepsis*	2	2
		Urinary tract infection	6	<1

		Sinusitis*	6	1
	Uncommon	Aspergillus infections*	1	<1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Non-Melanoma skin cancer*	1	<1
		Basal cell carcinoma	1	<1
Blood and lymphatic system disorders	Very common	Thrombocytopenia*	69	61
		Neutropenia*	63	60
		Febrile neutropenia	14	14
	Common	Leukocytosis	3	1
Immune system disorders	Common	Interstitial lung disease*	5	1
Metabolism and nutrition disorders	Common	Hyperuricaemia	8	3
		Tumour lysis syndrome*	3	3
Nervous system disorders	Very common	Peripheral neuropathy*	35	3
		Headache	11	1
	Common	Dizziness	6	<1
	Uncommon	Transient ischaemic attack	1	0
Eye disorders	Uncommon	Vision blurred	1	0
		Eye haemorrhage	<1	0
Cardiac disorders	Common	Atrial fibrillation	10	4
		Cardiac failure*	2	0
Vascular disorders	Very common	Haemorrhage*	14	2
		Hypertension*	14	5
	Common	Bruising*	8	1
		Epistaxis	6	1
		Petechiae	3	0
Gastrointestinal disorders	Very common	Nausea	32	4
		Diarrhoea	28	5
		Vomiting	18	4
		Stomatitis*	11	2
		Constipation	17	<1
	Common	Dyspepsia	8	0
Skin and subcutaneous tissue disorders	Very common	Rash*	23	2
	Common	Erythema	5	0
		Onychoclasis	2	0
	Uncommon	Urticaria	<1	0
		Angioedema	1	0
		Cutaneous vasculitis	<1	0
		Panniculitis*	1	0
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain*	19	2
	Common	Muscle spasms	9	1
		Arthralgia	8	1
Renal and urinary disorders	Very common	Acute kidney injury	11	5
General disorders and administration site conditions	Very common	Pyrexia	22	2
	Common	Oedema peripheral	5	0
Investigations	Very common	Blood creatinine increased	16	1

† Frequencies are rounded to the nearest integer.

* Terms required grouping.

Includes events with fatal outcome.

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. In the phase 3 TRIANGLE study involving 265 patients with previously untreated MCL who were eligible for ASCT treatment discontinuation due to adverse

reactions was observed in 13% in the IMBRUVICA arm. These included neutropenia, pneumonia, atrial fibrillation, acute kidney injury, diarrhoea, rash, and interstitial lung disease. Adverse reactions leading to dose reduction occurred in approximately 12% in the IMBRUVICA arm.

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 1 284 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%.

Paediatric population
The safety assessment is based on data from a phase 3 study of IMBRUVICA in combination with either a rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone (RICE) regimen, or a rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone (RVICI) regimen, as background therapy or background therapy alone in paediatric and young adult patients (aged 3 to 19 years) with relapsed or refractory mature B-cell non-Hodgkin lymphoma (see section 5.1). No new adverse reactions were observed in this study.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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-tumour 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
Combination treatment in patients previously untreated for MCL who were eligible for autologous stem cell transplantation (ASCT)

The safety and efficacy of IMBRUVICA in patients with previously untreated MCL and who were eligible for autologous stem cell transplantation (ASCT) were evaluated in a randomised, phase 3, multi-centre, open-label, three arm study (TRIANGLE). The TRIANGLE study randomised 870 patients in a 1:1:1 ratio to receive either:

- IMBRUVICA Arm: IMBRUVICA 560 mg daily (Days 1-19) in combination with R-CHOP for three 21-day cycles (Cycles 1, 3, 5) alternating with three 21-day cycles of R-DHAP (Cycles 2, 4, 6) as induction therapy followed by 2 years IMBRUVICA 560 mg daily;
- IMBRUVICA + ASCT Arm: IMBRUVICA 560 mg daily (Days 1-19) in combination with R-CHOP for three 21-day cycles (Cycles 1, 3, 5) alternating with three 21-day cycles of R-DHAP

(Cycles 2, 4, 6) as induction therapy followed by high-dose chemotherapy and ASCT followed by 2 years IMBRUVICA 560 mg daily;
- ASCT Arm: R-CHOP for three 21-day cycles (Cycles 1, 3, 5) alternating with three 21-day cycles of R-DHAP (Cycles 2, 4, 6) as induction therapy followed by high-dose chemotherapy and ASCT (Control Arm).

The efficacy analyses were conducted based on 809 patients in the full analysis set (FAS) population using 3 pairwise comparisons of the 3 treatment arms: IMBRUVICA + ASCT vs. ASCT; IMBRUVICA vs. ASCT; and IMBRUVICA + ASCT vs. IMBRUVICA. The FAS population included patients that have either provided explicit permission for their data to be included as per EU General Data Protection Regulation or were deceased. The results presented are from the IMBRUVICA (N=265) arm and the ASCT (N=268) arm, only.

Induction with R-CHOP (rituximab 375 mg/m^2 on Day 0 or 1, cyclophosphamide 750 mg/m^2 on Day 1, doxorubicin 50 mg/m^2 on Day 1, vincristine 1.4 mg/m^2 up to maximum of 2 mg on Day 1, and prednisone 100 mg on days 1-5) alternating with R-DHAP (rituximab 375 mg/m^2 on Day 0 or 1, dexamethasone 40 mg on days 1-4, Ara-C 2x 2 g/m^2 every 12 hours on Day 2, cisplatin 100 mg/m^2 (alternatively oxaliplatin 130 mg/m^2) on Day 1, and G-CSF 5 µg/kg from Day 6 until recovery of WBC) was the same in all 3 treatment arms. Rituximab maintenance therapy was allowed in all treatment groups (59.7% in the IMBRUVICA arm; 62.5% in the ASCT arm) according to national treatment guidelines.

The median age was 57 years (range: 27 to 65 years), 78% were male and 99% were Caucasian. Ninety-eight percent of patients had a baseline ECOG performance status of 0 or 1. At baseline, 86% had Ann Arbor Stage IV disease, and 57%, 28%, and 15% of patients had low, intermediate, and high-risk score by MCL International Prognostic Index (MIPI), respectively. Of the patients 11.6% had blastoid or pleomorphic histology. P53 expression was assessed in 64.6% of patients; expression >50% was present in 14.1% of these patients. Ki-67 proliferation index was assessed in 88.3% of patients and 32.9% of these patients had a proliferation index of >30%.

Tumour response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria (2007). The primary endpoint was failure-free survival (FFS), defined as the time from randomisation to stable disease at end of induction chemoimmunotherapy, progressive disease, or death from any cause, whichever was earlier.

With a median follow-up time on study of 54.9 months, efficacy results for TRIANGLE are shown in Table 4. The Kaplan-Meier curves for FFS and OS are shown in Figures 1 and 2, respectively.

Table 4: Efficacy Results in patients with previously untreated MCL (TRIANGLE) (FAS population)

Endpoint	IMBRUVICA Arm N=268	ASCT Arm N=269
Failure-free Survival[±]		
Number of events (%)	61 (22.8%)	87 (32.3%)
Stable Disease at the end of induction	1 (0.4%)	5 (1.9%)
Disease progression	49 (18.3%)	60 (22.3%)
Death events	11 (4.1%)	22 (8.2%)
Median (95% CI), months	NE (NE, NE)	NE (NE, NE)
IMBRUVICA vs ASCT Arms HR (98.33% CI) (P-value)[*]	0.639 (0.428, 0.953) (0.0068)	
Overall Survival[§]		
Number of deaths (%)	33 (12.3%)	60 (22.3%)
IMBRUVICA vs ASCT Arms HR (95% CI) (P-value)[*]	0.522 (0.341, 0.799) (0.0023)	
Overall Response Rate (%)[§] (95% CI)	258 (96.3%) (93.3%, 98.2%)	248 (92.2%) (88.3%, 95.1%)
CR rate (%)[§] (95% CI)	180 (67.2%) (61.2%, 72.8%)	174 (64.7%) (58.7%, 70.4%)

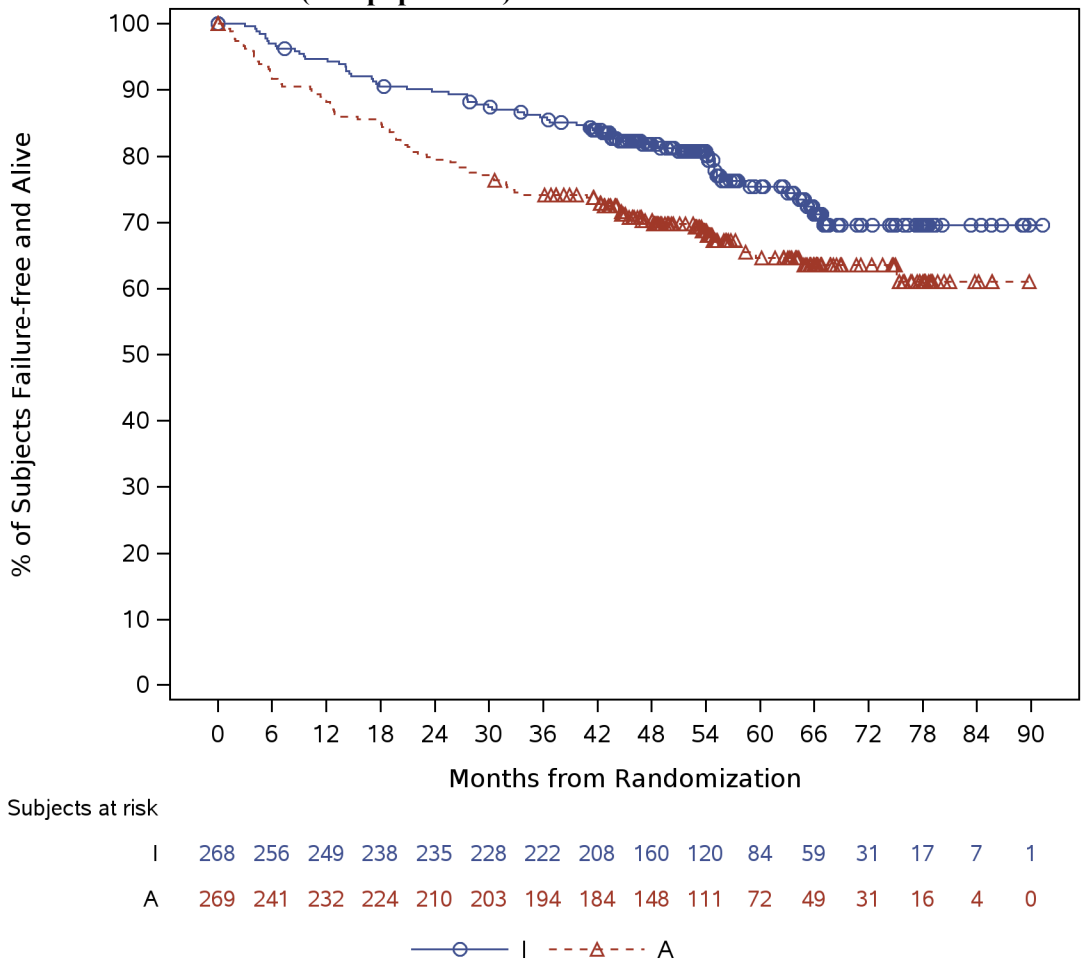
FFS=failure-free survival; NE=not estimable; HR=hazard ratio (based on unstratified Cox-regression model); RR=relative risk; CI=confidence interval; CR=complete response; FAS=full analysis set

[±] The FFS results are not controlled for type 1 error, as these analyses are derived from supplemental analyses conducted for registrational purposes

[*]Two-sided p-values are from unstratified log-rank test; p-values were tested based on $p<0.0167$

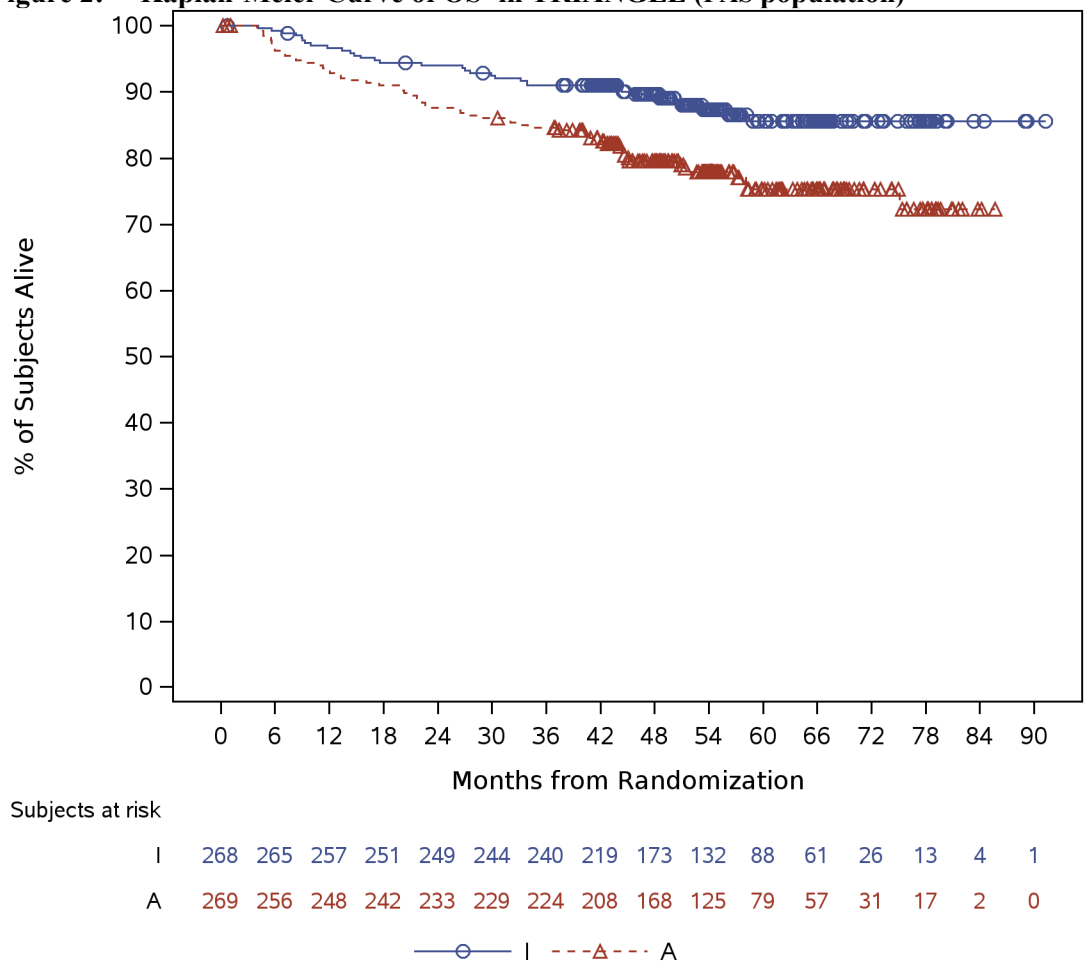
[§]Presented results are derived from descriptive analysis

Figure 1: Kaplan-Meier Curve of European MCL Network Assessed Failure-free Survival in TRIANGLE (FAS population)*



* I=IMBRUVICA; A=ASCT

Figure 2: Kaplan-Meier Curve of OS[§] in TRIANGLE (FAS population)*



*I=IMBRUVICA; A=ASCT
[§]Presented results are derived from descriptive analysis

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-centre 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 5.

Table 5: 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, multi-centre 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 6 and the Kaplan-Meier curve for PFS in Figure 3.

Table 6: Efficacy Results in patients with relapsed or refractory MCL (Study MCL3001)

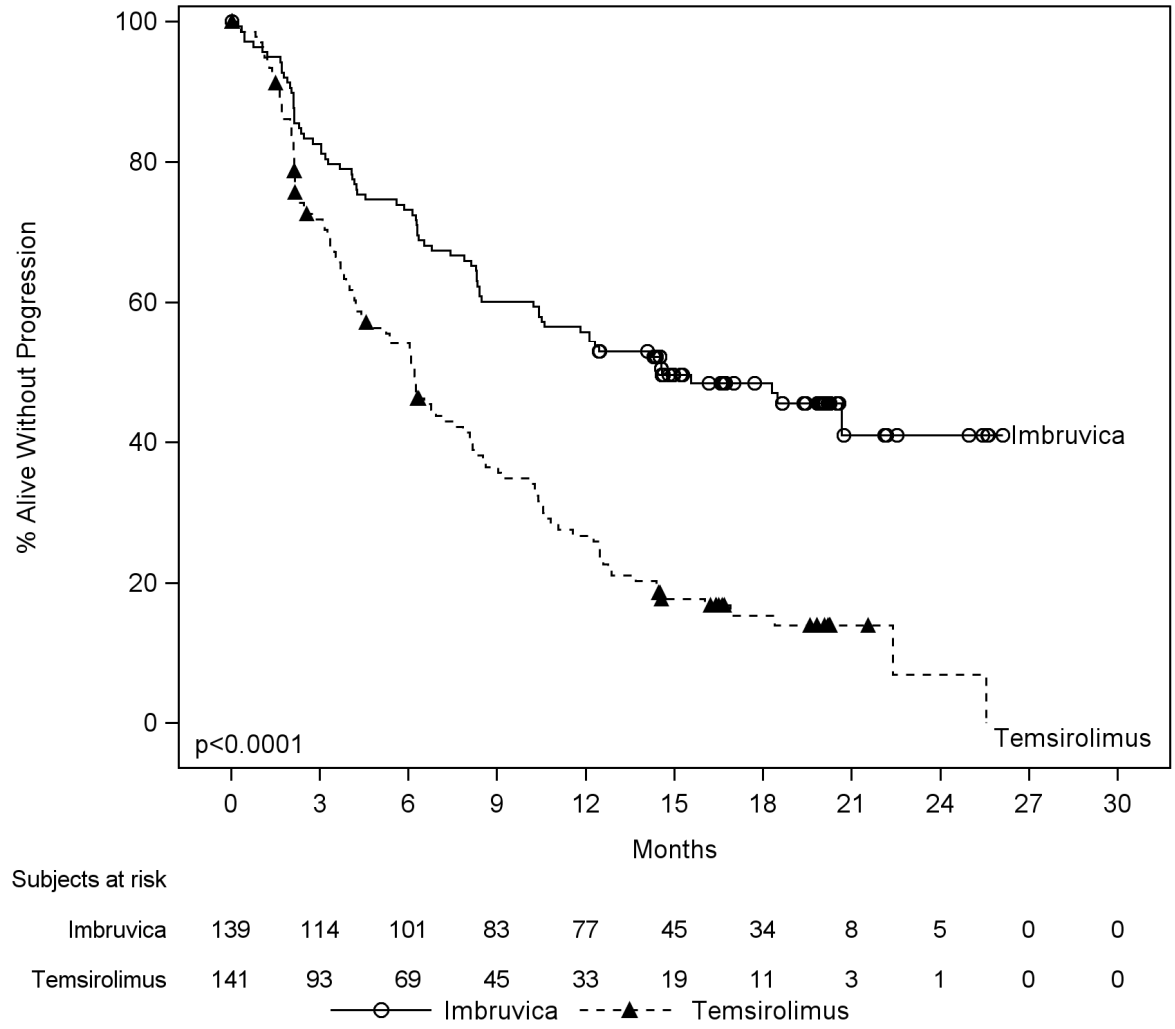
Endpoint	**IMBRUVICA N=139**	**Temsirolimus N=141**
PFS[a]		
Median PFS (95% CI), (months)	14.6 (10.4, NE)	6.2 (4.2, 7.9)
	HR=0.43 [95% CI: 0.32, 0.58]	
ORR (%)	71.9	40.4
p-value	p<0.0001	

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 3: Kaplan-Meier Curve of PFS (ITT Population) in Study MCL3001



CLL
Patients previously untreated for CLL
Single agent
A randomised, multi-centre, 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 tumour ≥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 del17p/tumour 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 7 and the Kaplan-Meier curves for PFS and OS are shown in Figures 4 and 5, 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 7: 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 4: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1115-CA

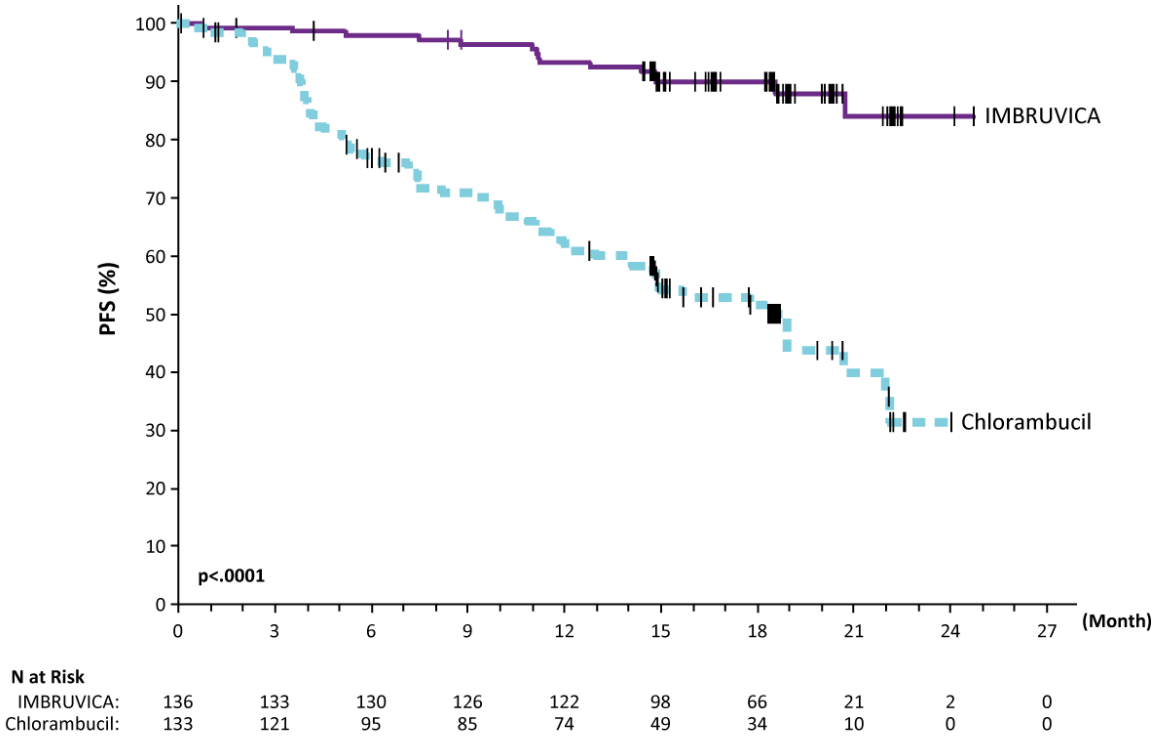
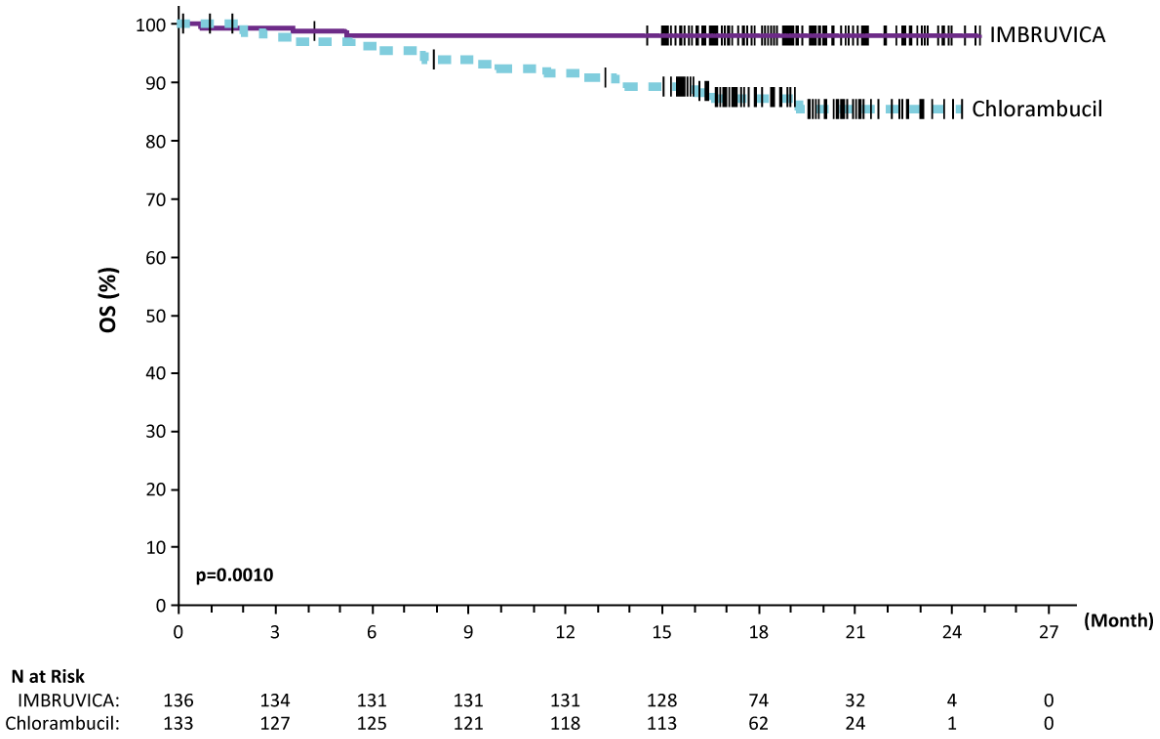


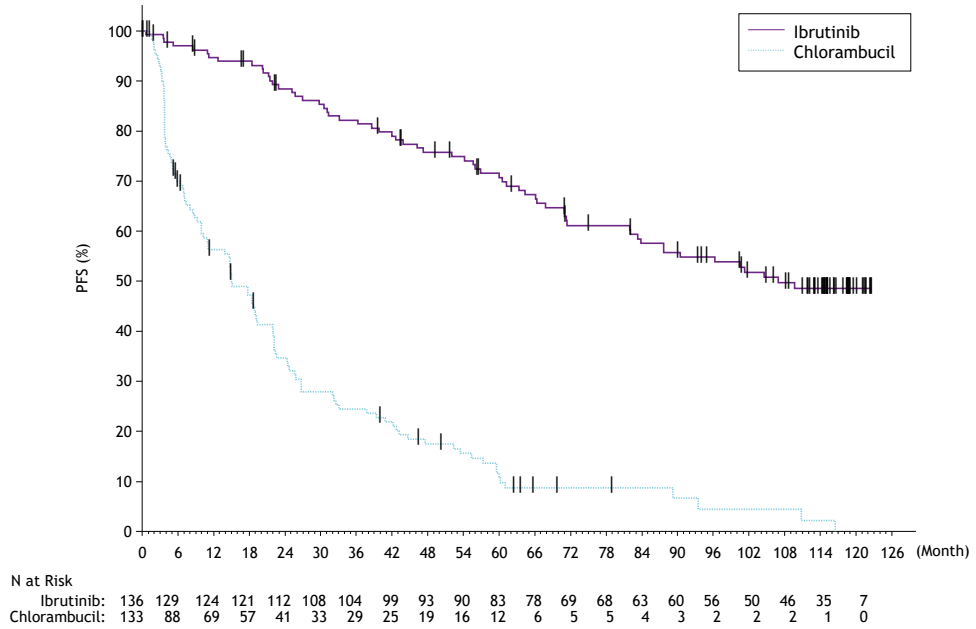
Figure 5: Kaplan-Meier Curve of OS (ITT Population) in Study PCYC-1115-CA



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 6. 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 6: 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-centre, 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 8 and the Kaplan-Meier curve for PFS is shown in Figure 7.

Table 8: 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

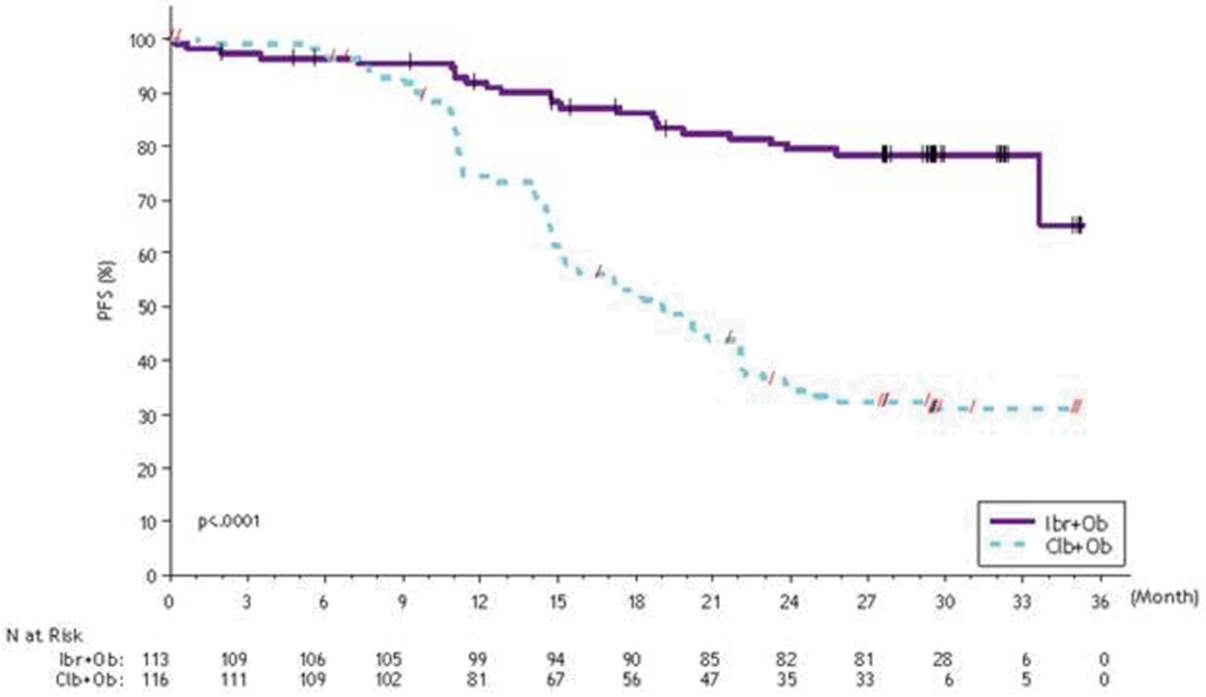
CI=confidence interval; HR=hazard ratio; CR=complete response; PR=partial response.

[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 7: 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 9. 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 9: 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-centre, 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/m^2, and cyclophosphamide was administered at a dose of 250 mg/m^2, both on Days 1, 2, and 3 of Cycles 1-6. Rituximab was initiated in Cycle 2 for the IR arm and in Cycle 1 for the FCR arm and was administered at a dose of 50 mg/m^2 on Day 1 of the first cycle, 325 mg/m^2 on Day 2 of the first cycle, and 500 mg/m^2 on Day 1 of 5 subsequent cycles, for a total of 6 cycles. Each cycle was 28 days.

The median age was 58 years (range, 28 to 70 years), 67% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 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 10. The Kaplan-Meier curves for PFS, assessed according to IWCLL criteria, and OS are shown in Figures 8 and 9, respectively.

Table 10: Efficacy results in Study E1912

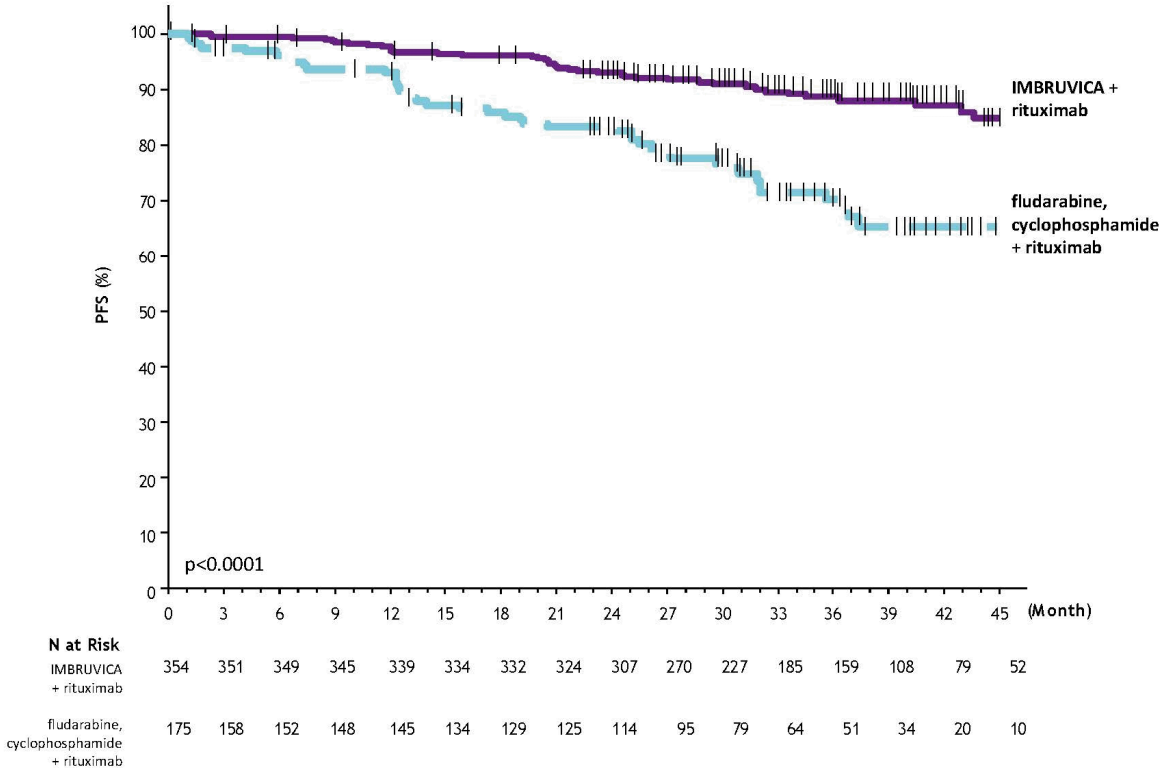
Endpoint	Ibrutinib+rituximab (IR) N=354	Fludarabine, Cyclophosphamide, and Rituximab (FCR) N=175
Progression-Free Survival		
Number of events (%)	41 (12)	44 (25)
Disease progression	39	38
Death events	2	6
Median (95% CI), months	NE (49.4, NE)	NE (47.1, NE)
HR (95% CI)	0.34 (0.22, 0.52)	
P-value[a]	<0.0001	
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 8: Kaplan-Meier Curve of PFS (ITT Population) in Study E1912



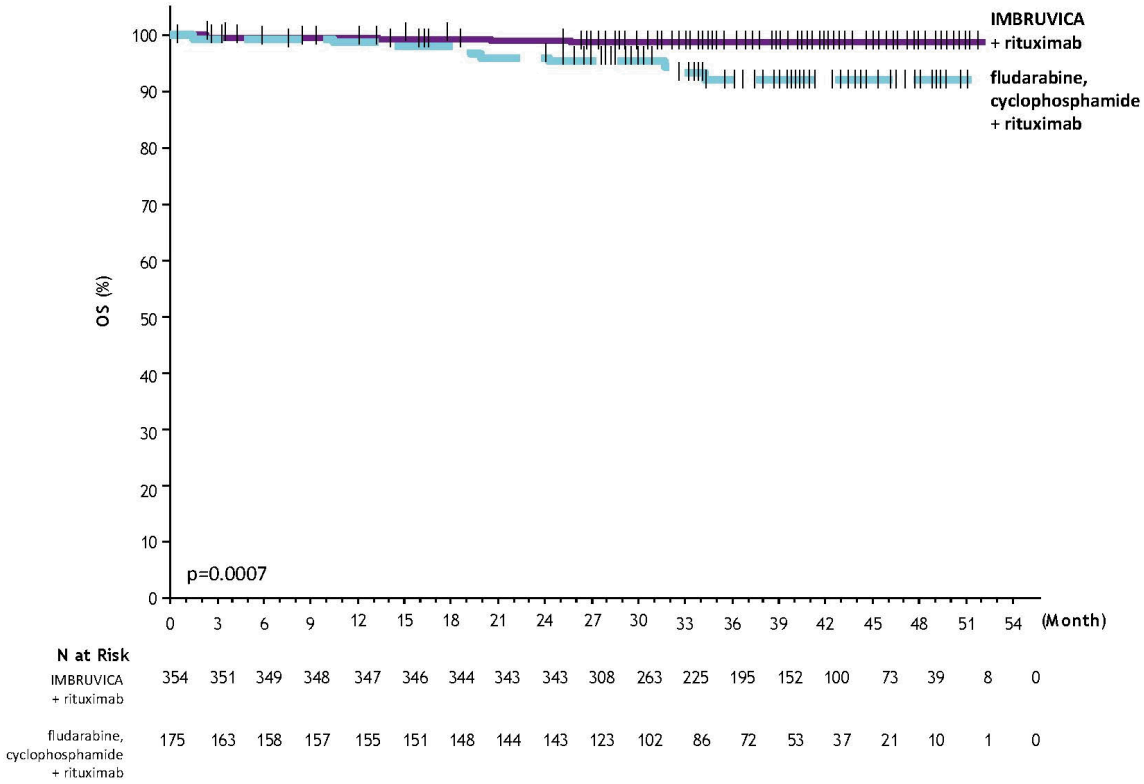
The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (TP53 mutation, del11q, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.40)], p <0.0001, as shown in Table 11. The 3-year PFS rate estimates for the high-risk CLL/SLL population were 90.4% [95% CI (85.4, 93.7)] and 60.3% [95% CI (46.2, 71.8)] in the IR and FCR arms, respectively.

Table 11: 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 9: 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 tumour lysis syndrome, 25% of patients had high tumour burden. After 3 cycles of single-agent IMBRUVICA lead-in therapy, 2% of patients had high tumour burden. High tumour burden was defined as any lymph node ≥10 cm; or any lymph node ≥5 cm and absolute lymphocyte count $\geq 25 \times 10^9$/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 12, the Kaplan-Meier curve for PFS is shown in Figure 10, and rates of minimal residual disease (MRD) negativity are shown in Table 13.

Table 12: 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

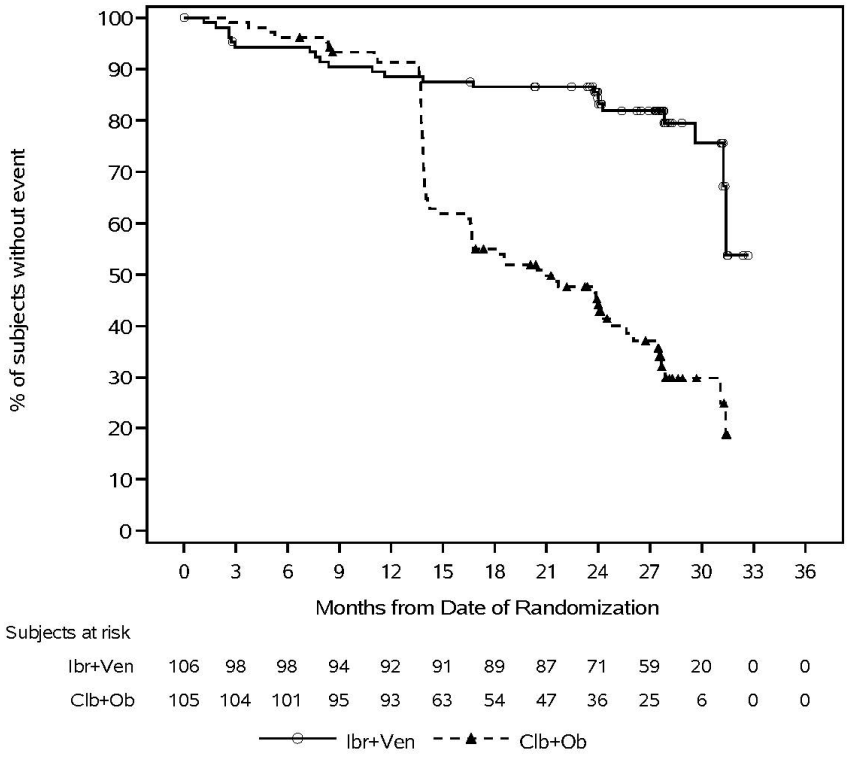
[c] Includes 3 patients in the IMBRUVICA + venetoclax arm with a complete response with incomplete marrow recovery (CRi)

[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 10: 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 13: Minimal residual disease negativity rates in Study CLL3011

	NGS Assay[a]		**Flow cytometry[b]**	
	IMBRUVICA + Venetoclax N=106	**Chlorambucil + Obinutuzumab N=105**	**IMBRUVICA + Venetoclax N=106**	**Chlorambucil + Obinutuzumab 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 ($<1\times10^4$).

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.

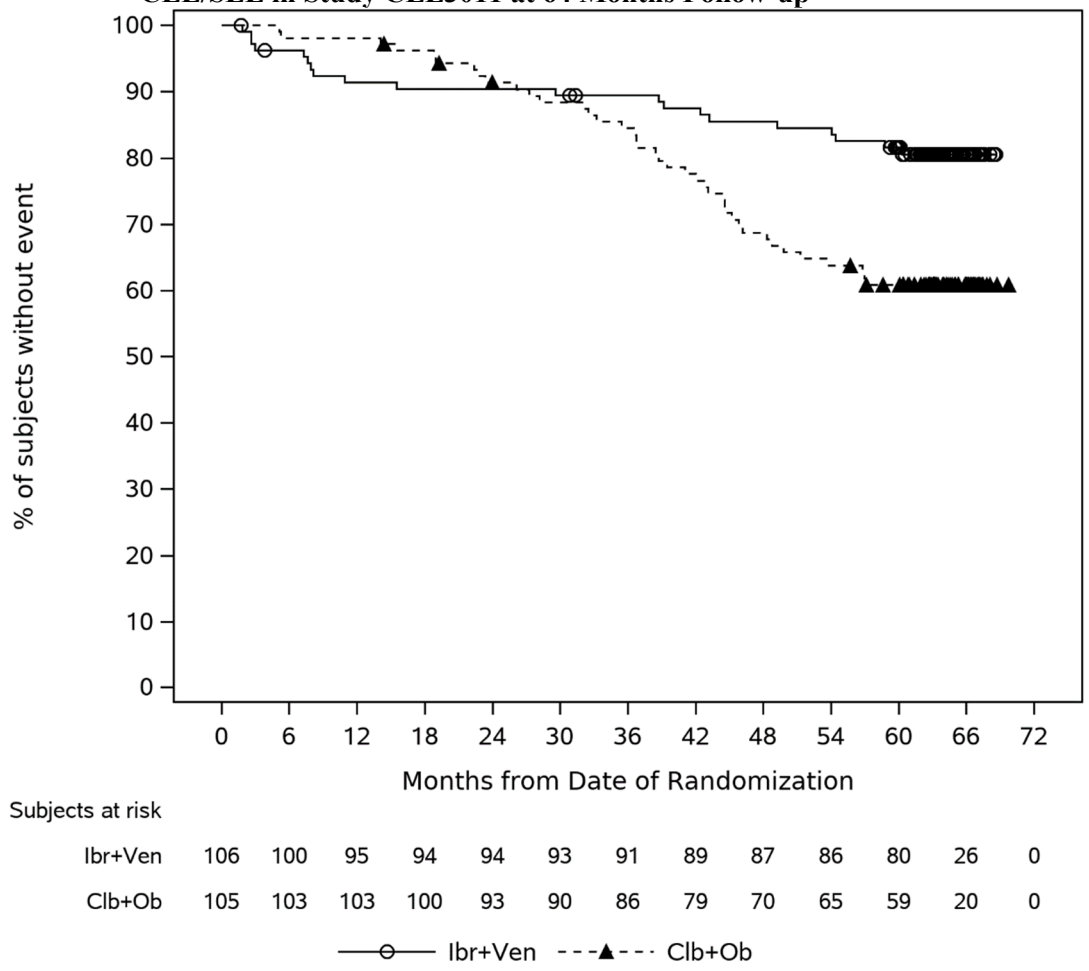
TLS was reported in 6 patients treated with chlorambucil plus obinutuzumab and no TLS was reported in IMBRUVICA in combination with venetoclax.

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 65 months 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 11.

Figure 11: 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-centre, 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 tumour lysis syndrome, 21% of patients had high tumour burden.

After 3 cycles of single-agent IMBRUVICA lead-in therapy, 1% of patients had high tumour burden. High tumour burden was defined as any lymph node ≥10 cm, or any lymph node ≥5 cm and absolute lymphocyte count $\geq 25 \times 10^9$/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 14, and rates of minimal residual disease (MRD) negativity are shown in Table 15.

Table 14: 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 15: 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-centre 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-centre, 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 16.

Table 16: 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 17).

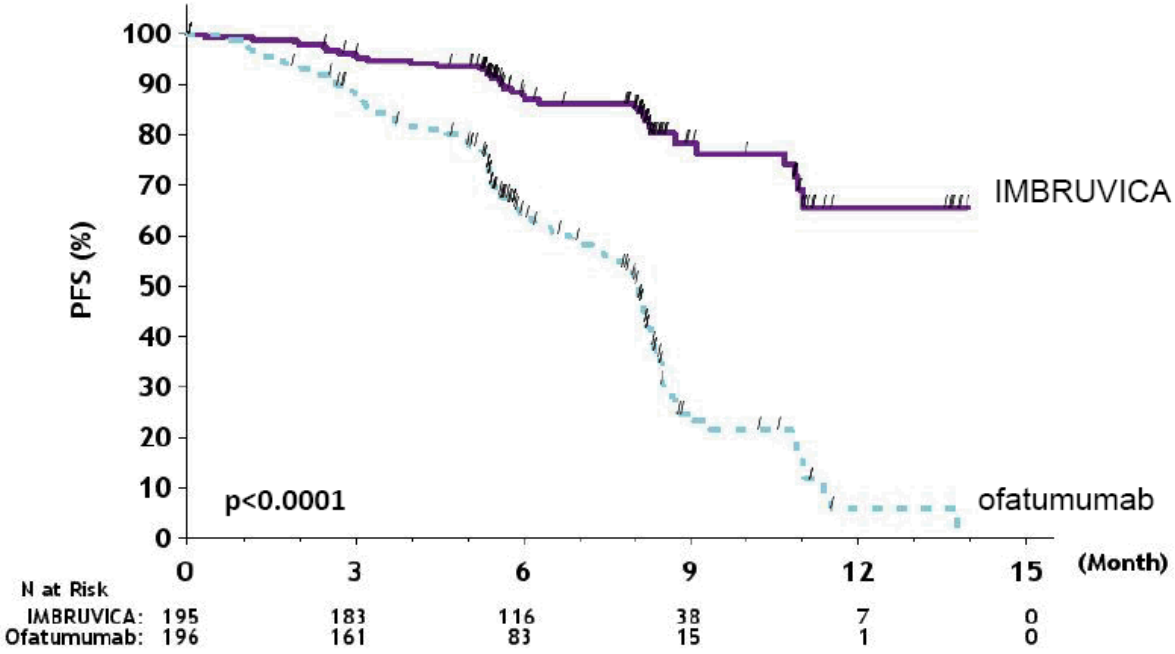
Table 17: Subgroup analysis of PFS (Study PCYC-1112-CA)

	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 12.

Figure 12: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1112-CA



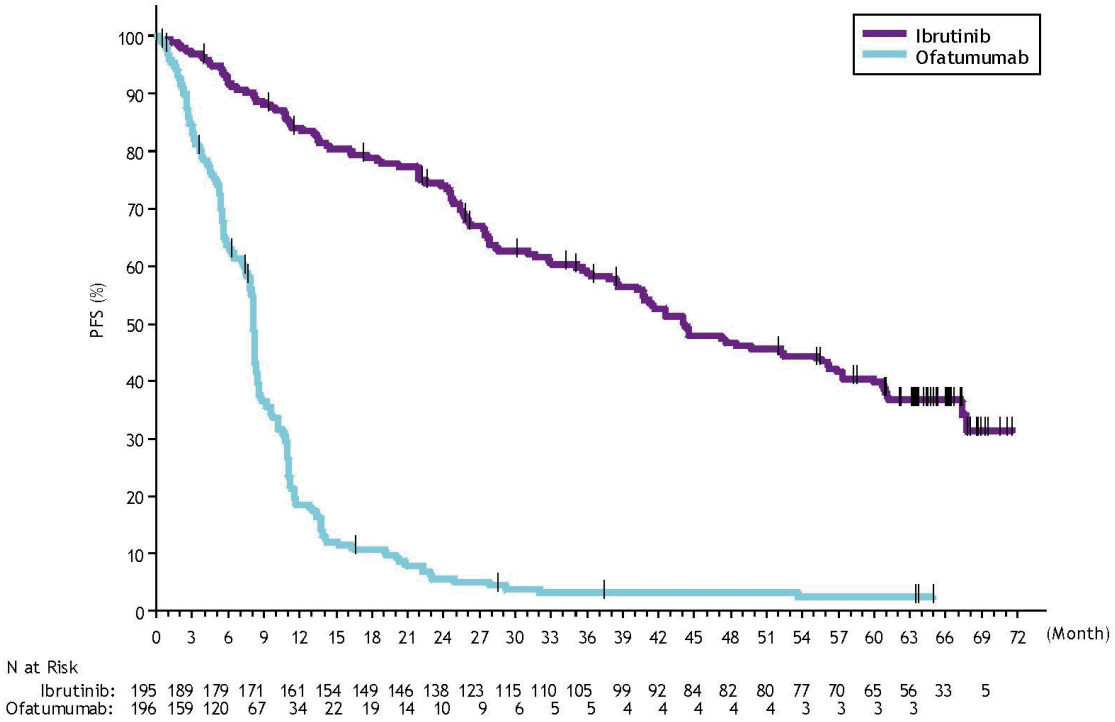
Final Analysis at 65-month follow-up

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 13. 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 13: 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, multi-centre, 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 18.

Table 18: Efficacy results in patients with CLL (Study CLL3001)

Endpoint	IMBRUVICA+BR N=289	Placebo+BR N=289
PFS[a]		
Median (95% CI), months	Not reached	13.3 (11.3, 13.9)
	HR=0.203 [95% CI: 0.150, 0.276]	
ORR[b] %	82.7	67.8
OS[c]	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-centre, 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 19.

Table 19: 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, multi-centre, 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/m^2 for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 consecutive weeks (weeks 17-20).

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were Caucasian. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were treatment-naïve, and 55% of patients were previously treated. The median time since diagnosis was 52.6 months (treatment-

naïve patients=6.5 months and previously treated patients=94.3 months). Among previously treated patients, the median number of prior treatments was 2 (range, 1 to 6 treatments). At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), 63% of patients were 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.

Tumour 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 20 and the Kaplan-Meier curve for PFS is shown in Figure 14. 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 20: 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.

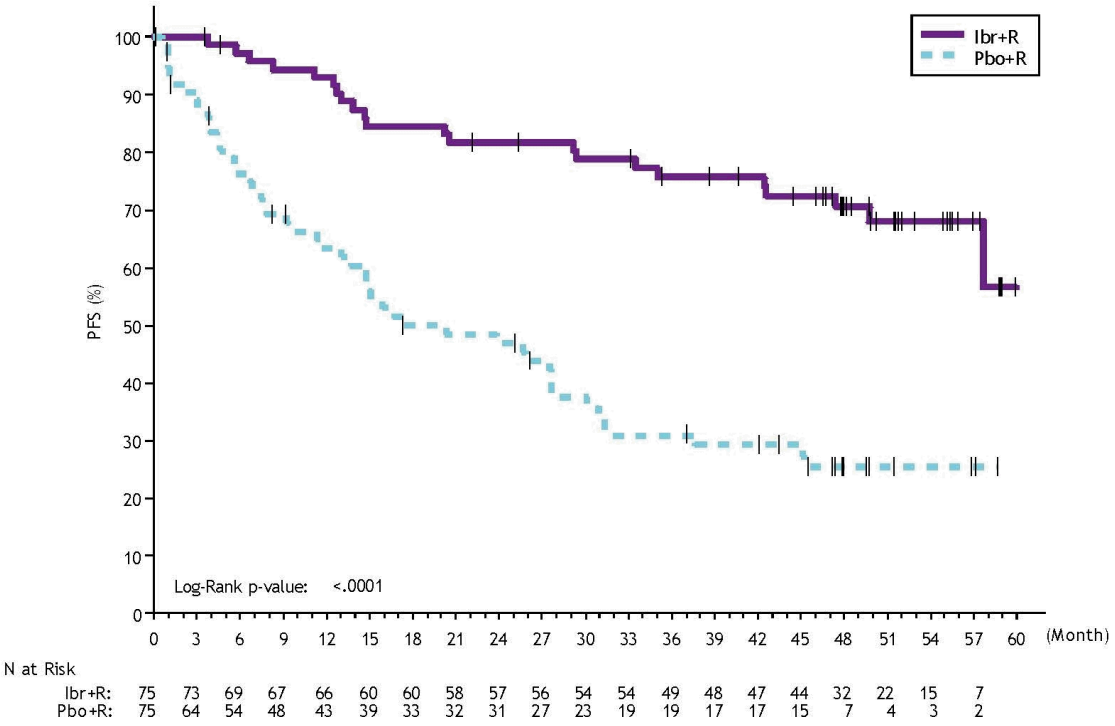
[b] 4-year PFS estimates were 70.6% [95% CI (58.1, 80.0)] in the IMBRUVICA + R arm versus 25.3% [95% CI (15.3, 36.6)] in the placebo + R arm.

[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 14: 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).

Paediatric population

The safety, efficacy, and pharmacokinetics of IMBRUVICA in paediatric and young adult patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma were evaluated in a two-part, multi-centre, open-label Phase 3 study (LYM3003) of IMBRUVICA in combination with either a rituximab, ifosfamide, carboplatin, etoposide and dexamethasone (RICE) regimen or a rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone (RVICI) regimen, as background therapy.

Part 1 of the study (21 patients aged 3 to 17 years) evaluated the dose to be used in part 2 (51 patients aged 3 to 19 years) (see section 5.2).

In part 2, patients were randomised 2:1 to receive either IMBRUVICA as 440 mg/m^2 daily (age below 12 years) or 329 mg/m^2 (age 12 years and older) with background therapy, or background therapy alone until completion of 3 cycles of therapy, transplantation, disease progression or unacceptable toxicity. The primary endpoint of event-free survival (EFS) superiority was not met suggesting no additional benefit from adding ibrutinib to RICE or RVICI (see section 4.2).

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. 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
Pharmacokinetic data show that ibrutinib exposures in children with relapsed or refractory mature B-cell non-Hodgkin lymphoma, aged 12 years and older receiving a daily dose of 329 mg/m^2 and those aged 3 years to below 12 years receiving a daily dose of 440 mg/m^2, were generally within the range of exposures observed in adult patients administered a daily dose of 560 mg.

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 2 000 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

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

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

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

IMBRUVICA 560 mg film-coated tablets
Macrogol
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Red iron oxide (E172)

Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Two polyvinyl chloride (PVC) laminated with polychlorotrifluoroethylene (PCTFE)/aluminium blisters with 7 film-coated tablets each in one cardboard wallet. Each carton contains (28 film-coated tablets) 2 wallets.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

IMBRUVICA 140 mg film-coated tablets
EU/1/14/945/007 – 28 tablets (2 wallet packs of 14)
EU/1/14/945/008 – 30 tablets (3 wallet packs of 10)

IMBRUVICA 280 mg film-coated tablets
EU/1/14/945/009 – 28 tablets (2 wallet packs of 14)
EU/1/14/945/010 – 30 tablets (3 wallet packs of 10)

IMBRUVICA 420 mg film-coated tablets
EU/1/14/945/011 – 28 tablets (2 wallet packs of 14)
EU/1/14/945/005 – 30 tablets (3 wallet packs of 10)

IMBRUVICA 560 mg film-coated tablets
EU/1/14/945/012 – 28 tablets (2 wallet packs of 14)
EU/1/14/945/006 – 30 tablets (3 wallet packs of 10)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 October 2014
Date of latest renewal: 25 June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

IMBRUVICA Hard Capsules
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Janssen-Cilag SpA
Via C. Janssen
Loc. Borgo S. Michele
04100 Latina
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

IMBRUVICA Film-Coated Tablets
Janssen-Cilag SpA
Via C. Janssen,
Loc. Borgo S. Michele,
04100 Latina,
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 140 MG CAPSULE

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg hard capsules
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 140 mg of ibrutinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

90 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/001 (90 hard capsules)
EU/1/14/945/002 (120 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL 140 MG CAPSULE

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg capsules
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 140 mg of ibrutinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

90 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/001 (90 hard capsules)
EU/1/14/945/002 (120 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 140 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 140 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/007 (28 tablets)
EU/1/14/945/008 (30 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 140 MG TABLET (28 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 140 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

Oral use

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 140 MG TABLET (30 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 140 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

When you take a tablet, fill in the day of the week or the date in the space provided.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 140 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg tablets
ibrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 280 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 280 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 280 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/009 (28 tablets)
EU/1/14/945/010 (30 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 280 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 280 MG TABLET (28 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 280 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 280 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

Oral use

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 280 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 280 MG TABLET (30 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 280 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 280 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

When you take a tablet, fill in the day of the week or the date in the space provided.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 280 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 280 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 280 mg tablets
ibrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 420 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 420 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 420 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/011 (28 tablets)
EU/1/14/945/005 (30 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 420 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 420 MG TABLET (28 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 420 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 420 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

Oral use

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 420 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 420 MG TABLET (30 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 420 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 420 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

When you take a tablet, fill in the day of the week or the date in the space provided.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 420 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 420 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 420 mg tablets
ibrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 560 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 560 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 560 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/012 (28 tablets)
EU/1/14/945/006 (30 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 560 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 560 MG TABLET (28 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 560 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 560 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

Oral use

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 560 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 560 MG TABLET (30 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 560 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 560 mg of ibrutinib.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

When you take a tablet, fill in the day of the week or the date in the space provided.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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B-2340 Beerse
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 560 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 560 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 560 mg tablets
ibrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

IMBRUVICA 140 mg hard capsules
ibrutinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMBRUVICA is and what it is used for
2. What you need to know before you take IMBRUVICA
3. How to take IMBRUVICA
4. Possible side effects
5. How to store IMBRUVICA
6. Contents of the pack and other information

1. What IMBRUVICA is and what it is used for

What IMBRUVICA is
IMBRUVICA is an anticancer medicine that contains the active substance ibrutinib. It belongs to a class of medicines called protein kinase inhibitors.

What IMBRUVICA is used for
It is used to treat the following blood cancers in adults:
- Mantle cell lymphoma (MCL), a type of cancer affecting the lymph nodes. IMBRUVICA is used in patients who have not previously been treated for MCL, and for whom blood stem cell transplant would be suitable, or when the disease has come back or has not responded to treatment.
- Chronic lymphocytic leukaemia (CLL) a type of cancer affecting white blood cells called lymphocytes that also involves the lymph nodes. IMBRUVICA is used in patients who have not previously been treated for CLL or when the disease has come back or has not responded to treatment.
- Waldenström's macroglobulinaemia (WM), a type of cancer affecting white blood cells called lymphocytes. It is used in patients who have not previously been treated for WM or when the disease has come back or has not responded to treatment or in patients for whom chemotherapy given together with an antibody is not a suitable therapy.

How IMBRUVICA works
In MCL, CLL and WM, IMBRUVICA works by blocking Bruton's tyrosine kinase, a protein in the body that helps these cancer cells grow and survive. By blocking this protein, IMBRUVICA helps kill and reduce the number of cancer cells. It also slows down the worsening of the cancer.

2. What you need to know before you take IMBRUVICA

Do not take IMBRUVICA
- if you are allergic to ibrutinib or any of the other ingredients of this medicine (listed in section 6)
- if you are taking a herbal medicine called St. John's Wort, used for depression. If you are not sure about this, talk to your doctor, pharmacist or nurse before taking this medicine.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking IMBRUVICA:
- if you have ever had unusual bruising or bleeding or are on any medicines or supplements that increase your risk of bleeding (see section **"Other medicines and IMBRUVICA"**)
- if you have irregular heart beat or have a history of irregular heart beat or severe heart failure, or if you feel any of the following: shortness of breath, weakness, dizziness, light-headedness, fainting or near fainting, chest pain or swollen legs
- if you have liver problems, including if you ever had or now have a hepatitis B infection (a liver infection)
- if you have high blood pressure
- if you have recently had any surgery, especially if this might affect how you absorb food or medicines from your stomach or gut
- if you are planning to have any surgery– your doctor may ask you to stop taking IMBRUVICA for a short time (3 to 7 days) before and after your surgery
- if you have kidney problems.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before or while taking this medicine (see section **"Possible side effects"**).

When taking IMBRUVICA, tell your doctor immediately if you notice or someone notices in you: memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare but serious brain infection which can be fatal (Progressive Multifocal Leukoencephalopathy or PML).

Tell your doctor immediately if you notice or someone notices in you: sudden numbness or weakness in the limbs (especially on one side of the body), sudden confusion, trouble speaking or understanding speech, sight loss, difficulty walking, loss of balance or lack of coordination, sudden severe headache with no known cause. These may be signs and symptoms of stroke.

Tell your doctor immediately if you develop left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of rupture of the spleen) after you stop taking IMBRUVICA.

Effects on the heart
Treatment with IMBRUVICA may affect the heart, especially if you already have heart diseases such as rhythm problems, heart failure, high blood pressure, have diabetes or are of advanced age. The effects may be severe and could cause death, including sometimes sudden death. Your heart function will be checked before and during treatment with IMBRUVICA. Tell your doctor immediately if you feel breathless, have difficulty breathing when lying down, swelling of the feet, ankles or legs and weakness/tiredness during treatment with IMBRUVICA – these may be signs of heart failure.

Infections
You may experience viral, bacterial, or fungal infections during treatment with IMBRUVICA. Contact your doctor if you have fever, chills, weakness, confusion, body aches, cold or flu symptoms, feel tired or feel short of breath, yellowing of the skin or eyes (jaundice). These could be signs of an infection.

Haemophagocytic lymphohistiocytosis
There have been rare reports of excessive activation of white blood cells associated with inflammation (haemophagocytic lymphohistiocytosis), which can be fatal if not diagnosed and treated early. If you experience multiple symptoms such as fever, swollen glands, bruising, or skin rash, contact your doctor immediately.

Tests and check-ups before and during treatment
Tumour lysis syndrome (TLS): Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your doctor or another healthcare provider may do blood tests to check for TLS.

Lymphocytosis: Laboratory tests may show an increase in white blood cells (called “lymphocytes”) in your blood in the first few weeks of treatment. This is expected and may last for a few months. This does not necessarily mean that your blood cancer is getting worse. Your doctor will check your blood counts before or during the treatment and in rare cases they may need to give you another medicine. Talk to your doctor about what your test results mean.

Events related to the liver: Your doctor will do some blood tests to check whether your liver is working properly or that you do not have a liver infection, known as viral hepatitis, or whether hepatitis B has become active again, which could be fatal.

Children and adolescents
IMBRUVICA should not be used in children and adolescents.

Other medicines and IMBRUVICA
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, herbal medicines and supplements. This is because IMBRUVICA may affect the way some other medicines work. Also some other medicines can affect the way IMBRUVICA works.

IMBRUVICA may make you bleed more easily. This means you should tell your doctor if you take other medicines that increase your risk of bleeding. This includes:
- acetyl salicylic acid and non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen or naproxen
- blood thinners such as warfarin, heparin or other medicines for blood clots
- supplements that may increase your risk of bleeding such as fish oil, vitamin E or flaxseed.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking IMBRUVICA.

Also tell your doctor if you take any of the following medicines – The effects of IMBRUVICA or other medicines may be influenced if you take IMBRUVICA together with any of the following medicines:
- medicines called antibiotics to treat bacterial infections – clarithromycin, telithromycin, ciprofloxacin, erythromycin or rifampicin
- medicines for fungal infections – posaconazole, ketoconazole, itraconazole, fluconazole or voriconazole
- medicines for HIV infection – ritonavir, cobicistat, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, or fosamprenavir
- medicines to prevent nausea and vomiting associated with chemotherapy - aprepitant
- medicines for depression - nefazodone
- medicines called kinase inhibitors for treatment of other cancers – crizotinib or imatinib
- medicines called calcium channel blockers for high blood pressure or chest pain – diltiazem or verapamil
- medicines called statins to treat high cholesterol - rosuvastatin
- heart medicines/anti-arrhythmics – amiodarone or dronedarone
- medicines to prevent seizures or to treat epilepsy, or medicines to treat a painful condition of the face called trigeminal neuralgia – carbamazepine or phenytoin.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking IMBRUVICA.

If you are taking digoxin, a medicine used for heart problems, or methotrexate, a medicine used to treat other cancers and to reduce the activity of the immune system (e.g., for rheumatoid arthritis or psoriasis), it should be taken at least 6 hours before or after IMBRUVICA.

IMBRUVICA with food
Do not take IMBRUVICA with grapefruit or Seville oranges (bitter oranges) – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because it can increase the amount of IMBRUVICA in your blood.

Pregnancy and breast-feeding
Do not get pregnant while you are taking this medicine. IMBRUVICA should not be used during pregnancy. There is no information about the safety of IMBRUVICA in pregnant women.

Women of childbearing age must use a highly effective method of birth control during and up to three months after receiving IMBRUVICA, to avoid becoming pregnant while being treated with IMBRUVICA.

- Tell your doctor immediately if you become pregnant.
- Do not breast-feed while you are taking this medicine.

Driving and using machines
You may feel tired or dizzy after taking IMBRUVICA, which may affect your ability to drive or use any tools or machines.

IMBRUVICA contains sodium
IMBRUVICA contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take IMBRUVICA

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
Mantle cell lymphoma (MCL)
The recommended dose of IMBRUVICA is four capsules (560 mg) once a day.

Chronic lymphocytic leukaemia (CLL)/Waldenström's macroglobulinaemia (WM)
The recommended dose of IMBRUVICA is three capsules (420 mg) once a day.

Your doctor may adjust your dose.

Taking this medicine
- Take the capsules orally (by mouth) with a glass of water.
- Take the capsules about the same time each day.
- Swallow the capsules whole. Do not open, break or chew them.

If you take more IMBRUVICA than you should
If you take more IMBRUVICA than you should, talk to a doctor or go to a hospital straight away. Take the capsules and this leaflet with you.

If you forget to take IMBRUVICA
- If you miss a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day.
- Do not take a double dose to make up for a forgotten dose.
- If you are not sure, talk to your doctor, pharmacist or nurse about when to take your next dose.

If you stop taking IMBRUVICA
Do not stop taking this medicine unless your doctor tells you.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The following side effects may happen with this medicine:

Stop taking IMBRUVICA and tell a doctor straight away if you notice any of the following side effects:
itchy bumpy rash, difficulty breathing, swelling of your face, lips, tongue or throat – you may be having an allergic reaction to the medicine.

Tell a doctor straight away if you notice any of the following side effects:

Patients treated with IMBRUVICA for B-cell malignancies:

Very common (may affect more than 1 in 10 people)
- fever, chills, body aches, feeling tired, cold or flu symptoms, being short of breath – these could be signs of an infection (viral, bacterial or fungal). These could include infections of the nose, sinus or throat (upper respiratory tract infection), or lung, or skin
- blood in your stomach, gut, stools or urine, heavier periods, or bleeding that you cannot stop from an injury
- bruising or increased tendency of bruising
- mouth sores
- feeling dizzy
- headache
- constipation
- feeling or being sick (nausea or vomiting)
- indigestion
- diarrhoea, your doctor may need to give you a fluid and salt replacement or another medicine
- skin rash
- painful arms or legs
- back pain or joint pain
- muscle cramps, aches or spasms
- fever
- low number of cells that help blood clot (platelets), very low number of white blood cells – shown in blood tests
- an increase in the number or proportion of white blood cells shown in blood tests
- swollen hands, ankles or feet
- high blood pressure
- increased level of “creatinine” in the blood.

Common (may affect up to 1 in 10 people)
- severe infections throughout the body (sepsis)
- infections of the urinary tract
- nose bleeds, small red or purple spots caused by bleeding under the skin
- heart failure
- missed heart beats, weak or uneven pulse, lightheadedness, shortness of breath, chest discomfort (symptoms of heart rhythm problems)
- low white blood cell counts with fever (febrile neutropenia)
- non-melanoma skin cancer, most frequently squamous cell and basal cell skin cancer
- blurred vision
- redness of the skin
- inflammation within the lungs that may lead to permanent damage
- high level of “uric acid” in the blood (shown in blood tests), which may cause gout

- breaking of the nails
- hives
- sudden kidney damage
- weakness, numbness, tingling or pain in your hands or feet or other parts of the body (peripheral neuropathy).

Uncommon (may affect up to 1 in 100 people)
- liver failure, including events with fatal outcome
- severe fungal infections
- 'reactivation' of hepatitis B (if you had previously had hepatitis B, it may come back)
- bleeding on the surface of the brain
- confusion, headache with slurred speech or feeling faint – these could be signs of serious internal bleeding in your brain
- unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment (tumour lysis syndrome)
- allergic reaction, sometimes severe, that may include a swollen face, lip, mouth, tongue or throat, difficulty swallowing or breathing, itchy rash (hives)
- inflammation of the fatty tissue underneath the skin
- temporary episode of decreased brain or nerve function caused by loss of blood flow, stroke
- bleeding in the eye (in some cases associated with loss of vision)
- inflammation inside the eye that may affect vision (uveitis)
- cardiac arrest (heart stops beating)
- abnormally fast heart beat
- painful skin ulceration (pyoderma gangrenosum) or red, raised painful patches on the skin, fever and an increase in white blood cells (these may be signs of acute febrile neutrophilic dermatosis or Sweet's syndrome)
- small, red bump on the skin that may bleed easily (pyogenic granuloma)
- inflamed blood vessels in the skin, which may lead to a rash (cutaneous vasculitis).

Rare (may affect up to 1 in 1 000 people)
- severely increased white blood cell count that may cause cells to clump together
- severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome).

Patients treated with IMBRUVICA for previously untreated MCL

Very common (may affect more than 1 in 10 people)
- low number of cells that help blood clot (platelets), very low number of white blood cells – shown in blood tests
- low white blood cell counts with fever (febrile neutropenia)
- feeling or being sick (nausea or vomiting)
- diarrhoea, your doctor may need to give you a fluid and salt replacement or another medicine
- mouth sores
- constipation
- fever
- fever, chills, body aches, feeling tired, cold or flu symptoms, being short of breath – these could be signs of an infection (viral, bacterial or fungal). These could include infections of the lung, or skin
- increased level of "creatinine" in the blood
- painful arms or legs
- weakness, numbness, tingling or pain in your hands or feet or other parts of the body (peripheral neuropathy).
- headache
- sudden kidney damage

- skin rash
- blood in your stomach, gut, stools or urine, heavier periods, or bleeding that you cannot stop from an injury
- high blood pressure.

Common (may affect up to 1 in 10 people)
- increased white blood cell count
- infections of the nose, sinus or throat (upper respiratory tract infection)
- missed heart beats, weak or uneven pulse, lightheadedness, shortness of breath, chest discomfort (symptoms of heart rhythm problems)
- heart failure
- indigestion
- swollen hands, ankles or feet
- inflammation within the lungs that may lead to permanent damage
- severe infections throughout the body (sepsis)
- infections of the urinary tract
- high level of "uric acid" in the blood (shown in blood tests), which may cause gout
- unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment (tumour lysis syndrome)
- muscle cramps, aches or spasms
- back pain or joint pain
- non-melanoma skin cancer, including basal cell skin cancer
- feeling dizzy
- redness of the skin
- breaking of the nails
- hives
- bruising or increased tendency of bruising
- nose bleeds, small red or purple spots caused by bleeding under the skin.

Uncommon (may affect up to 1 in 100 people)
- blurred vision
- severe fungal infections
- bleeding in the eye
- temporary episode of decreased brain or nerve function caused by loss of blood flow, stroke
- allergic reaction, sometimes severe, that may include a swollen face, lip, mouth, tongue or throat, difficulty swallowing or breathing, itchy rash (hives)
- inflamed blood vessels in the skin, which may lead to a rash (cutaneous vasculitis)
- inflammation of the fatty tissue underneath the skin.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IMBRUVICA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IMBRUVICA contains
- The active substance is ibrutinib. Each hard capsule contains 140 mg of ibrutinib.
- The other ingredients are:
  - capsule content: croscarmellose sodium, magnesium stearate, microcrystalline cellulose and sodium lauril sulfate (E487)
  - capsule shell: gelatin and titanium dioxide (E171)
  - printing ink: shellac, black iron oxide (E172), and propylene glycol (E1520).

What IMBRUVICA looks like and contents of the pack
IMBRUVICA are white opaque, hard capsules marked with “ibr 140 mg” in black ink on one side.

The capsules are provided in a plastic bottle with a child resistant polypropylene closure. Each bottle contains either 90 or 120 capsules. Each pack contains one bottle.

Marketing Authorisation Holder
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Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Janssen-Cilag SpA
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Italy

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: Information for the patient

IMBRUVICA 140 mg film-coated tablets
IMBRUVICA 280 mg film-coated tablets
IMBRUVICA 420 mg film-coated tablets
IMBRUVICA 560 mg film-coated tablets
ibrutinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMBRUVICA is and what it is used for
2. What you need to know before you take IMBRUVICA
3. How to take IMBRUVICA
4. Possible side effects
5. How to store IMBRUVICA
6. Contents of the pack and other information

1. What IMBRUVICA is and what it is used for

What IMBRUVICA is
IMBRUVICA is an anticancer medicine that contains the active substance ibrutinib. It belongs to a class of medicines called protein kinase inhibitors.

What IMBRUVICA is used for
It is used to treat the following blood cancers in adults:
- Mantle cell lymphoma (MCL), a type of cancer affecting the lymph nodes. IMBRUVICA is used in patients who have not previously been treated for MCL, and for whom blood stem cell transplant would be suitable, or when the disease has come back or has not responded to treatment.
- Chronic lymphocytic leukaemia (CLL) a type of cancer affecting white blood cells called lymphocytes that also involves the lymph nodes. IMBRUVICA is used in patients who have not previously been treated for CLL or when the disease has come back or has not responded to treatment.
- Waldenström's macroglobulinaemia (WM), a type of cancer affecting white blood cells called lymphocytes. It is used in patients who have not previously been treated for WM or when the disease has come back or has not responded to treatment or in patients for whom chemotherapy given together with an antibody is not a suitable therapy.

How IMBRUVICA works
In MCL, CLL and WM, IMBRUVICA works by blocking Bruton's tyrosine kinase, a protein in the body that helps these cancer cells grow and survive. By blocking this protein, IMBRUVICA helps kill and reduce the number of cancer cells. It also slows down the worsening of the cancer.

2. What you need to know before you take IMBRUVICA

Do not take IMBRUVICA
- if you are allergic to ibrutinib or any of the other ingredients of this medicine (listed in section 6)
- if you are taking a herbal medicine called St. John's Wort, used for depression. If you are not sure about this, talk to your doctor, pharmacist or nurse before taking this medicine.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking IMBRUVICA:
- if you have ever had unusual bruising or bleeding or are on any medicines or supplements that increase your risk of bleeding (see section **"Other medicines and IMBRUVICA"**)
- if you have irregular heart beat or have a history of irregular heart beat or severe heart failure, or if you feel any of the following: shortness of breath, weakness, dizziness, light-headedness, fainting or near fainting, chest pain or swollen legs
- if you have liver problems, including if you ever had or now have a hepatitis B infection (a liver infection)
- if you have high blood pressure
- if you have recently had any surgery, especially if this might affect how you absorb food or medicines from your stomach or gut
- if you are planning to have any surgery– your doctor may ask you to stop taking IMBRUVICA for a short time (3 to 7 days) before and after your surgery
- if you have kidney problems.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before or while taking this medicine (see section **"Possible side effects"**).

When taking IMBRUVICA, tell your doctor immediately if you notice or someone notices in you: memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare but serious brain infection which can be fatal (Progressive Multifocal Leukoencephalopathy or PML).

Tell your doctor immediately if you notice or someone notices in you: sudden numbness or weakness in the limbs (especially on one side of the body), sudden confusion, trouble speaking or understanding speech, sight loss, difficulty walking, loss of balance or lack of coordination, sudden severe headache with no known cause. These may be signs and symptoms of stroke.

Tell your doctor immediately if you develop left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of rupture of the spleen) after you stop taking IMBRUVICA.

Effects on the heart
Treatment with IMBRUVICA may affect the heart, especially if you already have heart diseases such as rhythm problems, heart failure, high blood pressure, have diabetes or are of advanced age. The effects may be severe and could cause death, including sometimes sudden death. Your heart function will be checked before and during treatment with IMBRUVICA. Tell your doctor immediately if you feel breathless, have difficulty breathing when lying down, swelling of the feet, ankles or legs and weakness/tiredness during treatment with IMBRUVICA – these may be signs of heart failure.

Infections
You may experience viral, bacterial, or fungal infections during treatment with IMBRUVICA. Contact your doctor if you have fever, chills, weakness, confusion, body aches, cold or flu symptoms, feel tired or feel short of breath, yellowing of the skin or eyes (jaundice). These could be signs of an infection.

Haemophagocytic lymphohistiocytosis
There have been rare reports of excessive activation of white blood cells associated with inflammation (haemophagocytic lymphohistiocytosis), which can be fatal if not diagnosed and treated early. If you

experience multiple symptoms such as fever, swollen glands, bruising, or skin rash, contact your doctor immediately.

Tests and check-ups before and during treatment
Tumour lysis syndrome (TLS): Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your doctor or another healthcare provider may do blood tests to check for TLS.

Lymphocytosis: Laboratory tests may show an increase in white blood cells (called "lymphocytes") in your blood in the first few weeks of treatment. This is expected and may last for a few months. This does not necessarily mean that your blood cancer is getting worse. Your doctor will check your blood counts before or during the treatment and in rare cases they may need to give you another medicine. Talk to your doctor about what your test results mean.

Events related to the liver: Your doctor will do some blood tests to check whether your liver is working properly or that you do not have a liver infection, known as viral hepatitis, or whether hepatitis B has become active again, which could be fatal.

Children and adolescents
IMBRUVICA should not be used in children and adolescents.

Other medicines and IMBRUVICA
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, herbal medicines and supplements. This is because IMBRUVICA may affect the way some other medicines work. Also some other medicines can affect the way IMBRUVICA works.

IMBRUVICA may make you bleed more easily. This means you should tell your doctor if you take other medicines that increase your risk of bleeding. This includes:
- acetyl salicylic acid and non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen or naproxen
- blood thinners such as warfarin, heparin or other medicines for blood clots
- supplements that may increase your risk of bleeding such as fish oil, vitamin E or flaxseed.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking IMBRUVICA.

Also tell your doctor if you take any of the following medicines – The effects of IMBRUVICA or other medicines may be influenced if you take IMBRUVICA together with any of the following medicines:
- medicines called antibiotics to treat bacterial infections – clarithromycin, telithromycin, ciprofloxacin, erythromycin or rifampicin
- medicines for fungal infections – posaconazole, ketoconazole, itraconazole, fluconazole or voriconazole
- medicines for HIV infection – ritonavir, cobicistat, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, or fosamprenavir
- medicines to prevent nausea and vomiting associated with chemotherapy - aprepitant
- medicines for depression - nefazodone
- medicines called kinase inhibitors for treatment of other cancers – crizotinib or imatinib
- medicines called calcium channel blockers for high blood pressure or chest pain – diltiazem or verapamil
- medicines called statins to treat high cholesterol - rosuvastatin
- heart medicines/anti-arrhythmics – amiodarone or dronedarone
- medicines to prevent seizures or to treat epilepsy, or medicines to treat a painful condition of the face called trigeminal neuralgia – carbamazepine or phenytoin.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking IMBRUVICA.

If you are taking digoxin, a medicine used for heart problems, or methotrexate, a medicine used to treat other cancers and to reduce the activity of the immune system (e.g., for rheumatoid arthritis or psoriasis), it should be taken at least 6 hours before or after IMBRUVICA.

IMBRUVICA with food
Do not take IMBRUVICA with grapefruit or Seville oranges (bitter oranges) – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because it can increase the amount of IMBRUVICA in your blood.

Pregnancy and breast-feeding
Do not get pregnant while you are taking this medicine. IMBRUVICA should not be used during pregnancy. There is no information about the safety of IMBRUVICA in pregnant women.

Women of childbearing age must use a highly effective method of birth control during and up to three months after receiving IMBRUVICA, to avoid becoming pregnant while being treated with IMBRUVICA.

- Tell your doctor immediately if you become pregnant.
- Do not breast-feed while you are taking this medicine.

Driving and using machines
You may feel tired or dizzy after taking IMBRUVICA, which may affect your ability to drive or use any tools or machines.

IMBRUVICA contains lactose
IMBRUVICA contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

IMBRUVICA contains sodium
IMBRUVICA contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How to take IMBRUVICA

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
Mantle cell lymphoma (MCL)
The recommended dose of IMBRUVICA is 560 mg once a day.

Chronic lymphocytic leukaemia (CLL)/Waldenström’s macroglobulinaemia (WM)
The recommended dose of IMBRUVICA is 420 mg once a day.

Your doctor may adjust your dose.

Taking this medicine
- Take the tablets orally (by mouth) with a glass of water.
- Take the tablets about the same time each day.
- Swallow the tablets whole. Do not break or chew them.

If you take more IMBRUVICA than you should
If you take more IMBRUVICA than you should, talk to a doctor or go to a hospital straight away. Take the tablets and this leaflet with you.

If you forget to take IMBRUVICA
- If you miss a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day.
- Do not take a double dose to make up for a forgotten dose.
- If you are not sure, talk to your doctor, pharmacist or nurse about when to take your next dose.

If you stop taking IMBRUVICA
Do not stop taking this medicine unless your doctor tells you.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The following side effects may happen with this medicine:

Stop taking IMBRUVICA and tell a doctor straight away if you notice any of the following side effects:
itchy bumpy rash, difficulty breathing, swelling of your face, lips, tongue or throat – you may be having an allergic reaction to the medicine.

Tell a doctor straight away if you notice any of the following side effects:

Patients treated with IMBRUVICA for B-cell malignancies:

Very common (may affect more than 1 in 10 people)
- fever, chills, body aches, feeling tired, cold or flu symptoms, being short of breath – these could be signs of an infection (viral, bacterial or fungal). These could include infections of the nose, sinus or throat (upper respiratory tract infection), or lung, or skin
- blood in your stomach, gut, stools or urine, heavier periods, or bleeding that you cannot stop from an injury
- bruising or increased tendency of bruising
- mouth sores
- feeling dizzy
- headache
- constipation
- feeling or being sick (nausea or vomiting)
- indigestion
- diarrhoea, your doctor may need to give you a fluid and salt replacement or another medicine
- skin rash
- painful arms or legs
- back pain or joint pain
- muscle cramps, aches or spasms
- fever
- low number of cells that help blood clot (platelets), very low number of white blood cells – shown in blood tests
- an increase in the number or proportion of white blood cells shown in blood tests
- swollen hands, ankles or feet
- high blood pressure
- increased level of “creatinine” in the blood.

Common (may affect up to 1 in 10 people)
- severe infections throughout the body (sepsis)
- infections of the urinary tract
- nose bleeds, small red or purple spots caused by bleeding under the skin
- heart failure
- missed heart beats, weak or uneven pulse, lightheadedness, shortness of breath, chest discomfort (symptoms of heart rhythm problems)
- low white blood cell counts with fever (febrile neutropenia)
- non-melanoma skin cancer, most frequently squamous cell and basal cell skin cancer
- blurred vision
- redness of the skin
- hives
- inflammation within the lungs that may lead to permanent damage
- high level of "uric acid" in the blood (shown in blood tests), which may cause gout
- breaking of the nails
- sudden kidney damage
- weakness, numbness, tingling or pain in your hands or feet or other parts of the body (peripheral neuropathy).

Uncommon (may affect up to 1 in 100 people)
- liver failure, including events with fatal outcome
- severe fungal infections
- 'reactivation' of hepatitis B (if you had previously had hepatitis B, it may come back)
- bleeding on the surface of the brain
- confusion, headache with slurred speech or feeling faint – these could be signs of serious internal bleeding in your brain
- unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment (tumour lysis syndrome)
- allergic reaction, sometimes severe, that may include a swollen face, lip, mouth, tongue or throat, difficulty swallowing or breathing, itchy rash (hives)
- inflammation of the fatty tissue underneath the skin
- temporary episode of decreased brain or nerve function caused by loss of blood flow, stroke
- bleeding in the eye (in some cases associated with loss of vision)
- inflammation inside the eye that may affect vision (uveitis)
- cardiac arrest (heart stops beating)
- abnormally fast heart beat
- painful skin ulceration (pyoderma gangrenosum) or red, raised painful patches on the skin, fever and an increase in white blood cells (these may be signs of acute febrile neutrophilic dermatosis or Sweet's syndrome)
- small, red bump on the skin that may bleed easily (pyogenic granuloma)
- inflamed blood vessels in the skin, which may lead to a rash (cutaneous vasculitis).

Rare (may affect up to 1 in 1 000 people)
- severely increased white blood cell count that may cause cells to clump together
- severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome).

Patients treated with IMBRUVICA for previously untreated MCL

Very common (may affect more than 1 in 10 people)
- low number of cells that help blood clot (platelets), very low number of white blood cells – shown in blood tests
- low white blood cell counts with fever (febrile neutropenia)
- feeling or being sick (nausea or vomiting)

- diarrhoea, your doctor may need to give you a fluid and salt replacement or another medicine
- mouth sores
- constipation
- fever
- fever, chills, body aches, feeling tired, cold or flu symptoms, being short of breath – these could be signs of an infection (viral, bacterial or fungal). These could include infections of the lung, or skin
- increased level of "creatinine" in the blood
- painful arms or legs
- weakness, numbness, tingling or pain in your hands or feet or other parts of the body (peripheral neuropathy).
- headache
- sudden kidney damage
- skin rash
- blood in your stomach, gut, stools or urine, heavier periods, or bleeding that you cannot stop from an injury
- high blood pressure.

Common (may affect up to 1 in 10 people)
- increased white blood cell count
- infections of the nose, sinus or throat (upper respiratory tract infection)
- missed heart beats, weak or uneven pulse, lightheadedness, shortness of breath, chest discomfort (symptoms of heart rhythm problems)
- heart failure
- indigestion
- swollen hands, ankles or feet
- inflammation within the lungs that may lead to permanent damage
- severe infections throughout the body (sepsis)
- infections of the urinary tract
- high level of "uric acid" in the blood (shown in blood tests), which may cause gout
- unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment (tumour lysis syndrome)
- muscle cramps, aches or spasms
- back pain or joint pain
- non-melanoma skin cancer, including basal cell skin cancer
- feeling dizzy
- redness of the skin
- breaking of the nails
- hives
- bruising or increased tendency of bruising
- nose bleeds, small red or purple spots caused by bleeding under the skin.

Uncommon (may affect up to 1 in 100 people)
- blurred vision
- severe fungal infections
- bleeding in the eye
- temporary episode of decreased brain or nerve function caused by loss of blood flow, stroke
- allergic reaction, sometimes severe, that may include a swollen face, lip, mouth, tongue or throat, difficulty swallowing or breathing, itchy rash (hives)
- inflamed blood vessels in the skin, which may lead to a rash (cutaneous vasculitis)
- inflammation of the fatty tissue underneath the skin.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IMBRUVICA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IMBRUVICA contains
- The active substance is ibrutinib.
  - IMBRUVICA 140 mg film-coated tablets: Each tablet contains 140 mg of ibrutinib.
  - IMBRUVICA 280 mg film-coated tablets: Each tablet contains 280 mg of ibrutinib.
  - IMBRUVICA 420 mg film-coated tablets: Each tablet contains 420 mg of ibrutinib.
  - IMBRUVICA 560 mg film-coated tablets: Each tablet contains 560 mg of ibrutinib.
- The other ingredients are:
- Tablet core: colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate (see section 2 **"IMBRUVICA contains lactose"**), magnesium stearate, microcrystalline cellulose, povidone, sodium lauril sulfate (E487).
- Tablet film-coat: polyvinyl alcohol, macrogol, talc, titanium dioxide (E171);
  IMBRUVICA 140 mg and IMBRUVICA 420 mg film-coated tablets also contain black iron oxide (E172) and yellow iron oxide (E172);
  IMBRUVICA 280 mg film-coated tablets also contain black iron oxide (E172) and red iron oxide (E172);
  IMBRUVICA 560 mg film-coated tablets also contain red iron oxide (E172) and yellow iron oxide (E172).

What IMBRUVICA looks like and contents of the pack
IMBRUVICA 140 mg film-coated tablets
Yellow-green to green round (9 mm) tablets, written with "ibr" on one side and "140" on the other side. Each 28 day carton contains 28 film-coated tablets in 2 cardboard wallets of 14 film-coated tablets each. Each 30 day carton contains 30 film-coated tablets in 3 cardboard wallets of 10 film-coated tablets each.

IMBRUVICA 280 mg film-coated tablets
Purple oblong (15 mm in length and 7 mm in width), written with "ibr" on one side and "280" on the other side. Each 28 day carton contains 28 film-coated tablets in 2 cardboard wallets of 14 film-coated tablets each. Each 30 day carton contains 30 film-coated tablets in 3 cardboard wallets of 10 film-coated tablets each.

IMBRUVICA 420 mg film-coated tablets
Yellow-green to green oblong tablets (17.5 mm in length and 7.4 mm in width), written with "ibr" on one side and "420" on the other side. Each 28 day carton contains 28 film-coated tablets in 2

cardboard wallets of 14 film-coated tablets each. Each 30 day carton contains 30 film-coated tablets in 3 cardboard wallets of 10 film-coated tablets each.

IMBRUVICA 560 mg film-coated tablets
Yellow to orange oblong tablets (19 mm in length and 8.1 mm in width), written with “ibr” on one side and “560” on the other side. Each 28 day carton contains 28 film-coated tablets in 2 cardboard wallets of 14 film-coated tablets each. Each 30 day carton contains 30 film-coated tablets in 3 cardboard wallets of 10 film-coated tablets each.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.