IMBRUVICA®

ibrutinib

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

IMBRUVICA® 140 mg capsules

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules

140 mg capsules

IMBRUVICA capsules contain 140 mg of ibrutinib as the active ingredient.

Film-coated tablets

140 mg tablets

IMBRUVICA tablets contain 140 mg of ibrutinib as the active ingredient.

280 mg tablets

IMBRUVICA tablets contain 280 mg of ibrutinib as the active ingredient.

420 mg tablets

IMBRUVICA tablets contain 420 mg of ibrutinib as the active ingredient.

560 mg tablets

IMBRUVICA tablets contain 560 mg of ibrutinib as the active ingredient.

Excipients with known effect: sugars as lactose

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Capsules

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

Film-coated tablets

140 mg tablets

Yellow-green to green round film-coated tablet debossed with “ibr” on one side and “140” on the other.

280 mg tablets

Purple oblong film-coated tablet debossed with “ibr” on one side and “280” on the other.

420 mg tablets

Yellow-green to green oblong film-coated tablet debossed with “ibr” on one side and “420” on the other.

560 mg tablets

Yellow to orange oblong film-coated tablet debossed with “ibr” on one side and “560” on the other

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMBRUVICA is indicated for the treatment of

- patients with MCL who have received at least one prior therapy
- patients with CLL/SLL
- patients with CLL with deletion 17p
- patients with Waldenström's macroglobulinemia (WM)

4.2 Dose and method of administration

Dosage

IMBRUVICA should be administered orally once daily with a glass of water at approximately the same time each day. The capsules or tablets should be swallowed whole with water. Do not open, break, or chew the capsules. Do not break or chew the tablets. IMBRUVICA must not be taken with grapefruit juice.

Mantle Cell Lymphoma

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

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL) and Waldenström's Macroglobulinemia (WM)

The recommended dose of IMBRUVICA for CLL/SLL or WM is 420 mg once daily.

For WM, IMBRUVICA can be administered until disease progression or is no longer tolerated as a single agent, or in combination with rituximab.

For CLL/SLL, IMBRUVICA can be administered until disease progression or is no longer tolerated by the patient as a single agent, or in combination with anti-CD20 therapy (rituximab or Obinutuzumab), or in combination with bendamustine and rituximab (BR). In combination with venetoclax, IMBRUVICA should be administered as a single agent for 3 cycles (1 cycle is 28 days), followed by 12 cycles of IMBRUVICA plus venetoclax.

For additional information concerning rituximab, BR, or obinutuzumab see the corresponding rituximab, bendamustine, or obinutuzumab data sheet. 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 modification guidelines

Dose modifications are required for the concomitant use of moderate and strong CYP3A inhibitors as these can increase the exposure of ibrutinib (see **section 4.5**).

IMBRUVICA therapy should be withheld for any new onset or worsening Grade 2 cardiac failure, Grade ≥ 3 non-haematological, 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.

Table 1: Recommended dose modifications for non-cardiac events are described below.

Events	Toxicity occurrence	MCL dose modification after recovery	CLL/SLL/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 140 mg daily
	Fourth	discontinue IMBRUVICA	

* 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.

Table 2: Recommended dose modifications for events of cardiac failure or cardiac arrhythmias are described below:

Events	Toxicity occurrence	MCL dose modification after recovery	CLL/SLL/WM dose modification after recovery
Grade 2 cardiac failure	First	restart at 420 mg daily	restart at 280 mg daily
	Second	restart at 280 mg daily	restart at 140 mg daily
	Third	discontinue IMBRUVICA	
Grade 3 cardiac arrhythmias	First	restart at 420 mg daily†	restart at 280 mg daily†
	Second	discontinue IMBRUVICA	
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	discontinue IMBRUVICA	

† Evaluate the benefit-risk before resuming treatment.

Missed dose

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

Special populations

Paediatrics (18 years of age and younger)

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

Renal impairment

Ibrutinib has minimal renal clearance. No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in ibrutinib clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There are no data in patients with severe renal impairment or patients on dialysis (see **section 5.2**).

Hepatic impairment

Ibrutinib is metabolized in the liver. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN) were excluded from IMBRUVICA clinical studies. In a dedicated hepatic impairment study in non-cancer patients, preliminary data showed an increase in ibrutinib exposure (see **section 5.2**). For patients with

mild and moderate liver impairment (Child-Pugh classes A and B), start treatment at 280 mg and 140 mg, respectively. Monitor patients for signs of ibrutinib 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.

Immunisations

There is no clinical data on the safety and efficacy of immunisations concomitantly administered with ibrutinib.

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

Bleeding-related events

There have been reports of bleeding events in patients treated with ibrutinib, 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 ibrutinib. In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed (see section 5.1).

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

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

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

Patients with congenital bleeding diathesis have not been studied.

Leukostasis

There were isolated cases of leukostasis reported in patients treated with ibrutinib. A high number of circulating lymphocytes (> 400000/mcL) may confer increased risk. Consider temporarily withholding ibrutinib. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

Infections

Infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) were observed in patients treated with ibrutinib. Some of these infections have been associated with hospitalisation and death. Most patients with fatal infections also had neutropenia. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Cases of hepatitis E, which may be chronic, have occurred in patients treated with ibrutinib. Patients should be monitored for signs and symptoms (such as fever, chills, weakness, confusion, vomiting, jaundice and abnormal liver function tests) and appropriate therapy should be instituted as indicated.

Progressive multifocal leukoencephalopathy (PML)

Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Patients should be monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. If these occur, ibrutinib should be held pending appropriate investigations.

Cytopenias

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

Interstitial Lung Disease (ILD)

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

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

In patients with pre-existing 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, and benefit-risk evaluation dictates the treatment with anticoagulants, patients should be closely monitored.

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.

Cerebrovascular Accidents

Cases of cerebrovascular accident, transient ischemic attack and ischemic stroke including fatalities have been reported with the use of ibrutinib, with and without concomitant atrial fibrillation and/or hypertension. Latency from the initiation of treatment with ibrutinib to the onset of ischemic central nervous vascular conditions was in the most cases after several months emphasising the need for regular monitoring of patients (please see Section 4.4 Cardiac events and Hypertension and Section 4.8).

Non melanoma skin cancer

Non melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

Hypertension

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

Hepatitis B reactivation

Cases of hepatitis B reactivation, including fatal events have been reported in patients receiving ibrutinib. Hepatitis B virus (HBV) status should be established before initiating treatment with ibrutinib. For patients with hepatitis B serology indicative of prior infection, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Paediatric Use

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

4.5 Interactions with other medicines

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4.

Agents that may increase ibrutinib plasma concentrations

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

Strong CYP3A inhibitors

Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects, increased exposure (C_{max} and $AUC_{0\text{-last}}$) of ibrutinib by 29- and 24-fold, respectively. In a dedicated drug-drug interaction study in patients with B-cell malignancies, co-administration of voriconazole increased C_{max} and AUC by 6.7-fold and 5.7-fold, respectively. In clinical studies, the maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Voriconazole and posaconazole can be used concomitantly with IMBRUVICA as per dose recommendations in **Table 3**. All other strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, and cobicistat) should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, see recommended dose modifications in **Table 3.**

Moderate and mild CYP3A4 inhibitors

In patients with B cell malignancies, co administration of CYP3A inhibitor erythromycin increased C_{max} and AUC by 3.4-fold and 3.0-fold, respectively. If a moderate CYP3A inhibitor (e.g., erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) is indicated, reduce IMBRUVICA dose as per recommended dose modifications in **Table 3**. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during IMBRUVICA treatment as these contain moderate inhibitors of CYP3A (see **sections 4.2** and **5.2**).

Table 3: Recommended dose modifications based on CYP3A inhibitor use:

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

[a] Monitor for adverse reactions to IMBRUVICA and interrupt or modify dose as recommended (see Section **4.2 DOSE AND METHOD OF ADMINISTRATION**).
[b] Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

After discontinuation of a CYP3A inhibitor, resume previous dose of IMBRUVICA (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Agents that may decrease ibrutinib plasma concentrations

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

Drugs that may have their plasma concentrations altered by ibrutinib

In vitro studies indicated that ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes *in vitro*. However, in a drug interaction study in patients with B-cell malignancies, a single 560 mg dose of ibrutinib did not have a clinically meaningful effect on the exposure of the CYP3A4 substrate midazolam. In the same study, 2 weeks of treatment with ibrutinib at 560 mg daily had no clinically relevant effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel), the CYP3A4 substrate midazolam, nor the CYP2B6 substrate bupropion.

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

4.6 Fertility, pregnancy and lactation

Fertility

Fertility studies with ibrutinib have not been conducted. Men should be advised not to father a child or donate sperm while receiving IMBRUVICA, and for 3 months following completion of treatment.

Fertility studies with ibrutinib have not been conducted in animals.

Pregnancy

Category D

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

IMBRUVICA should not be used during pregnancy. Women of child bearing potential must use highly effective contraceptive measures while taking IMBRUVICA. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a foetus. The time period following treatment with IMBRUVICA where it is safe to become pregnant is unknown. Men should be advised not to father a child or donate sperm while receiving IMBRUVICA, and for 3 months following completion of treatment.

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

Breast-feeding

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

4.7 Effect on Ability to Drive or Operate Machinery

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

4.8 Adverse effects

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

Leukostasis

Isolated cases of leukostasis have been observed (see **section 4.4**).

Elderly

Of the 1981 patients treated with IMBRUVICA, 50% were 65 years of age or older. Grade 3 or higher pneumonia occurred more frequently (>5%) among elderly patients treated with

IMBRUVICA (11% of patients ≥ 65 years of age versus 4% of patients <65 years of age.) and thrombocytopenia (11% of patients ≥ 65 years of age versus 5% of patients < 62 years of age).

Non-melanoma skin cancer

Based on an integrated analysis of the randomized, controlled phase 3 studies (PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, MCL3001, PCYC-1127-CA, E1912, and CLL3011), the incidence of non-melanoma skin cancer was 5% in IMBRUVICA-treated patients and 2% in comparator-treated patients.

Mantle Cell Lymphoma

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

The most commonly occurring adverse reactions for MCL (≥ 20%,) were diarrhoea, hemorrhage (e.g., bruising), fatigue, musculoskeletal pain, nausea, upper respiratory tract infection, cough and rash. (see **Table 4**).

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

Discontinuation and dose reduction due to AEs

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

Adverse reactions from Study 1104 are described below in **Table 4** to reflect exposure to IMBRUVICA in patients with MCL who received at least one prior therapy with a median treatment duration of 8.3 months.

Table 4: Treatment-emergent adverse reactions reported in ≥10% of patients with MCL treated with 560 mg IMBRUVICA– Study 1104 (N=111)

		Frequency	
System Organ Class	**Adverse Reaction**	**All grades (%)**	**Grades 3 or 4 (%)**
Infections and infestations	Pneumonia	12	5
	Urinary tract infection	14	3
	Sinusitis	14	1
	Upper respiratory tract infection	26	0
Neoplasms benign and malignant (including cysts and polyps)	Non melanoma skin cancer*	6	1
	Basal cell carcinoma	3	<1
	Squamous cell carcinoma	2	<1
Blood and lymphatic system disorders	Neutropenia	19	17
	Thrombocytopenia	21	12
	Anemia	15	10
Metabolism and nutrition disorders	Dehydration	14	4
	Hyperuricemia	17	5
	Decreased appetite	23	2
Nervous system disorders	Dizziness	14	0
	Headache	12	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	28	4
	Epistaxis	11	0
	Cough	18	0
Gastrointestinal disorders	Diarrhea	53	5
	Abdominal pain	18	5
	Vomiting	23	0
	Stomatitis	13	1
	Constipation	28	0
	Nausea	32	1
	Dyspepsia	11	0
Skin and subcutaneous tissue disorders	Rash	16	2
Musculoskeletal and connective tissue disorders	Muscle spasms	14	0
	Myalgia	14	0
	Arthralgia	14	0
	Back pain	14	1
	Pain in extremity	12	0
General disorders and administration site conditions	Pyrexia	19	1
	Fatigue	43	5
	Asthenia	12	3
	Edema peripheral	30	2
Injury, poisoning and procedural complications	Contusion	18	0

Serious adverse reactions

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

Adverse reactions from Study MCL3001 are described below in **Table 5** reflecting exposure to IMBRUVICA in patients with MCL who received at least one prior therapy, treated with a median treatment duration of 14.4 months.

Table 5: Adverse reactions reported in patients with MCL treated with 560 mg IMBRUVICA – Study MCL3001 (n=139)

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

Includes multiple adverse reaction terms.

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

The data described below reflect exposure to ibrutinib in an single arm, open-label clinical studies (Study PCYC-1102-CA and PCYC 1142-CA) and six randomized clinical studies (Study PCYC-1115-CA, Study PCYC-1112-CA, Study CLL3001, PCYC-1130-CA, E1912 and CLL3011) in patients with CLL/SLL (n=1562).

The most commonly occurring adverse reactions in studies PCYC-1102-CA, PCYC-1142-CA, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912 and CLL3011 (≥ 20%), were diarrhoea, neutropenia, rash, musculoskeletal pain, haemorrhage (e.g., bruising), nausea, thrombocytopenia, arthralgia, headache, upper respiratory tract infection, and pyrexia.

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

Discontinuation and dose reduction due to AEs

Six percent of patients receiving ibrutinib in studies PCYC-1102-CA, PCYC-1142-CA, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912 and CLL3011 discontinued treatment due to adverse events. The most frequent adverse reactions leading to treatment discontinuation included pneumonia, atrial fibrillation, neutropenia, and rash. Adverse events leading to dose reduction occurred in approximately 9% of patients.

Patients with previously untreated CLL/SLL

Single agent

Adverse reactions described below in **Table 6** reflect exposure to IMBRUVICA with a median duration of 17.4 months, which is approximately 2.5 times the median exposure to chlorambucil of 7.1 months in Study PCYC 1115 CA.

Table 6: Adverse reactions reported in previously untreated patients with CLL/SLL treated with 420 mg IMBRUVICA - Study PCYC 1115 CAa,

	IMBRUVICA (N=135)		Chlorambucil (N=132)	
System Organ Class Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Neoplasms benign, malignant, and unspecified (including cysts and polyps)				
Basal cell carcinoma	9	1	2	0
Metabolism and nutrition disorders				
Hyponatremia	7	3	1	0
Eye disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Cardiac disorders				
Atrial fibrillation	6	1	1	0
Vascular disorders				
Hypertension*	14	4	1	0
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
Gastrointestinal disorders				
Diarrhoea	42	4	17	0
Stomatitis*	14	1	4	1
Dyspepsia	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
General disorders and administrative site conditions				
Peripheral oedema	19	1	9	0

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

*Includes multiple adverse reaction terms

Combination therapy

Adverse reactions described below in **Table 7** reflect exposure to IMBRUVICA + obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median duration of 5.1 months in Study PCYC-1130-CA.

Table 7: Adverse reactions reported in previously untreated patients with CLL/SLL treated with IMBRUVICA in combination with obinutuzumab in Study PCYC-1130-CA[a]

	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
System Organ Class Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Blood and lymphatic system disorders				
Thrombocytopenia*	36	19	28	11
Skin and subcutaneous tissue disorders				
Rash*	36	3	11	0
Bruising*	32	3	3	0
Gastrointestinal disorders				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
Respiratory, thoracic and mediastinal disorders				
Cough	27	1	12	0
Vascular disorders				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3
Infections and infestations				
Pneumonia*	16	9	9	3
Upper respiratory tract infection	14	1	6	0
Skin infection*	13	1	3	0
Urinary tract infection	12	3	7	1
Conjunctivitis	11	0	2	0
Metabolism and nutrition disorders				
Hyperuricemia	13	1	0	0
Cardiac disorders				
Atrial fibrillation	12	5	0	0
General disorders and administration site conditions				
Peripheral edema	12	0	7	0
Psychiatric disorders				
Insomnia	12	0	4	0

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

* Includes multiple adverse reaction terms

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

Adverse reactions and laboratory abnormalities described below in **Table 8** and **9** reflect exposure to IMBRUVICA in combination with rituximab (IR) or received fludarabine, cyclophosphamide, and rituximab (FCR) with a median duration of 34.3 months for IR and 4.7 months for FCR in Study E1912.

Table 8: Adverse reactions reported in previously untreated patients with CLL/SLL treated with IMBRUVICA in combination with Rituximab in Study E1912

System Organ Class Adverse Drug Reaction Term	IMBRUVICA + Rituximab (N=352) (%)		Fludarabine + Cyclophosphamide + Rituximab (N=158) (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Gastrointestinal disorders				
Diarrhoea	53	4	27	1
Nausea	40	1	64	1
Stomatitis*	22	1	8	1
Vomiting	18	2	28	0
Constipation	17	0	32	0
Abdominal pain	16	1	9	1
Dyspepsia	14	0	3	0
Gastrooesphageal reflux disease	13	0	6	0
General disorders and administration site conditions				
Fatigue	80	2	78	3
Oedema peripheral	28	1	17	0
Pyrexia	27	1	27	1
Pain	23	2	8	0
Chills	11	<1	17	1
Infections and infestations				
Upper respiratory tract infection	29	1	19	2
Skin infection*	16	1	3	1
Pneumonia*	11	3	6	3
Investigations				
Blood creatinine increased	36	1	20	1
Metabolism and nutrition disorders				
Hyperuricaemia	18	1	4	0
Decreased appetite	15	0	20	1
Hypokalaemia	13	1	11	1
Hypoalbuminaemia	11	0	8	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	61	5	35	2
Arthralgia	41	5	9	1
Muscle spasms	12	0	1	0
Nervous system disorders				
Headache	40	1	27	1
Dizziness	21	1	13	1
Neuropathy peripheral*	19	1	13	1
Psychiatric disorders				
Insomnia	16	1	19	1
Anxiety	14	<1	10	0

System Organ Class Adverse Drug Reaction Term	IMBRUVICA + Rituximab (N=352) (%)		Fludarabine + Cyclophosphamide + Rituximab (N=158) (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Respiratory, thoracic and mediastinal disorders				
Cough	32	<1	25	0
Dyspnoea	22	2	21	1
Oropharyngeal pain	13	<1	5	0
Nasal congestion	12	0	7	0
Skin and subcutaneous tissue disorders				
Rash*	49	4	29	5
Bruising*	36	1	4	1
Pruritus	13	<1	8	0
Dry skin	11	<1	6	0
Vascular disorders				
Hypertension*	42	19	22	6
Haemorrhage*	31	2	8	1

* Includes multiple adverse reaction terms

Table 9: Treatment-Emergent* Hematologic Laboratory Abnormalities reported in previously untreated patients with CLL/SLL treated with IMBRUVICA in combination with Rituximab in Study E1912

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

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

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

Adverse reactions and laboratory abnormalities described below in Tables 10 and 11 reflect exposure to IMBRUVICA in combination with venetoclax with a median duration of 14.1 months in patients with previously untreated CLL/SLL who were 70 years or younger in Study PCYC-1142-CA.

Table 10: Adverse reactions reported in at least 15% patient previously untreated with CLL/SLL in Study PCYC-1142-CA

System Organ Class Adverse Reaction Term	IMBRUVICA + Venetoclax (N=323) (%)	
	All Grades	Grade 3 or 4
Gastrointestinal disorders		
Diarrhea	67	4
Nausea	44	1
Stomatitis*	30	1
Abdominal pain*	24	1
Vomiting	22	1
Dyspepsia	18	0
Constipation	16	0
General disorders and administration site conditions		
Fatigue	26	2
Infections and infestations		
Upper respiratory tract infection	26	0
Skin infection*	20	2
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	41	1
Arthralgia	34	2
Muscle spasms	24	0
Nervous system disorders		
Headache	27	1
Dizziness	16	0
Respiratory, thoracic and mediastinal disorders		
Cough	17	0
Skin and subcutaneous tissue disorders		
Bruising*	47	0
Rash*	38	3
Vascular disorders		
Hemorrhage*	33	1
Hypertension*	16	7

Pooled safety data is from the Fixed Duration (FD) cohort and first 16 cycles of the Minimal Residual Disease (MRD) cohort.

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple adverse reaction terms

Table 11: Select Laboratory Abnormalities (≥20% Any Grade), New or Worsening from Baseline in patients with CLL/SLL treated with IMBRUVICA in combination with venetoclax in Study PCYC-1142-CA

	IMBRUVICA + venetoclax (N=323) (%)	
	All Grades	**Grade 3 or 4**
Hematology abnormalities*		
Neutrophils decreased	72	37
Platelets decreased	60	11
Hemoglobin decreased	22	<1
Chemistry abnormalities		
Hypernatremia	43	0
Hypocalcemia	38	<1
Hypomagnesemia	32	1
Bilirubin increased	28	3
Hyperkalemia	26	2
Hyperuricemia	26	26
AST increased	23	2
ALP increased	22	<1
ALT increased	20	2
Creatinine increased	20	0

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

<1 used for frequency above 0 and below 0.5%

Adverse reactions and laboratory abnormalities described below in Tables 12 and 13 reflect exposure to IMBRUVICA + venetoclax with a median duration of 13.8 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in Study CLL3011 in patients with previously untreated CLL/SLL who were 65 years or older, or adult patients <65 years of age with a CIRS score >6 or CrCL <70 mL/min.

Table 12: Adverse reactions reported in at least 15% of Patients in the IMBRUVICA arm in Patients with CLL/SLL in Study CLL3011

System Organ Class Adverse Reaction Term	IMBRUVICA + Venetoclax (N=106) (%)		Chlorambucil + Obinutuzumab (N=105) (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Gastrointestinal disorders				
Diarrhea	51	10	12	1
Nausea	26	0	26	0
Stomatitis*	15	0	3	0
Skin and subcutaneous tissue disorders				
Rash*	28	7	14	1
Bruising*	23	1	3	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	24	3	17	0
Vascular disorders				
Hemorrhage*	23	4	5	1
Infections and infestations				
Urinary tract infection	16	2	5	2
General disorders and administration site conditions				
Peripheral edema	15	0	3	0
Fatigue	15	1	10	0

* Includes multiple adverse reaction terms

Table 13: Select Laboratory Abnormalities (≥20% Any Grade), New or Worsening from Baseline in previously untreated patients with CLL/SLL in Study CLL3011

	IMBRUVICA + venetoclax (N=106) (%)		Chlorambucil + Obinutuzumab (N=105) (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Hematology abnormalities*				
Neutrophils decreased	76	42	90	54
Platelets decreased	49	13	74	31
Hemoglobin decreased	36	0	40	0
Chemistry abnormalities				
Hypocalcemia	25	0	29	0
Bilirubin increased	34	2	24	1
Hyperkalemia	29	2	21	1
Hyperuricemia	35	8	18	5
AST increased	22	2	29	3
ALT increased	21	3	25	3
Creatinine increased	31	1	16	0
Creatinine clearance decreased	38	5	16	1
Hypoalbuminemia	34	0	19	2
Hypokalemia	24	3	9	0

Hyponatremia	24	8	25	1

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

Patients with CLL/SLL who received at least one prior therapy

Single agent

Adverse reactions described in **Table 14** below reflect exposure to ibrutinib with a median duration of 8.6 months and exposure to ofatumumab with a median duration of 5.3 months in Study PCYC-1112-CA.

Table 14: Adverse reactions reported in patients with CLL/SLL treated with IMBRUVICA as single agent in Study PCYC-1112-CA[a]

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
System Organ Class Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Infections and infestations				
Upper respiratory tract infection	16	1	10	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin infection*	7	2	3	1
Sepsis*	4	2	4	3
Blood and lymphatic system disorders				
Anemia	23	5	17	8
Neutropenia	22	16	15	14
Thrombocytopenia	17	6	12	4
Lymphocytosis	4	2	3	1
Leukocytosis	4	3	1	0
Febrile neutropenia	2	2	3	3
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Eye disorders				
Vision blurred	10	0	3	0
Cardiac disorders				
Atrial fibrillation	5	3	1	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	9	0	3	1
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Bruising*	21	0	4	0
Petechiae	14	0	1	0
Musculoskeletal and connective tissue disorders				

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
System Organ Class Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Injury, poisoning and procedural complications				
Subdural hematoma	1	0	0	0

[a] Occurring at ≥10% incidence and 5% greater in the IMBRUVICA arm when compared to the ofatumumab arm or serious adverse reactions ≥ 2% incidence and 2% greater in the IMBRUVICA arm when compared to the ofatumumab arm or biologically plausible.

*Includes multiple adverse reaction terms.

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

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

Combination therapy

Adverse reactions described below in **Table 15** reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study CLL3001.

Table 15: Adverse reactions reported in patients with CLL/SLL treated with IMBRUVICA in combination with BR in Study CLL3001[a]

	IMBRUVICA + BR (N=287)		Placebo + BR (N=287)	
System Organ Class Adverse Reaction Term	**All Grades %**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
Blood and lymphatic system disorders				
Thrombocytopenia	31	15	24	15
Cardiac disorders				
Atrial fibrillation	7	3	2	1
Vascular disorders				
Hypertension*	10	5	5	2
Gastrointestinal disorders				
Diarrhoea	36	2	23	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	18	1
Bruising*	18	<1	6	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms				

[a] Occurred at an incidence of at least 5% higher for AEs or 2% higher for SAEs.

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

*Includes multiple adverse reaction terms

<1 used for frequency above 0 and below 0.5%

Waldenström's Macroglobulinemia (WM)

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

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

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

Discontinuation and dose reduction due to ARs

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

Adverse reactions described below in **Table 16** reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study PCYC-1118E.

Table 16: Adverse reactions reported in ≥10% of patients with WM treated with 420 mg IMBRUVICA - Study 1118E (N=63)

System Organ Class	Adverse Reaction	All Grades (%)	Grades 3-4 (%)
Infections and infestations	Sinusitis	19	0
	Upper respiratory tract infection	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin cancer*	11	0
Blood and lymphatic system disorders	Neutropenia	25	17
	Thrombocytopenia	17	13
	Anaemia	16	3
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Gastrointestinal disorders	Diarrhoea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
General disorders and administration site conditions	Fatigue	21	0

*Includes multiple adverse reaction terms.

Adverse reactions from Study PCYC-1127-CA are described below in **Table 17** reflecting exposure to IMBRUVICA + rituximab with a median duration of 25.8 months and exposure to

placebo + rituximab with a median duration of 15.5 months in patients with treatment-naïve or previously treated WM.

Table 17: Adverse reactions reported in patients with WM treated with IMBRUVICA in combination with Rituximab in Study PCYC-1127-CA[a]

System Organ Class Adverse Reaction Term	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Skin and subcutaneous tissue disorders				
Bruising*	37	1	5	0
Rash*	24	1	11	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	35	4	21	3
Arthralgia	24	3	11	1
Muscle spasms	17	0	12	1
Vascular disorders				
Haemorrhage*	32	3	17	3
Hypertension*	20	13	5	4
Gastrointestinal disorders				
Diarrhea	28	0	15	1
Nausea	21	0	12	0
Dyspepsia	16	0	1	0
Constipation	13	1	11	1
Infections and infestations				
Pneumonia*	19	13	5	3
Skin infection*	17	3	3	0
Urinary tract infection	13	0	0	0
Bronchitis	12	3	7	0
Influenza	12	0	7	1
Viral upper respiratory tract infection	11	0	7	0
General disorders and administration site conditions				
Peripheral edema	17	0	12	1
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	11	0
Blood and lymphatic system disorders				
Neutropenia*	16	12	11	4
Cardiac disorders				
Atrial fibrillation	15	12	3	1
Nervous system disorders				
Dizziness	11	0	7	0
Psychiatric disorders				
Insomnia	11	0	4	0
Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1

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

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

*Includes multiple adverse reaction terms

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

Long-term safety

The long-term safety data over 5 years from 1284 patients (treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, WM n=106 and relapsed/refractory MCL n=370) treated with IMBRUVICA 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 5% (year 0-1), 6% (year 1-2), 8% (year 2-3), 8% (year 3-4) and 8% (year 4-5). The incidence for the 5-year period was 11%.

Postmarketing data

Adverse reactions identified during post-marketing experience with frequency category estimated from spontaneous reporting rates:

System Organ Class: Eye Disorders

Uncommon: Eye hemorrhage

System Organ Class: Cardiac disorders

Rare: Ventricular tachyarrhythmias*†

Uncommon: Cardiac failure*†

System Organ Class: Immune system disorders

Uncommon: Interstitial lung disease*†

System Organ Class: Infections and infestations

Uncommon: Hepatitis B reactivation†

System Organ Class: Metabolism and nutrition disorders

Very rare: Tumour lysis syndrome

System Organ Class: Skin and subcutaneous tissue disorders

Uncommon: Onychoclasis

Rare: Panniculitis*

Rare: Stevens-Johnson syndrome

Rare: Neutrophilic dermatoses*

Very rare: Angioedema, erythema, urticaria.

System Organ Class: Hepatobiliary disorders

Uncommon: Hepatic failure*†

System Organ Class: Nervous system disorders

Uncommon: Peripheral neuropathy*; Cerebrovascular accident†

Rare: Transient ischemic attack; Ischemic stroke†

*Includes multiple adverse reaction terms

†Includes events with fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https//nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms and signs

There are limited data on the effects of IMBRUVICA overdose. No Maximum Tolerated Dose was reached in the Phase 1 study in which patients received up to 12.5 mg/kg/day (1400 mg/day). In a separate study, one healthy subject who received a dose of 1680 mg experienced reversible Grade 4 hepatic enzyme increases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)].

Treatment

There is no specific antidote for IMBRUVICA. Patients who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 B cell 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 inhibits malignant B cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

BTK inhibition by ibrutinib increases CLL cell dependence on BCL-2, a cell survival pathway, while venetoclax inhibits BCL-2 leading to apoptosis. In preclinical tumour models, the combination of ibrutinib and venetoclax resulted in increased cellular apoptosis and anti-tumour activity compared to either agent alone.

Lymphocytosis

Upon initiation of single agent treatment with IMBRUVICA, a reversible increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (66%) with CLL/SLL. This effect has also been observed in some patients (35%) with MCL treated with ibrutinib. 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 ibrutinib therapy and typically resolves within a median of 8 weeks in patients with MCL and 14 weeks in patients with CLL/SLL (range 0.1 to 104 weeks).

A large increase in the number of circulating lymphocytes (e.g., >400000/mcL) has been observed in some patients.

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

When IMBRUVICA was administered in combination, lymphocytosis was infrequent (7% with IMBRUVICA + BR versus 6% with placebo + BR and 7% with IMBRUVICA + obinutuzumab versus 1% with chlorambucil + obinutuzumab).

In vitro platelet aggregation

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

Effects on the QT/QTc interval and cardiac electrophysiology

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

Clinical trials

Mantle Cell Lymphoma

PCYC-1104-CA

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

Ibrutinib 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 18**.

Table 18: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with Mantle Cell Lymphoma

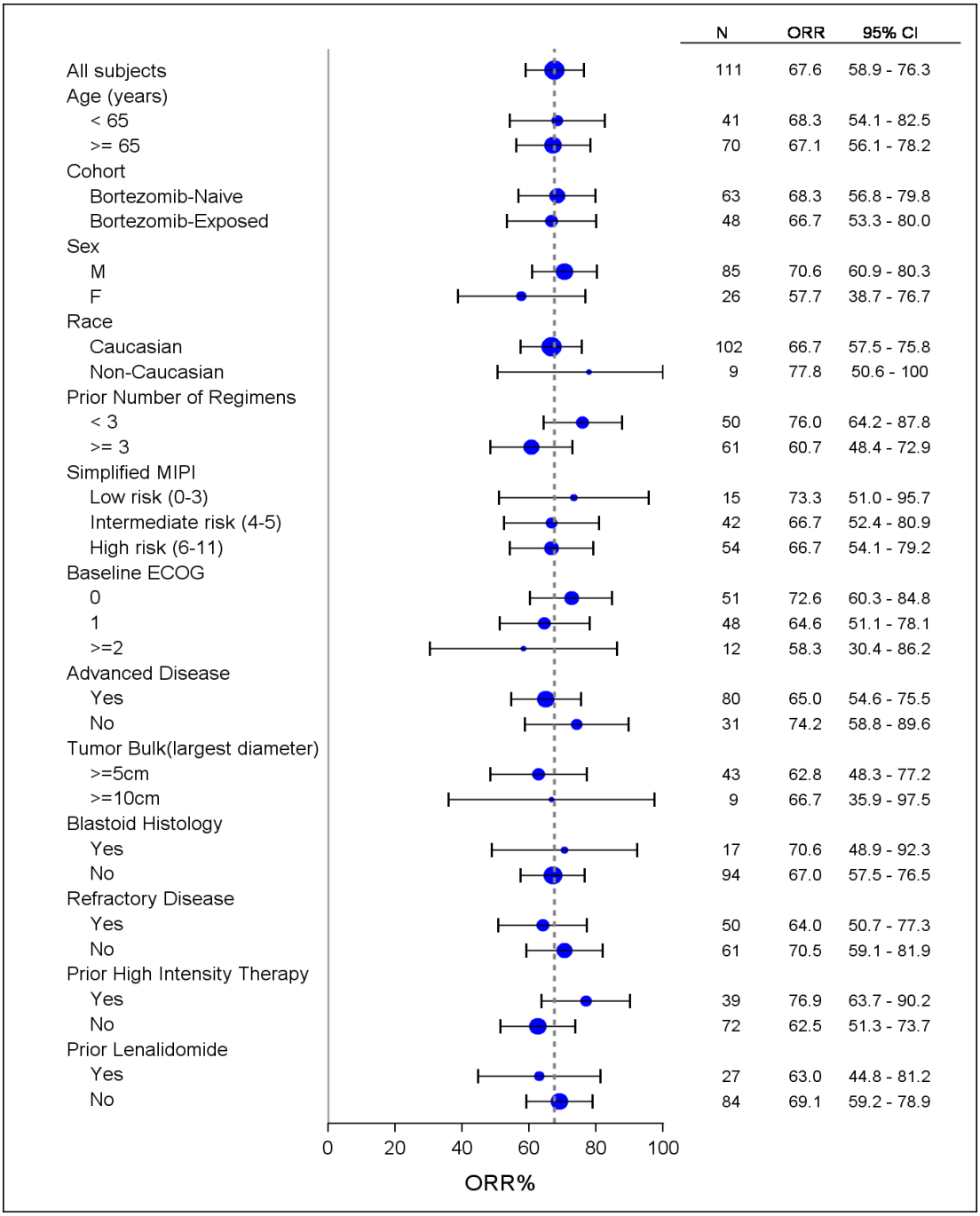
	Total N=111
ORR (%)	67.6
95% CI (%)	(58.0, 76.1)
CR (%)	20.7
PR (%)	46.8
Median DOR (CR+PR) (months)	17.5 (15.8, NR)
Median Time to Initial Response, months (range)	1.9 (1.4-13.7)
Median Time to CR, months (range)	5.5 (1.7, 11.5)

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

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

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

Figure 1: Subgroup Analysis of Overall Response Rate by Investigator Assessment (Study PCYC-1104-CA; 560 mg)



MCL3001 (Ray)

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

Progression-free survival (PFS) as assessed by IRC according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria showed a 57% statistically significant reduction in the risk of death or progression for patients in the IMBRUVICA arm. Efficacy results for Study MCL3001 are shown in **Table 19** and the Kaplan-Meier curve for PFS **Figure 2**.

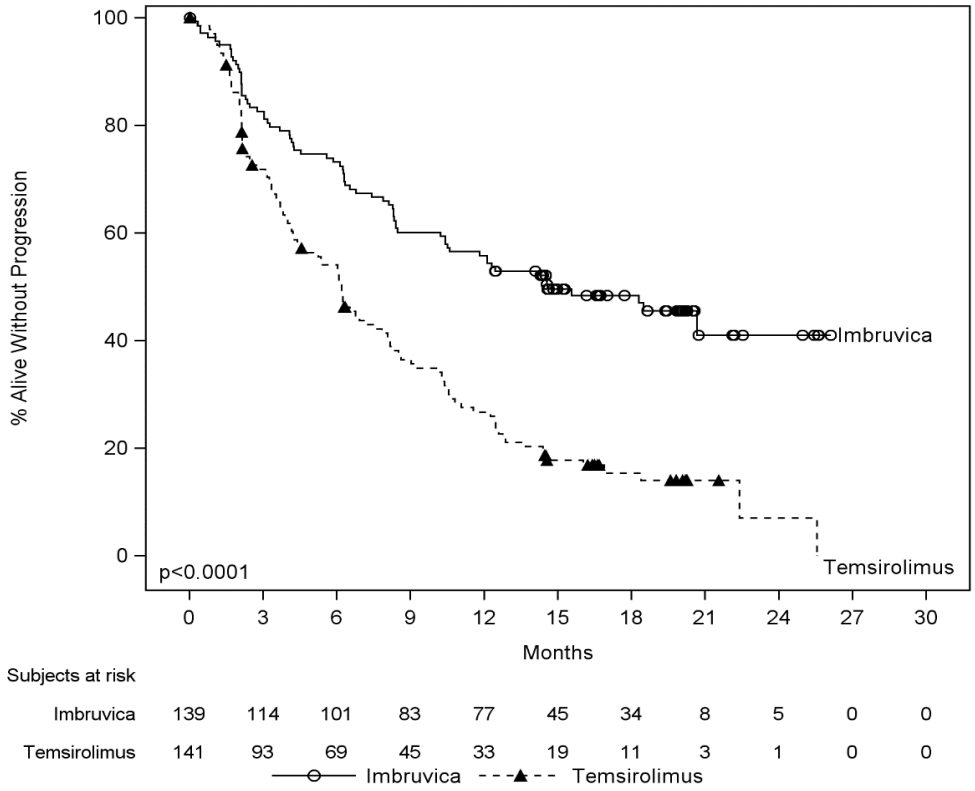
Table 19: Efficacy results in Study MCL3001

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

NE = not estimable; HR = hazard ratio; CI = confidence interval; CR = complete response; PR = partial response; [a]IRC evaluated

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

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



Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma

The safety and efficacy of ibrutinib in patients with CLL/SLL were demonstrated in one uncontrolled study and six randomised, controlled studies.

Patients with treatment naïve CLL/SLL

Single agent

PCYC-1115-CA (RESONATE-2)

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

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety-one percent of patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and 9% had an ECOG performance status of 2. The study enrolled 269 patients with CLL or SLL. 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 > 3500 µg/L, 47% had a CrCL < 60 mL/min, 20% of patients presented with del11q, 6% of patients presented with del 17p/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 IWCLL criteria indicated an 84% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm. With a median follow up of 18 months, the median PFS was not reached in the ibrutinib arm and was 19 months in the chlorambucil arm. Significant improvement in ORR was observed in the ibrutinib arm (82%) versus the chlorambucil arm (35%). The results from investigator and IRC assessments for PFS and ORR were consistent. Analysis of overall survival (OS) also

demonstrated an 84% statistically significant reduction in the risk of death for patients in the IMBRUVICA arm. Efficacy results for Study PCYC-1115-CA are shown in **Table 20** and the Kaplan-Meier curves for PFS and OS are shown in **Figure 3** and **Figure 4**, respectively.

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

Table 20: Efficacy results in Study PCYC-1115-CA

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

[a]IRC evaluated; [b]HR = hazard ratio; [c]Median OS not reached for both arms p<0.005 for OS

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

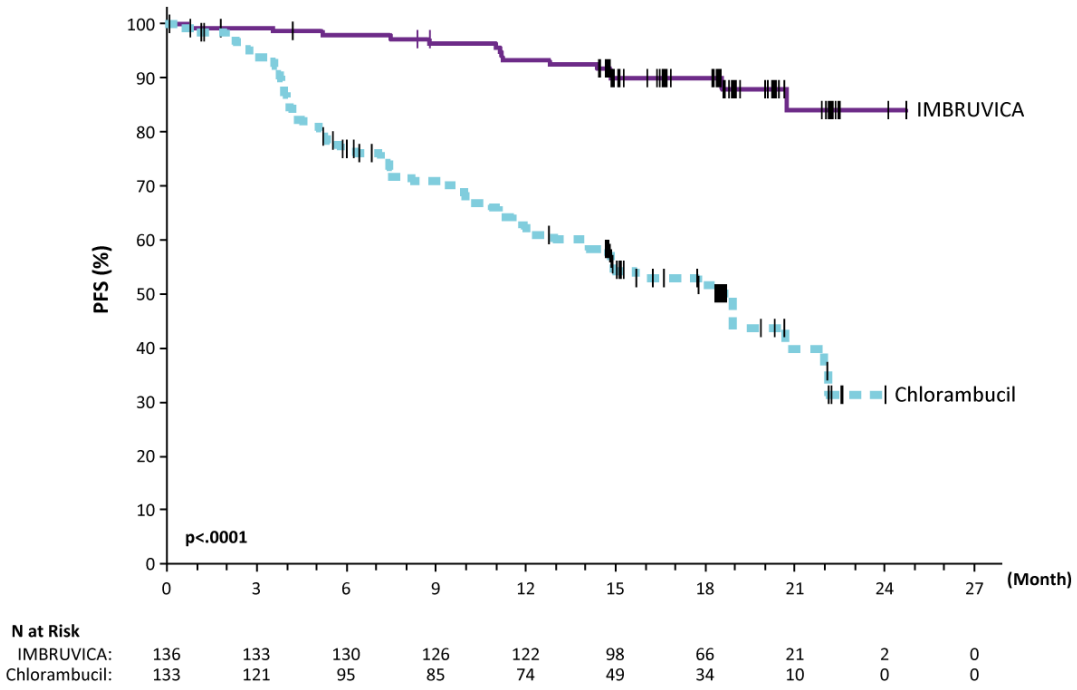
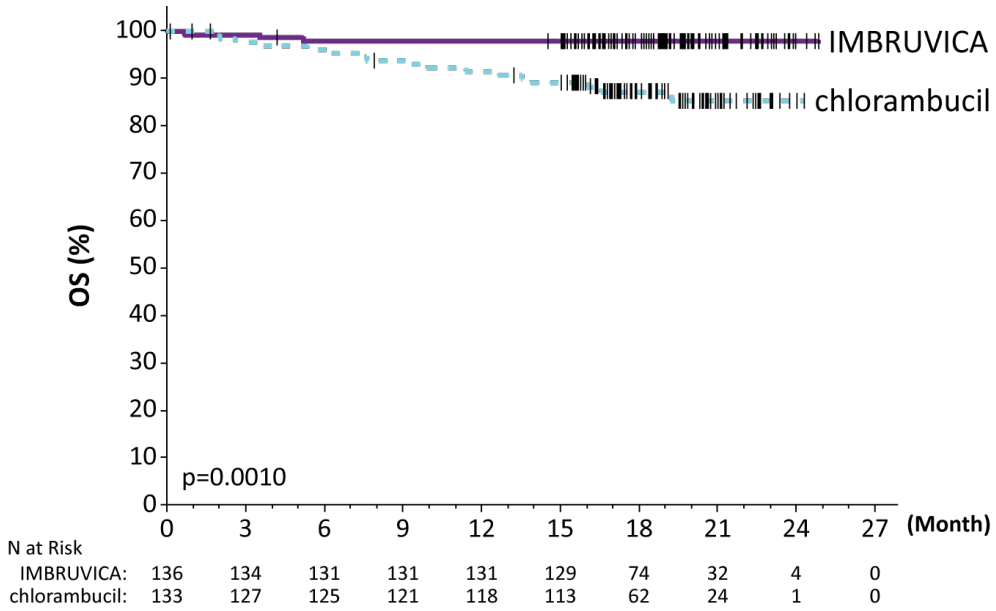


Figure 4: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1115-CA

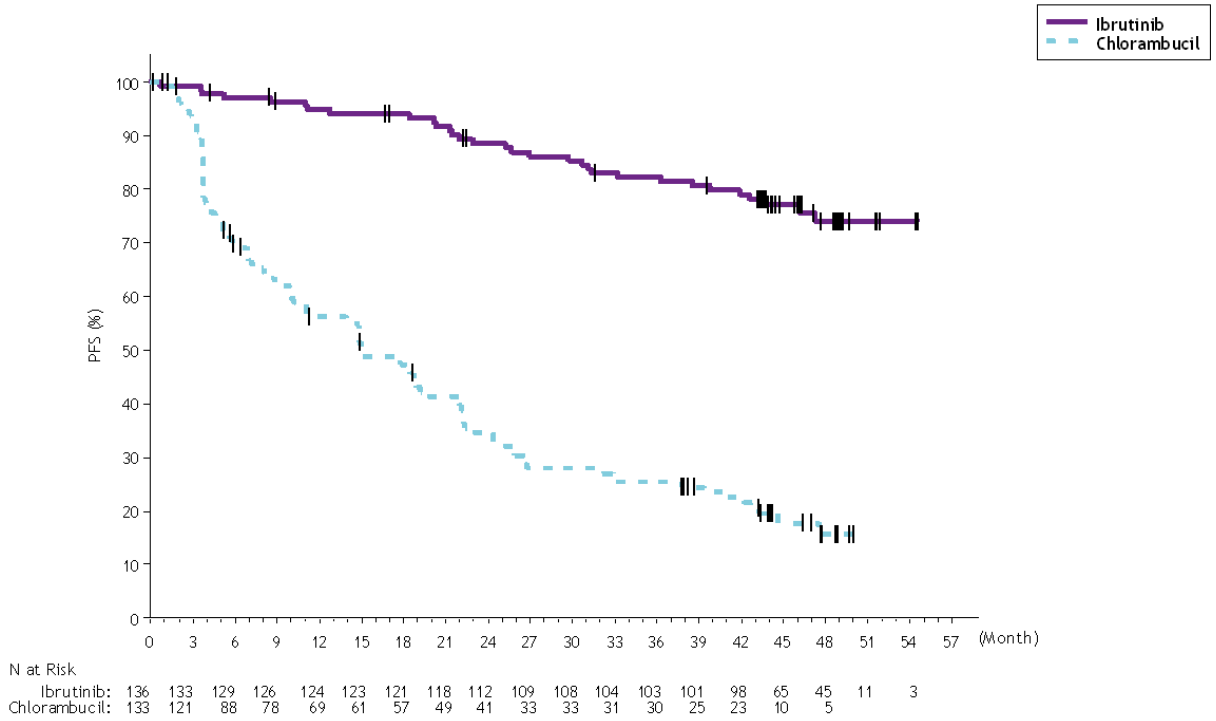


Overall follow-up of 55 months (median of 48 months)

With an overall follow-up of 55 months (median of 48 months) in Study PCYC-1115-CA and its extension study, an 86% reduction in the risk of death or progression by investigator assessment was observed for patients in the IMBRUVICA arm. The median investigator-assessed PFS was not reached in the IMBRUVICA arm and was 15 months [95% CI (10.22, 19.35)] in the chlorambucil arm; (HR = 0.14 [95% CI (0.09, 0.21)]). The 4-year PFS estimate was 73.9% in the IMBRUVICA arm and 15.5% in the chlorambucil arm, respectively. The updated Kaplan-Meier curve for PFS is shown in **Figure 5**. The investigator-assessed ORR was 91.2% in the IMBRUVICA arm versus 36.8% in the chlorambucil arm. The CR rate according to IWCLL criteria was 16.2% in the IMBRUVICA arm versus 3.0% in the chlorambucil arm. At the time of long-term follow-up, a total of 73 subjects (54.9%) originally randomized to the chlorambucil arm subsequently received ibrutinib as cross-over treatment. The Kaplan-Meier landmark estimate for OS at 48-months was 85.5% in the IMBRUVICA arm.

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

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



Combination therapy

PCYC-1130-CA (iLLUMINATE)

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

The median age was 71 years (range, 40 to 87 years), 64% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (48%) or 1-2 (52%). At baseline, 52% had advanced clinical stage (Rai Stage III or IV), 32% of patients had bulky disease (≥ 5 cm), 44% with baseline 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 (del 17p/TP53 mutation [18%], del 11q [15%], or unmutated IGHV [54%]).

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

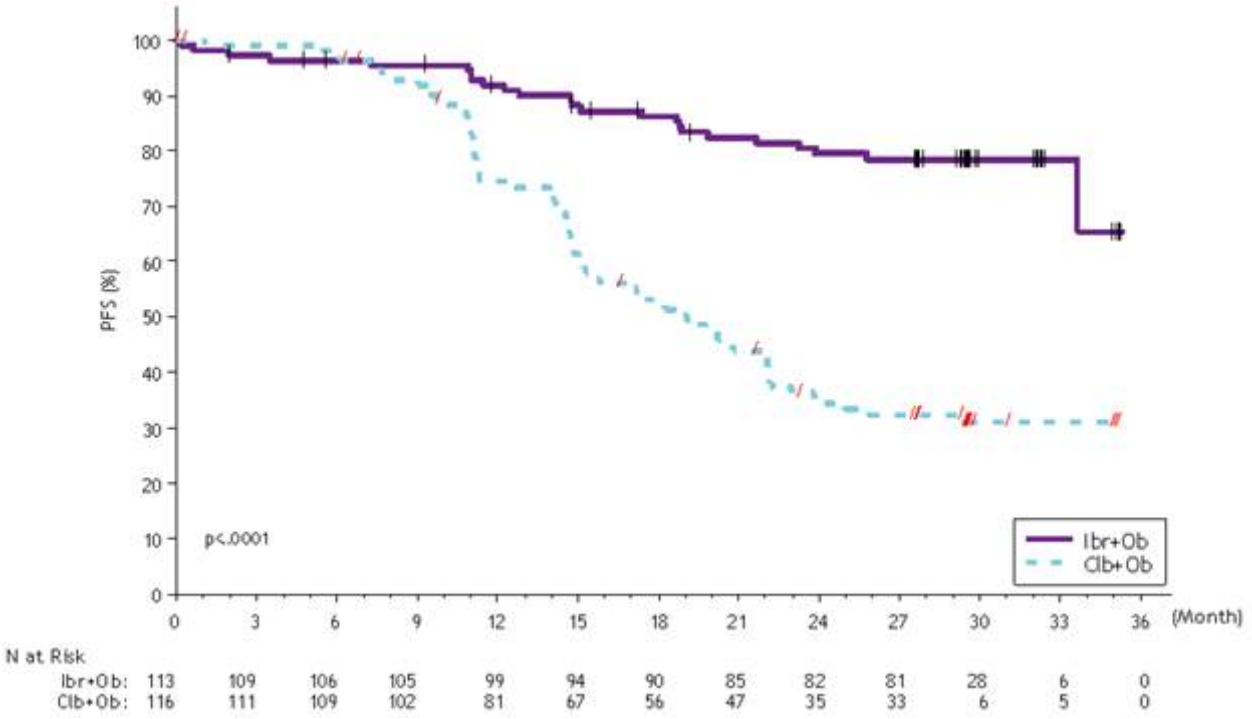
Efficacy results for Study PCYC 1130 CA are shown in **Table 21** and the Kaplan-Meier curve for PFS is shown in **Figure 6**.

Table 21: Efficacy results in Study PCYC-1130-CA

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

CI = confidence interval; HR = hazard ratio; CR = complete response; PR = partial response.
[a] IRC evaluated.
[b] Includes 1 patient in the IMBRUVICA + obinutuzumab arm with a complete response with incomplete marrow recovery (CRi).
[c] PR = PR + nPR.

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



The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), with a PFS HR of 0.15 [95% CI (0.09, 0.27)], as shown in **Table 22**. 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 22: Subgroup Analysis of PFS (Study PCYC-1130-CA)

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

Hazard ratio based on non-stratified analysis

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

Study E1912/PCYC-1126e-CA

A randomised, multicentre, open-label, safety and efficacy, Phase 3 study E1912 (also known as PCYC-1126e-CA) of IMBRUVICA in combination with rituximab versus standard fludarabine, cyclophosphamide, and rituximab [FCR] chemoimmunotherapy was conducted in patients with treatment naïve CLL/SLL who were 70 years or younger. Patients (n=529) were randomized 2:1 to receive either IR or FCR. IMBRUVICA was administered at 420 mg daily until disease progression or unacceptable toxicity. Fludarabine was administered at a dose of 25 mg/m^2, and cyclophosphamide was administered at a dose of 250 mg/m^2, both on Days 1, 2, and 3 of Cycles 1-6. Rituximab was initiated in Cycle 2 for the IR arm and in Cycle 1 for the FCR arm and was administered at 50 mg/m^2 on Day 1 of the first cycle, 325 mg/m^2 on Day 2 of the first cycle, and 500 mg/m^2 on Day 1 of 5 subsequent cycles, for a total of 6 cycles. Each cycle was 28 days.

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

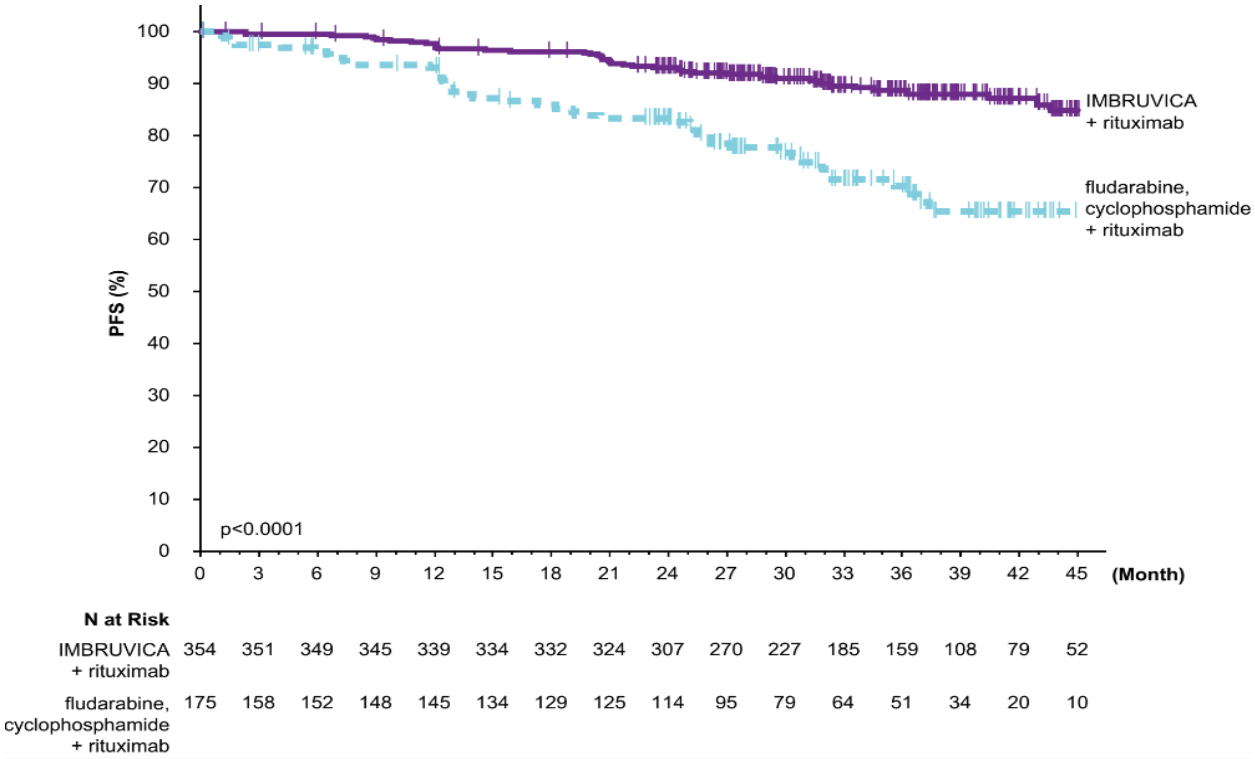
With a median follow-up time on study of 37 months, efficacy results for E1912 are shown in **Table 23**. Statistically significant improvements in the primary endpoint (PFS) and secondary endpoint (OS) were observed with IR compared to FCR. Three-year PFS estimates were 88.7% with IR compared to 70.3% for FCR, while the 3-year OS estimates were 98.8% with IR and 92.2% with FCR. The Kaplan-Meier curves for PFS, assessed according to IWCLL criteria, and OS are shown in Figures 7 and 8, respectively.

Table 23: Efficacy results in Study E1912

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

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

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



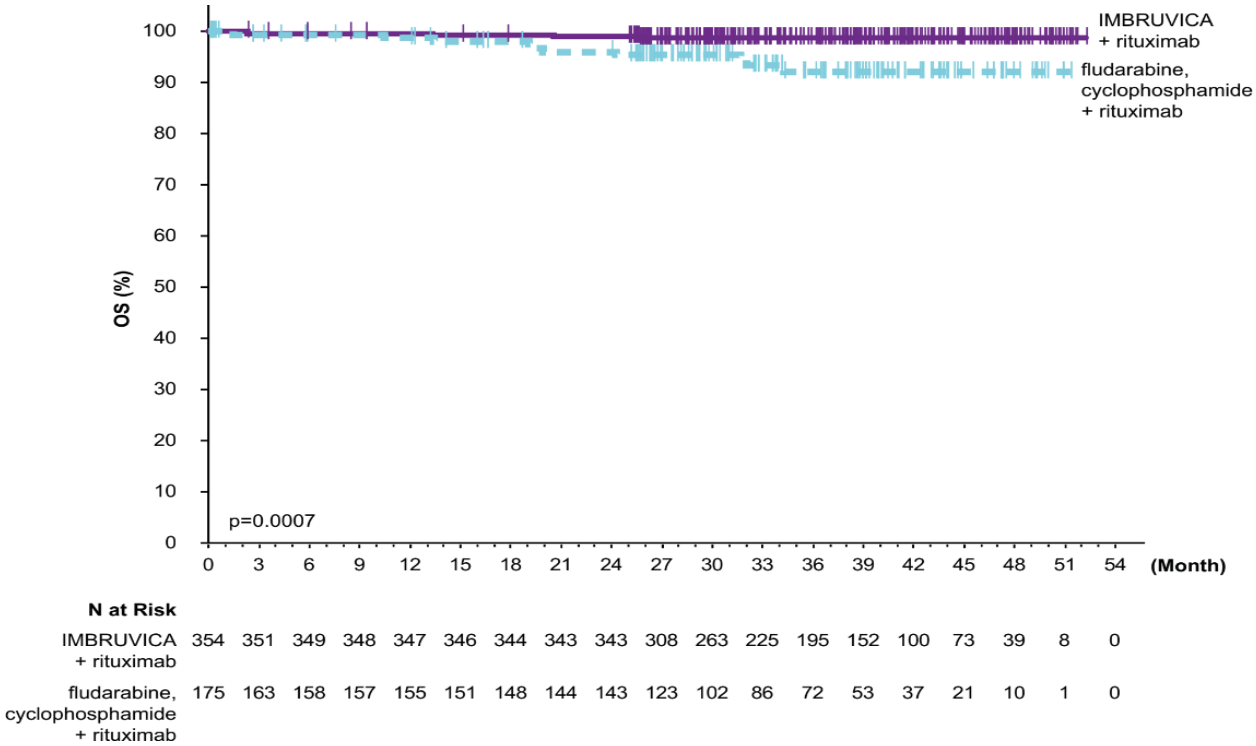
The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (del17p/TP53 mutation, del11q, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.40)], p <0.0001, as shown in **Table 24.** The 3-year PFS rate estimates for the high-risk CLL/SLL population were 90.4% [95% CI (85.4, 93.7)] and 60.3% [95% CI (46.2, 71.8)] in the IR and FCR arms, respectively.

Table 24: Subgroup Analysis of PFS (Study E1912)

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

Hazard ratio based on non stratified analysis

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



Fixed duration combination therapy

Study PCYC-1142-CA

A Phase 2, multi-centre, 2-cohort study assessing both minimal residual disease (MRD)-guided discontinuation and fixed duration therapy with IMBRUVICA in combination with venetoclax, was conducted in adult patients who were 70 years or younger with previously untreated CLL or SLL. 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 ramp-up). 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 White. All patients had a baseline ECOG performance status of 0 (69%) or 1 (31%). The trial enrolled 146 patients with CLL and 13 patients with SLL. At baseline, 13% of patients had CLL/SLL with del 17p, 18% with del 11q, 17% with del 17p/TP53 mutation, 56% with unmutated IGHV and 19% with complex karyotype. The most common reasons for initiating CLL therapy included: lymphadenopathy (65%), progressive lymphocytosis (51%), splenomegaly (30%), fatigue (24%), progressive marrow failure demonstrated by anemia and/or thrombocytopenia (23%), and night sweats (21%). 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 ≥25x10^9/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 25**, and rates of minimal residual disease (MRD) negativity are shown in **Table 26**.

Table 25: 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 26: 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 3 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 ($<1 \times 10^4$).

CI = confidence interval

At this assessment, 84 patients who were MRD negative in peripheral blood had matched bone marrow specimens; of these, 76 patients (90%) were MRD negative in both peripheral blood and bone marrow.

In the fixed duration cohort, no TLS was reported in patients treated with IMBRUVICA in combination with venetoclax.

CLL/SLL with del 17p/TP53 in PCYC 1142-CA

In patients with del 17p/TP53 mutation (n = 27) 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.

Study CLL3011

A randomized, open-label, Phase 3 study of IMBRUVICA in combination with venetoclax versus chlorambucil in combination with obinutuzumab, was conducted in patients with previously untreated CLL or SLL 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 randomized 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 ramp up). 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 randomized to the chlorambucil plus obinutuzumab arm received treatment for 6 cycles. Obinutuzumab was administered at a dose of 1000 mg on Days 1, 8 and 15 in Cycle 1. In Cycles 2 to 6, 1000 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%). The trial enrolled 197 patients with CLL and 14 patients with SLL. At baseline, 18% of patients presented with CLL/SLL with del 11q and 52% with unmutated IGHV. The most common reasons for initiating CLL therapy included: constitutional symptoms (59%), progressive marrow failure (48%), lymphadenopathy (36%), splenomegaly (28%) and progressive lymphocytosis (19%). 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 ≥25x10^9/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 27**, the Kaplan-Meier curve for PFS is shown in Figure 9, and rates of minimal residual disease (MRD) negativity are shown in **Table 28**.

Table 27: 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	
Overall Response Rate (%)[c]	86.8	84.8
95% CI	(80.3, 93.2)	(77.9, 91.6)
Complete Response Rate (%)[d]	38.7	11.4
95% CI	(29.4, 48.0)	(5.3, 17.5)
P-value[e]	<0.0001	

[a] Based on IRC assessment

[b] P-value is from stratified log-rank test

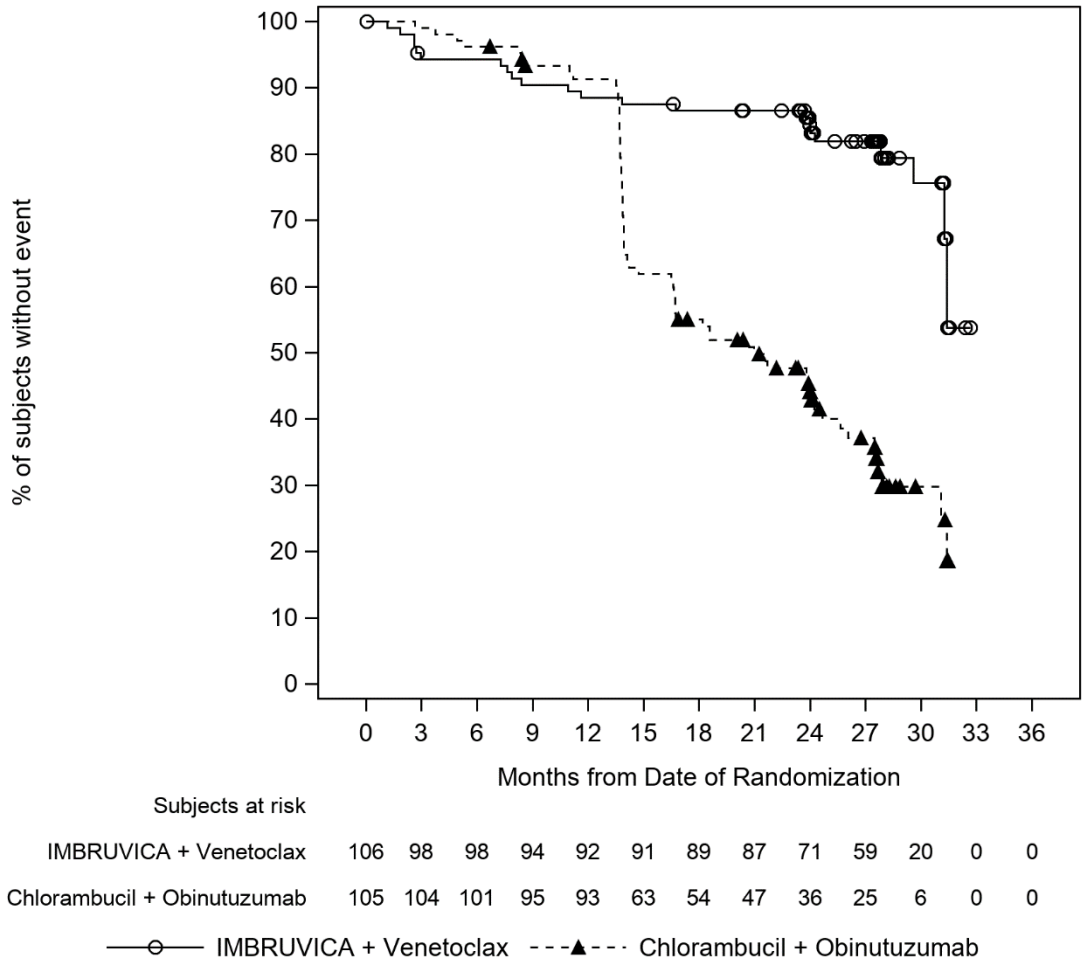
[c] Overall response = CR+CRi+nPR+PR

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

[e] P-value is from Cochran-Mantel-Haenszel chi-square test

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

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



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

With a median follow-up of 28 months, overall survival data were not mature 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.

Table 28: 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		<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)
P-value	0.0055		<0.0001	
MRD Negativity Rate at 3 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)
P-value	<0.0001		<0.0001	
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-value	0.0259		0.0038	

P-values are from Cochran-Mantel-Haenszel chi-square test. Except the p-value for MRD negativity rate in bone marrow by NGS, which is the primary MRD analysis, all other p-values are nominal.

[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

At three months after completion of treatment, 56 patients in IMBRUVICA plus venetoclax arm who were MRD negative in peripheral blood by NGS assay had matched bone marrow specimens; of these, 52 patients (92.9%) were MRD negative in both peripheral blood and bone marrow.

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.

Patients with CLL/SLL who received at least one prior therapy

Single agent

PCYC-1102-CA

An open label, multi-centre study was conducted in 51 patients with CLL/SLL who received 420 mg once daily. Ibrutinib was administered until disease progression or unacceptable toxicity. The median age was 68 (range, 37 to 82 years), median time since diagnosis was 80 months, and median number of prior treatments was 4 (range, 1 to 12 treatments), including 92.2% with a prior nucleoside analog, 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% were del 17p positive, 31.4% were del 11q positive.

ORR was investigator-assessed according to the 2008 International Workshop on CLL (IWCLL) criteria. At a median duration of follow up of 16.4 months, responses to IMBRUVICA for the 51 patients are shown in **Table 29**.

Table 29: Overall Response Rate in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma treated with 420 mg IMBRUVICA - Study PCYC-1102-CA (N=51)

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

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

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

The efficacy data were further evaluated using IWCLL criteria by an independent review committee (IRC), demonstrating an ORR of 64.7% (95% CI: 50.1%, 77.6%), all partial responses. The DOR ranged from 3.9 to 24.2+ months. The median DOR was not reached.

PCYC-1112-CA (RESONATE)

A randomized, multi-centre, open-label Phase 3 study of ibrutinib versus ofatumumab was conducted in patients with CLL/SLL. Patients (n=391) were randomized 1:1 to receive either ibrutinib 420 mg daily until disease progression or unacceptable toxicity, or ofatumumab for up to 12 doses (300/2000mg). Fifty-seven (n=57) patients randomized to ofatumumab crossed over following progression to receive ibrutinib. 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-three percent (33%) 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 independent review committee (IRC) according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the ibrutinib arm. The results from investigator and IRC assessments for PFS were consistent. Analysis of OS demonstrated a 57% statistically significant reduction in the risk of death for patients in the ibrutinib arm. Efficacy results for Study PCYC-1112-CA are shown in **Table 30**.

Table 30: Efficacy results in patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Study PCYC-1112-CA)

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

[a] Median OS not reached for both arms.

[b] Patients randomised to ofatumumab who progressed were censored when starting ibrutinib if applicable.

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

[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 Kaplan-Meier curves for PFS and OS are shown in **Figure 10** and **Figure 11**, respectively.

Figure 10: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1112-CA

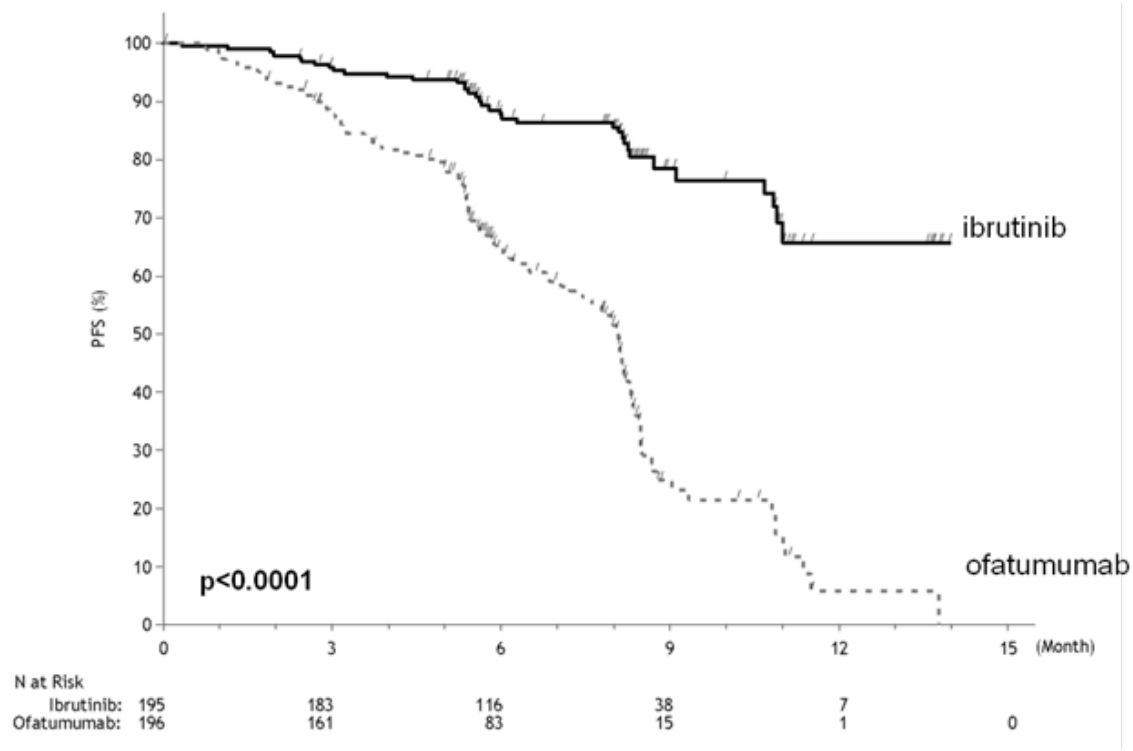
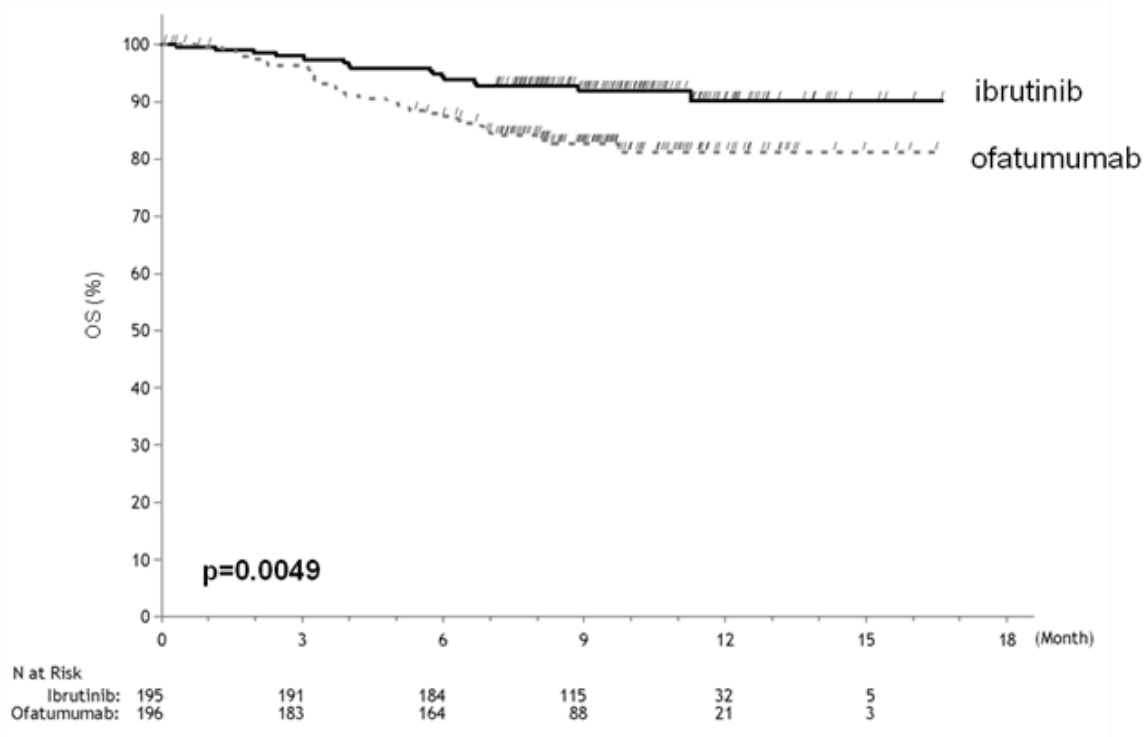
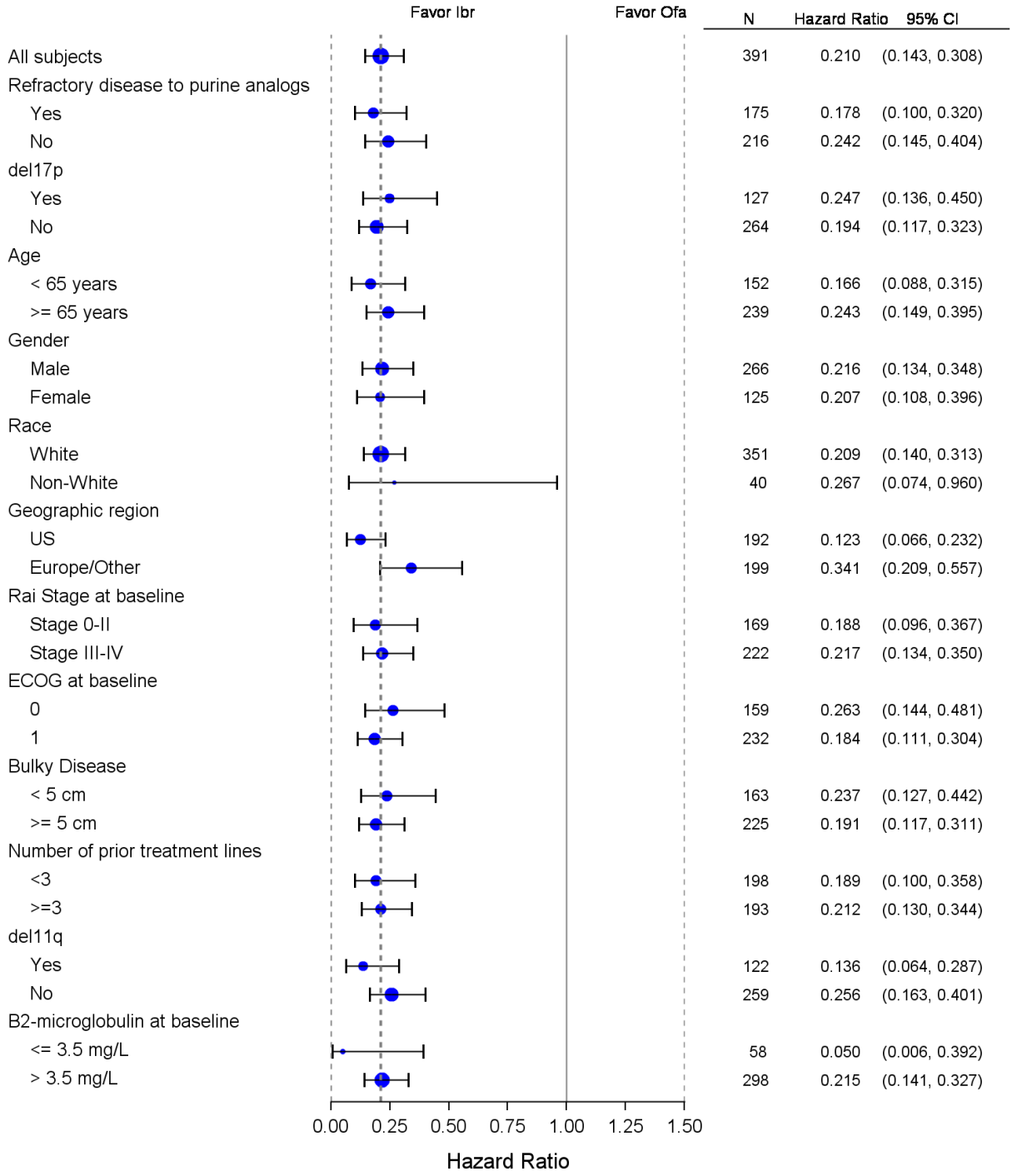


Figure 11: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1112-CA



The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (**Figure 12**).

Figure 12:Subgroup Analysis of Progression Free Survival by IRC (Study PCYC-1112-CA; 420 mg)

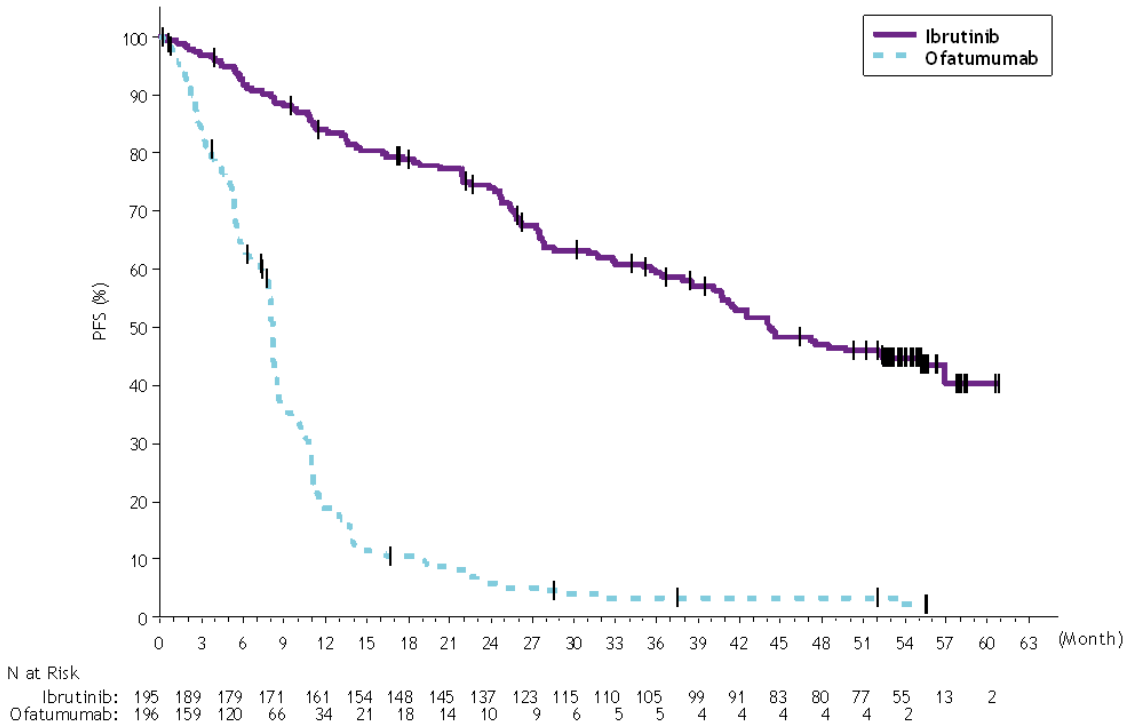


Overall follow-up of 63 months (median of 56 months)

With an overall follow-up of 63 months (median of 56 months) in Study PCYC-1112-CA, an 86% reduction in the risk of death or progression by investigator assessment was observed for patients in the IMBRUVICA arm. The median investigator-assessed PFS according to IWCLL criteria was 44.1 months [95% CI (38.54, 56.87)] in the IMBRUVICA arm and 8.1 months [95% CI (7.79, 8.25)] in the ofatumumab arm, respectively; HR = 0.14 [95% CI (0.11, 0.19)]. The updated Kaplan-Meier curve for PFS is shown **in Figure 13**. The investigator-assessed ORR in the IMBRUVICA arm was 87.2% versus 22.4% in the ofatumumab arm. At the time of long-term follow-up, 133 (67.9%) of the 196 subjects originally randomized to the ofatumumab treatment arm had crossed over to ibrutinib treatment. The Kaplan-Meier landmark estimate for OS at 60-months was 62.2% in the IMBRUVICA arm.

The treatment effect of ibrutinib in Study PCYC-1112-CA was consistent across high-risk patients with del 17p/TP53 mutation, del 11q, and/or unmutated IGHV.

Figure 13: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) by Investigator in Study PCYC-1112-CA with 63 Months Follow-up



Combination therapy

CLL3001 (HELIOS)

The safety and efficacy of IMBRUVICA in patients previously treated for CLL/SLL were further evaluated in a randomized, multicentre, double-blinded Phase 3 study of IMBRUVICA in combination with BR versus placebo + BR. Patients (n = 578) were randomized 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 randomized 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 5.9 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% presented with del11q, and 72% had unmutated IGHV.

Progression free survival (PFS) as assessed by IRC according to IWCLL criteria indicated an 80% statistically significant reduction in the risk of death or progression. Efficacy results for Study CLL3001 are shown in **Table 31** and the Kaplan-Meier curves for PFS are shown in **Figure 14**.

Table 31: Efficacy results in Study CLL3001

Endpoint	ibrutinib + BR N=289	placebo + BR N=289
Progression Free Survival		
Number of events (%)	56 (19.4)	183 (63.3
Median (95% CI), months	Not reached	13.3 (11.3,13.9)
HR (95% CI)	0.20 (0.15,0.28)	
Overall Response Rate[a]	82.7%	67.8%
CR/CRi[b]	10.4	2.8
Overall Survival[c]	0.628 (0.385, 1.024)	
Minimal Residual Disease – negative status[d] (%)	12.8	4.8

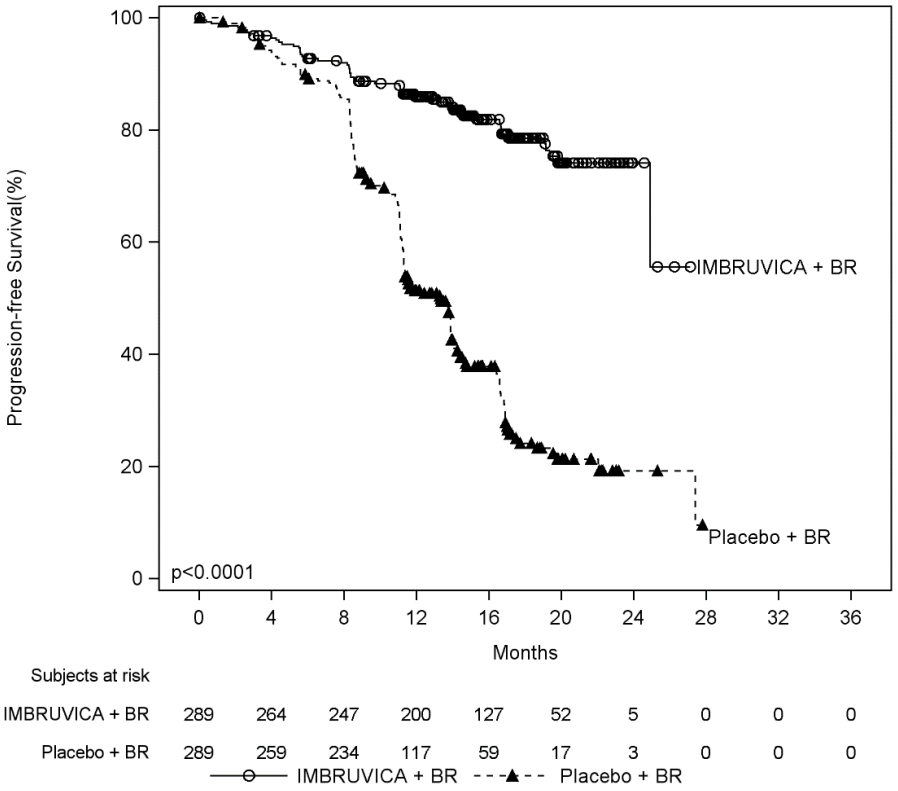
[a] IRC evaluated, ORR (CR, Cri, nPR, PR)

[b] CRi=complete response with incomplete marrow recovery

[c] Median OS not reached for both arms

[d] MRD was evaluated in patients with suspected complete response; 120 patients for ibrutinib, 57 patients for placebo had MRD samples obtained

Figure 14: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study CLL3001



Waldenström's Macroglobulinemia (WM)

PCYC-1118E

The safety and efficacy of IMBRUVICA in WM (IgM excreting lymphoplasmacytic lymphoma) were evaluated in an open-label, multicentre, 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 (range, 0.7 to 8.4 g/dL), and 60% of patients were anaemic (haemoglobin ≤11 g/dL).

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The primary endpoint in this study was ORR per investigator assessment.

The ORR and DOR were assessed using criteria adopted from the Third International Workshop of Waldenstrom's Macroglobulinemia. Responses to IMBRUVICA are shown in **Table 32**.

Table 32: Overall response rate (ORR) and duration of response (DOR) based on investigator assessment in patients with WM in Study PCYC-1118E

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

CI = confidence interval; NR = not reached; MR = minor response; PR = partial response; VGPR = very good partial response; ORR = MR+PR+VGPR

Median follow-up time on study = 14.8 months

The median time to response was 1.0 month (range: 0.7-13.4 months).

Efficacy results were also assessed by an IRC demonstrating an ORR of 82.5%, with a 11% VGPR rate and a 51% PR rate.

PCYC-1127-CA (iNNOVATE)

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

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were Caucasian. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were treatment-naïve, and 55% of patients were previously treated. The median time since diagnosis was 52.6 months (treatment-naïve patients = 6.5 months and previously treated patients = 94.3 months). Among previously treated patients, the median number of prior treatments was 2 (range, 1 to 6 treatments). At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), 63% of patients were anemic (hemoglobin ≤11 g/dL) and MYD88 L265P mutations were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status.

Progression free survival (PFS) as assessed by IRC indicated an 80% statistically significant reduction in the risk of death or progression. Efficacy results for Study PCYC-1127-CA are shown in **Table 33** and the Kaplan-Meier curve for PFS is shown in **Figure 15**. PFS hazard ratios for treatment-naïve patients, previously treated patients, and patients with or without MYD88 L265P mutations were consistent with the PFS hazard ratio for the ITT population.

Table 33: Efficacy results in Study PCYC-1127-CA

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

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

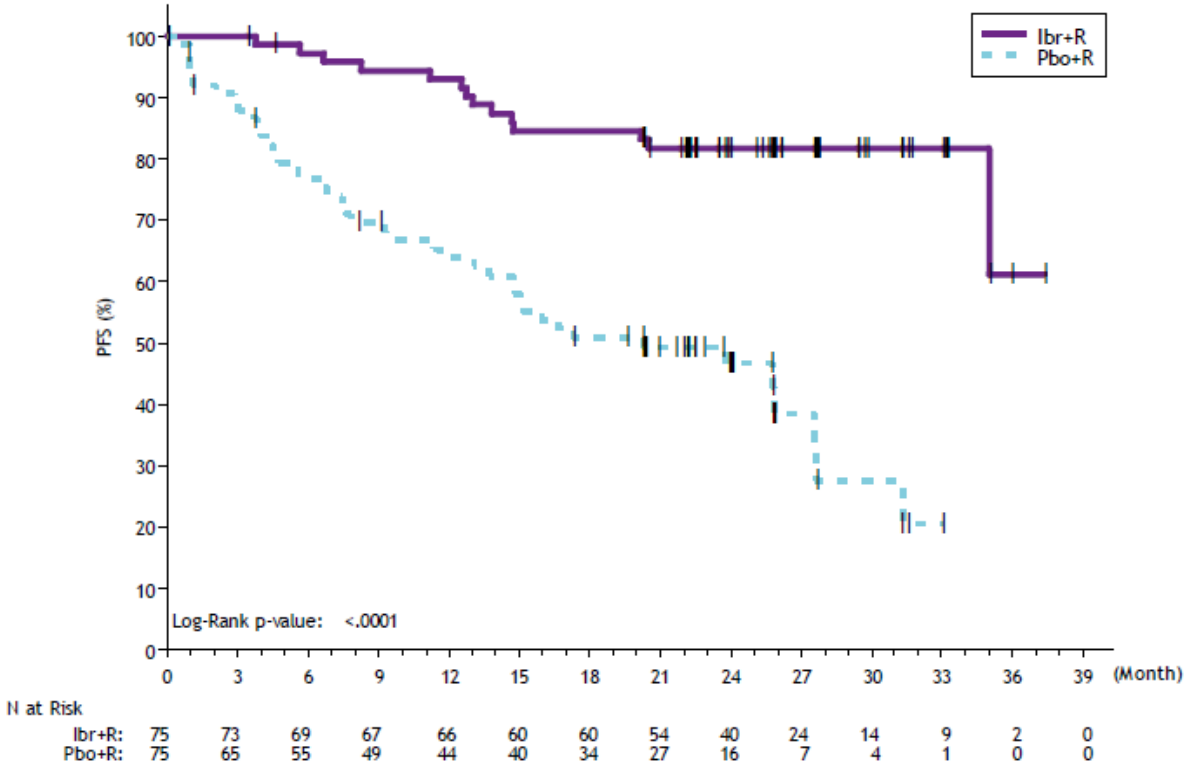
[a] IRC evaluated.

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

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

Median follow-up time on study = 26.5 months.

Figure 15: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1127-CA



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.

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

5.2 Pharmacokinetics

Absorption

Ibrutinib is rapidly absorbed after oral administration with a median T_{max} of 1 to 2 hours. 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 with food increases ibrutinib exposure approximately 2 fold compared to administration after overnight fasting.

Distribution

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

Metabolism

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

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

Elimination

Apparent clearance (CL/F) is approximately 1000 L/h. The half-life of ibrutinib is 4 to 6 hours.

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

Additional information on special populations

Paediatrics (18 years of age and younger)

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

Elderly (65 years of age and older)

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

Renal impairment

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

Hepatic impairment

Ibrutinib is metabolized in the liver. In a dedicated hepatic impairment study in non-cancer patients administered a single dose of 140 mg of IMBRUVICA, preliminary data showed an approximate 4, 8 , and 9 fold increase in ibrutinib exposure in subjects with mild (n=6), moderate (n=10) and severe (n=8) 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. An increase in unbound ibrutinib exposure is estimated to be 4, 9, and 13 fold in subjects with mild, moderate, and severe hepatic impairment, respectively.

Gender

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

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules

Croscarmellose sodium

Magnesium stearate

Microcrystalline cellulose

Sodium lauryl sulfate.

The capsule shell contains:

Gelatin

Titanium dioxide

Black ink.

Film-coated tablets

Colloidal anhydrous silica

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Sodium lauryl sulfate

Film-coating

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Capsules: 36 months

Tablets: 24 months

6.4 Special precautions for Storage

Store below 30°C.

6.5 Nature and contents of container

Capsules

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

Each HDPE bottle with a polypropylene closure contains 90 or 120 hard capsules.

Film-coated tablets

IMBRUVICA film-coated tablets are supplied in blisters of polyvinyl chloride (PVC)/ polychlorotrifluoroethylene (PCTFE) laminated film and aluminium foil.

Each carton contains 6 blisters of 5 tablets or 12 blisters of 10 tablets (140 mg strength only). Two blisters are enclosed within a wallet pack.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland

NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

Email: medinfo@janau.jnj.com

9. DATE OF FIRST APPROVAL

30 July 2015

10. DATE OF REVISION OF TEXT

19 April 2023

Co-developed with Pharmacyclics

Summary table of changes

Section changes	Summary of new information
6.5	Update to content description for film-coated tablets