janssen

AUSTRALIAN PRODUCT INFORMATION

IMBRUVICA®

IBRUTINIB

CAPSULES AND TABLETS

1. NAME OF THE MEDICINE

Ibrutinib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules

140 mg capsules

IMBRUVICA capsules contain 140 mg ibrutinib as the active ingredient.

Film-coated tablets

IMBRUVICA tablets contain 140 mg, 280 mg, 420 mg or 560 mg of ibrutinib.

Excipients with known effect: sugars as lactose

The characterization data demonstrate that ibrutinib at pH 1.2 is considered slightly soluble and at pH 3 to 8 ibrutinib is considered practically insoluble as defined by USP and European Pharmacopoeia nomenclature. Ibrutinib is non-hygroscopic and the melting onset temperature is 149-158 ˚C. The drug substance has one ionizable group, the protonated pyrimidine moiety, with a pKa of 3.74 in an aqueous solution with methanol as a co-solvent.

For a full list of excipients, see section **6.1 LIST OF EXCIPIENTS**.

3. PHARMACEUTICAL FORM

Capsules

140 mg capsules

White opaque, size 0, hard gelatin capsule is 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.

IMBRUVICA as a single agent is indicated for the treatment of adult patients with Waldenström’s macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with Waldenstrom’s macroglobulinaemia (WM).

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

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

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. IMBRUVICA can be taken with or without food. 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 or Seville Oranges.

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.

Waldenström’s Macroglobulinemia (WM)

The recommended dose of IMBRUVICA is 420 mg once daily

IMBRUVICA can be administered as a single agent, or in combination with rituximab, until disease progression or it is no longer tolerated by the patient.

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL)

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

IMBRUVICA can be administered as a single agent, or in combination with anti-CD20 therapy (rituximab or obinutuzumab), or in combination with bendamustine and rituximab (BR) until disease progression or is no longer tolerated by the patient.

In combination with venetoclax, IMBRUVICA should be administered as a single agent for an initial 3 cycles (1 cycle is 28 days), followed by 12 cycles of IMBRUVICA plus venetoclax.

For additional information concerning rituximab, BR, obinutuzumab, or venetoclax, see the corresponding local rituximab, bendamustine, obinutuzumab, or venetoclax prescribing information. When administering IMBRUVICA in combination with anti-CD20 therapies, it is recommended to administer IMBRUVICA prior to anti-CD20 therapy when given on the same day.

Dose modification guidelines

Dose modifications are required for the concomitant use of moderate and strong CYP3A inhibitors as these can increase the exposure of ibrutinib (see section **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

IMBRUVICA therapy should be withheld for any new onset or worsening Grade 2 cardiac failure, Grade 3 cardiac arrhythmias, Grade ≥ 3 non-haematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 haematological toxicities. If ≥ Grade 3 elevations in liver function tests occur, with or without a rise in bilirubin, therapy should be withheld.

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-hematological toxicities Grade 3 or 4 neutropenia with infection or fever Grade 4 hematological toxicities	First*	restart at 560 mg daily	restart at 420 mg daily
	Second	restart at 420 mg daily	restart at 280 mg daily
	Third	restart at 280 mg daily	restart 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 is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra doses to make up the missed dose.

Special populations

Elderly

No specific dose adjustment is required for elderly patients (aged ≥ 65 years).

Severe cardiac disease

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

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 **5.2 PHARMACOKINETIC PROPERTIES**).

Hepatic impairment

Ibrutinib is metabolized in the liver. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3 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 **5.2 PHARMACOKINETIC PROPERTIES**). For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280mg daily. For patients with moderate liver impairment, the recommended dose is 140mg daily. 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).

Immunisations

There is no clinical data on the safety and efficacy of immunisations concomitantly administered with ibrutinib. Immunisations may be less effective in patients on ibrutinib therapy.

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.

In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed (see **5.1 PHARMACODYNAMIC PROPERTIES**). Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major

bleeding. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA without antiplatelet or anticoagulant therapy experienced major haemorrhage. 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 withheld 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.

Cardiac events

Fatal and serious cardiac arrhythmias or cardiac failure have occurred in patients treated with IMBRUVICA. Patients with significant cardiac co-morbidities may be at greater risk of events, including sudden fatal cardiac events. Atrial fibrillation, atrial flutter,ventricular tachyarrhythmia, and cardiac failure, have been reported, particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes melllitus and a previous history of cardiac arrhythmia. In some of these cases cardiac failure resolved or improved after IMBRUVICA withdrawal or dose reduction. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.3% of patients and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1981 patients who received IMBRUVICA in clinical trials. Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating IMBRUVICA. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns. Consider the risks and benefits of IMBRUVICA treatment and follow the dose modification guidelines.

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

In patients with 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.

Leukostasis

There were isolated cases of leukostasis reported in patients treated with ibrutinib. Leukostasis is characterized by abnormal intravascular leukocyte aggregation and clumping, and may cause local hypoxemia and haemorrhage manifesting as headache, blurred vision, transient ischemic attacks, cerebrovascular accidents and dyspnoea. A high number of circulating lymphocytes ($> 400 \times 10^9$/L) 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. 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, neutropenia, vomiting, jaundice, abnormal liver function tests and infections) and appropriate anti-infective therapy should be instituted as indicated. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

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.

Hypertension

Hypertension has occurred in patients treated with IMBRUVICA. Hypertension occurred in 18% of 1981 patients who received IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months). Regularly monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust antihypertensive medication throughout treatment with IMBRUVICA as appropriate.

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 were reported more frequently in patients treated with IMBRUVICA than in patients treated with comparators in pooled comparative randomised phase 3 studies. Other malignancies (8%), including non-skin carcinomas (3%), occurred among the 1981 patients who received IMBRUVICA in clinical trials. Monitor patients for the appearance of non melanoma skin cancer.

Splenic rupture

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

Tumour lysis syndrome

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

Haemophagocytic lymphohistiocytosis (HLH)

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

Hepatotoxicity

Severe liver toxicity, such as hepatic failure (Grade 3 and 4 elevations in ALT and AST), including fatal events, have occurred in the post-marketing setting in patients taking ibrutinib. The time to onset was variable (5 days – 3 months after commencing ibrutinib) and monitoring of liver function tests is recommended. These events were very rare and in most cases resolved upon dose modification. Ibrutinib treatment should be interrupted if ≥ Grade 3 liver function abnormalities develop (see **4.2 DOSE AND METHOD OF ADMINISTRATION**). Liver function status should be assessed before initiating treatment with IMBRUVICA. Patients should be monitored for signs and symptoms (such as vomiting and jaundice) and periodically for changes in liver function parameters during treatment.

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.

Use in the elderly

Please refer to section 4.8 Adverse Effects (Undesirable effects) – Elderly

Paediatric use

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

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Ibrutinib is primarily metabolised by cytochrome P450 enzyme 3A4.

Agents that may increase ibrutinib plasma concentrations
Concomitant use of IMBRUVICA and drugs that strongly or moderately inhibit CYP3A4 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 CYP3A4 inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A4 inhibitors (n=19) did not reveal meaningful increases in toxicities. Voriconazole and posaconazole can be used concomitantly with IMBRUVICA as per dose recommendations in the table below. All other strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, cobicistat and posaconazole) should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If the benefit clearly outweighs the risk and a strong CYP3A4 inhibitor must be used, see recommended dose modifications in the Table 1.

Moderate and mild CYP3A4 inhibitors
In patients with B cell malignancies, co administration of CYP3A inhibitors erythromycin and voriconazole increased C_{max} by 3.4-fold and 6.7-fold and increased AUC by 3.0-fold and 5.7-fold,

respectively. If a moderate CYP3A4 inhibitor (e.g., fluconazole, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, 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 CYP3A4 (see **4.2 DOSE AND METHOD OF ADMINISTRATION** and **5.2 PHARMACOKINETIC PROPERTIES**).

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

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 ***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 CYP3A4 decreases ibrutinib plasma concentrations by approximately 90%. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampicin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A4 induction. If a CYP3A4 inducer must be used, closely monitor patients for lack of efficacy with IMBRUVICA.

As ibrutinib solubility is pH dependent, there is a theoretical risk that medicinal products increasing stomach pH (e.g., proton pump inhibitors) may decrease ibrutinib exposure. This interaction has not been studied *in vivo*.

Agents that may have their plasma concentrations altered by ibrutinib
Based on *in vitro* data, ibrutinib is predicted to be a weak OCT2 inhibitor *in vivo.* Ibrutinib is a P-gp and breast cancer resistance protein (BCRP) inhibitor *in vitro*. As no clinical data are available on this interaction, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. To minimise the potential for an interaction in the GI tract, 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.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day with estimated systemic exposures in female rats approximately 14 times the AUC of ibrutinib and 8 times the AUC of the dihydrodiol metabolite in patients dosed 560 mg ibrutinib daily (exposures in male rats were less than half the exposures in female rats).

Fertility studies with ibrutinib have not been conducted in animals.

Use in pregnancy

Category D

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

IMBRUVICA should not be used during pregnancy. Women of child bearing potential must use highly effective contraceptive measures while taking IMBRUVICA. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 months 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 fetal development in pregnant rats given oral doses of 10, 40 and 80 mg/kg/day. Ibrutinib at 80 mg/kg/day (approximately 14 times the AUC of ibrutinib and 10 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 ≥ 40 mg/kg/day (approximately 6 times the AUC of ibrutinib and 4 times the AUC of the dihydrodiol metabolite compared to patients at a dose of 560 mg daily) was associated with decreased maternal and fetal weights and increased skeletal variations (unossified sternebrae).

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

Use in lactation

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 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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 (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety profile is based on pooled data from 1981 patients with B-cell malignancies treated with IMBRUVICA in four phase 2 clinical studies (PCYC-1102-CA, PCYC-1104-CA, PCYC-1118E and PCYC-1142-CA) and eight phase 3 studies (PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, MCL3001, PCYC-1127-CA, E1912 and CLL3011). Patients treated for MCL received IMBRUVICA at 560 mg once daily and patients treated for CLL/SLL and WM received IMBRUVICA at 420 mg once daily. All patients received IMBRUVICA until disease progression or no longer tolerated.

The most commonly occurring adverse reactions (≥ 20%) were diarrhoea, musculoskeletal pain, haemorrhage, bruising, rash, nausea, neutropenia, arthralgia, upper respiratory tract infection and thrombocytopaenia. The most common grade 3/4 adverse reactions (≥ 5%) were neutropenia, lymphocytosis, pneumonia, hypertension and thrombocytopenia.

Tabulated list of adverse reactions

Treatment emergent adverse reactions for MCL, CLL/SLL or WM are listed below by system organ class and frequency grouping. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4 Treatment-emergent Adverse drug reactions (ADR) in patients treated with ibrutinib for B-cell malignancies (N = 1981)

System organ class	Frequency (All grades)	Adverse drug reactions
Infections and infestations	Very common	Pneumonia*† Upper respiratory tract infection Skin infection*
	Common	Sepsis*† Urinary tract infection Sinusitis*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Non melanoma skin cancer* Basal cell carcinoma Squamous cell carcinoma
Blood and lymphatic system disorders	Very common	Neutropenia Thrombocytopenia Lymphocytosis
	Common	Febrile neutropenia Leukocytosis
	Uncommon	Leukostasis syndrome
Metabolism and nutrition disorders	Common	Tumour lysis syndrome Hyponatraemia Hyperuricaemia
Nervous system disorders	Very common	Headache Dizziness
Eye disorders	Common	Vision blurred
Cardiac disorders	Common	Atrial fibrillation
Vascular disorders	Very common	Haemorrhage*† Bruising* Hypertension*

System organ class	Frequency (All grades)	Adverse drug reactions
	Common	Haemorrhage*† Subdural haematoma† Petechiae Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Stomatitis* Nausea Constipation Dyspepsia
Skin and subcutaneous tissue disorders	Very common	Rash*
	Common	Erythema Urticaria
	Uncommon	Angioedema
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Muscle spasms Musculoskeletal pain*
General disorders and administration site conditions	Very common	Pyrexia Oedema peripheral
Investigations	Very common	Blood creatinine increased

* Includes multiple adverse reaction terms.
† Includes events with fatal outcome.

Discontinuation and dose reduction due to ADRs

Of the 1981 patients treated with IMBRUVICA for B-cell malignancies 6% discontinued treatment primarily due to adverse reactions. These included pneumonia, atrial fibrillation, haemorrhage, neutropenia, rash, arthralgia and thrombocytopenia. Adverse reactions leading to dose reduction occurred in approximately 8% of patients.

Elderly

Of the 1981 patients treated with IMBRUVICA,50% were above 65 years of age. 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 <65 years of age).

Long-term safety

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

Postmarketing data

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: Immune system disorders

Uncommon: Interstitial lung disease*†

System Organ Class: Metabolism and nutrition disorders

Very rare: Tumour lysis syndrome

System Organ Class: Cardiac disorders

Common: Cardiac failure*†; Ventricular tachyarrhythmia*†

System Organ Class: Hepatobiliary disorders

Uncommon: Hepatic failure*†

Very rare:; hepatotoxicity

System Organ Class: Infections and infestations

Uncommon: Hepatitis B reactivation†

System Organ Class: Renal and Urinary Disorders

Common: Acute kidney Injury†

System Organ Class: Skin and subcutaneous tissue disorders

Uncommon: Onychoclasis, Pyogenic granuloma

Rare: Neutrophilic dermatoses*

Rare: Stevens-Johnson syndrome, Panniculitis*

Very rare: Angioedema, erythema, urticaria, cutaneous vasculitis

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 suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

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)]. 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 information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE27.

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys 481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important signalling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B cell malignancies, including MCL, diffuse large B cell lymphoma (DLBCL), follicular lymphoma, and CLL/SLL. 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 B cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

In primary tumour cells, cultured tumour cell lines and preclinical tumour models, the combination of ibrutinib and venetoclax resulted in increased cytotoxicity, cellular apoptosis and/or 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., $>400x10^9$/L) 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 (n=32), ibrutinib at therapeutically relevant concentrations demonstrated inhibition of collagen induced platelet aggregation in samples from 4 cohorts of subjects (n=8 in each) with either renal dysfunction, those on warfarin, healthy subjects or healthy subjects on aspirin. 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

A randomized, double-blind, placebo- and positive-controlled, single-dose crossover study was performed to evaluate the effects of ibrutinib at supratherapeutic doses of 840 mg and 1680 mg on ECG interval parameters in healthy subjects. The study was early terminated after 20 subjects (out of 52 planned) received 3 out of 4 treatments. Results were based on the 20 treated subjects, 9 of whom received ibrutinib (either 840 or 1680 mg), the negative control (placebo), and the positive control (moxifloxacin). In this study, ibrutinib did not prolong the QTc interval to any clinically relevant extent. 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

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 (PCYC-1104-CA) 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 5.

Table 5: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with Mantle Cell Lymphoma

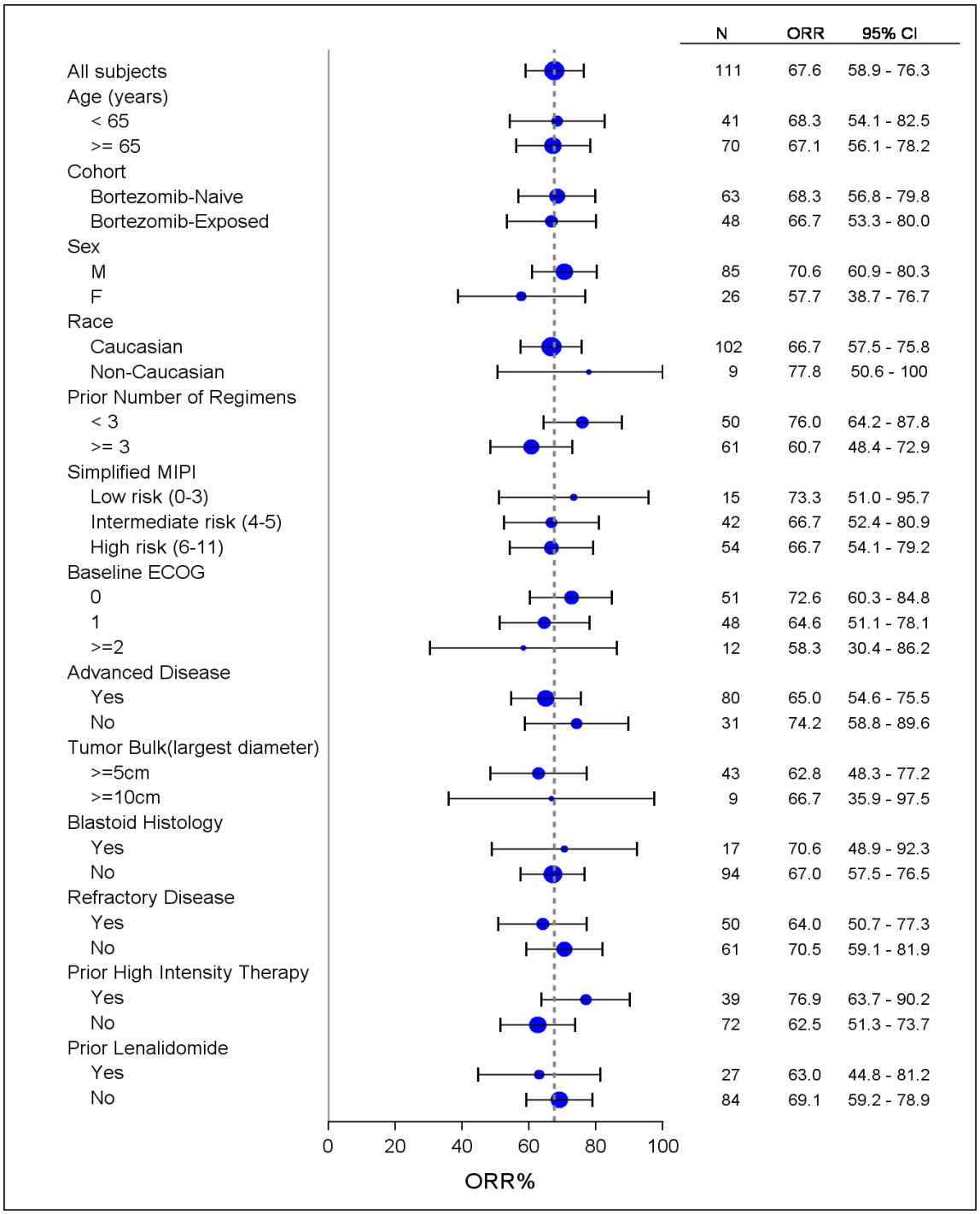
	Total N=111
ORR (%)	67.6
95% CI (%)	(58.0, 76.1)
CR (%)	20.7
PR (%)	46.8
Median DOR (CR+PR) (months)	17.5 (15.8, NR)
Median Time to Initial Response, months (range)	1.9(1.4-13.7)
Median Time to CR, months (range)	5.5 (1.7, 11.5)

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 6 and the Kaplan-Meier curve for PFS Figure 2.

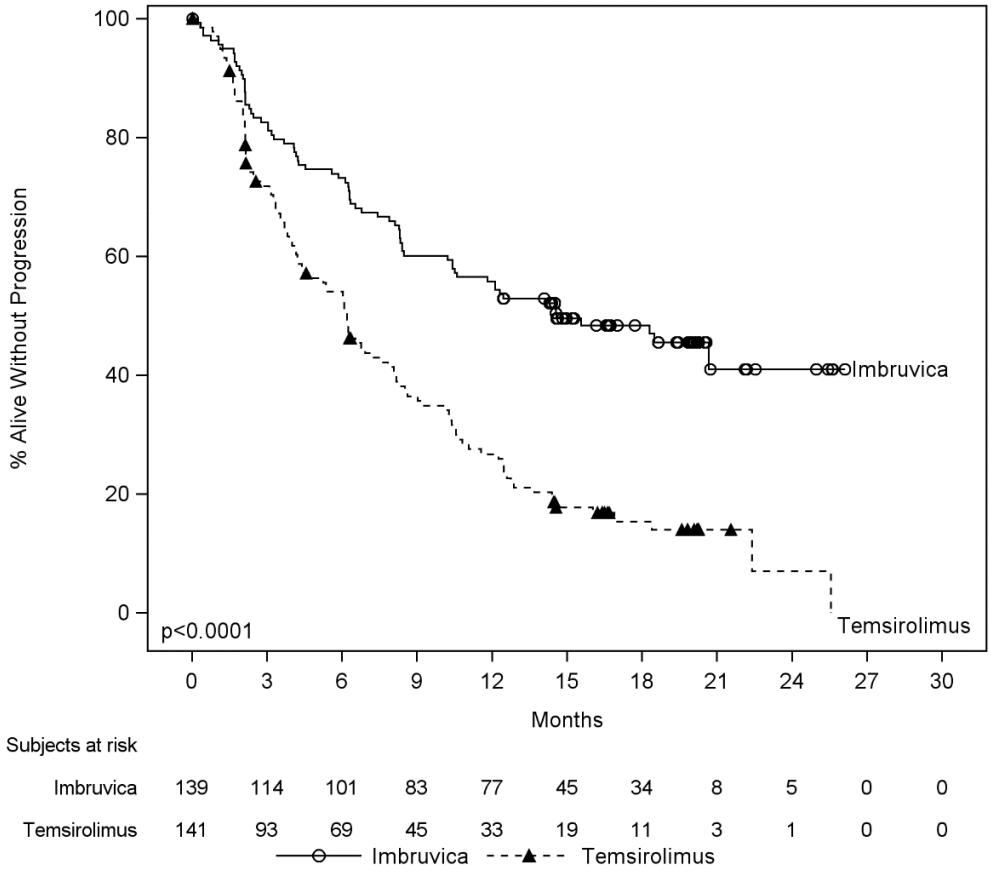
Table 6: Efficacy results in Study MCL3001

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 estimated; HR = hazard ration; 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 two uncontrolled studies 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. Patients between 65 and 70 years of age were required to have at least 1 of the following additional comorbidities that could preclude the use of frontline chemoimmunotherapy combination with fludarabine, cyclophosphamide, and rituximab (FCR): Creatinine clearance < 70 mL/min; Platelet count < 100,000 µL or hemoglobin < 10 g/dL; Clinically apparent autoimmune cytopenia (autoimmune hemolytic anemia or immune thrombocytopenia); Eastern Cooperative Oncology Group (ECOG) PS score of 1 or 2. Forty-two percent of patients had a baseline ECOG performance status of 0, 49% had an ECOG performance status of 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/tumor protein 53 (TP53) mutation, and 44% of patients presented with unmutated immunoglobulin heavy chain variable region (IGHV).

Progression free survival (PFS) as assessed by IRC according to IWCLL criteria indicated an 84% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm. With a median follow up of 18 months, the median PFS was not reached in the ibrutinib arm and was 19 months in the chlorambucil arm. Significant improvement in ORR was observed in the ibrutinib arm (82%) versus the chlorambucil arm (35%). The results from investigator and IRC assessments for PFS and ORR were consistent. Analysis of overall survival (OS) also demonstrated an 84% statistically significant reduction in the risk of death for patients in the IMBRUVICA arm. Efficacy results for Study PCYC-1115-CA are shown in Table 7 and the Kaplan-Meier curves for PFS and OS are shown in Figures 3 and 4, respectively.

There was a statistically significant sustained platelet or haemoglobin improvement in the ITT population in favour of ibrutinib 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 7: 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)	

Endpoint	ibrutinib N=136	chlorambucil N=133
Overall Response Rate (CR+PR)[a]	82.4%	35.3%
p-value	p<0.0001	
CR/CRi[c]	4.4%	1.5%
Overall Survival[d]		
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]CRi=complete response with incomplete marrow recovery; [d]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

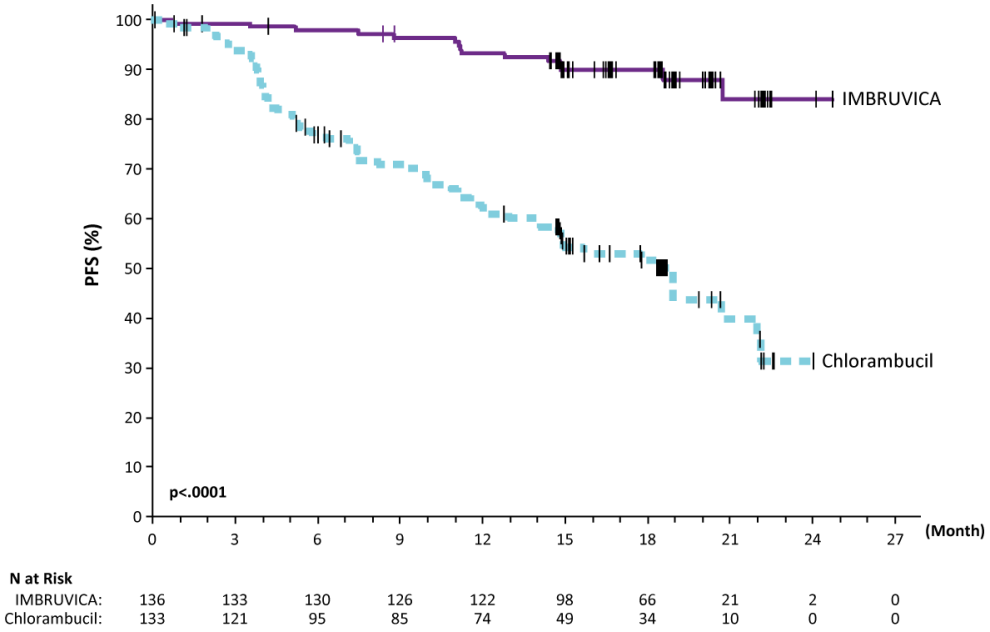
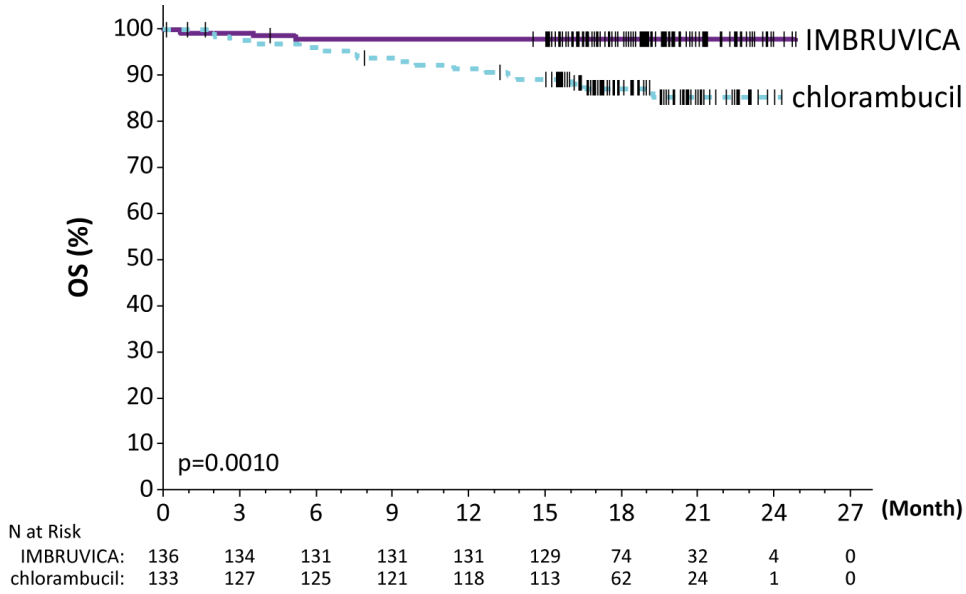


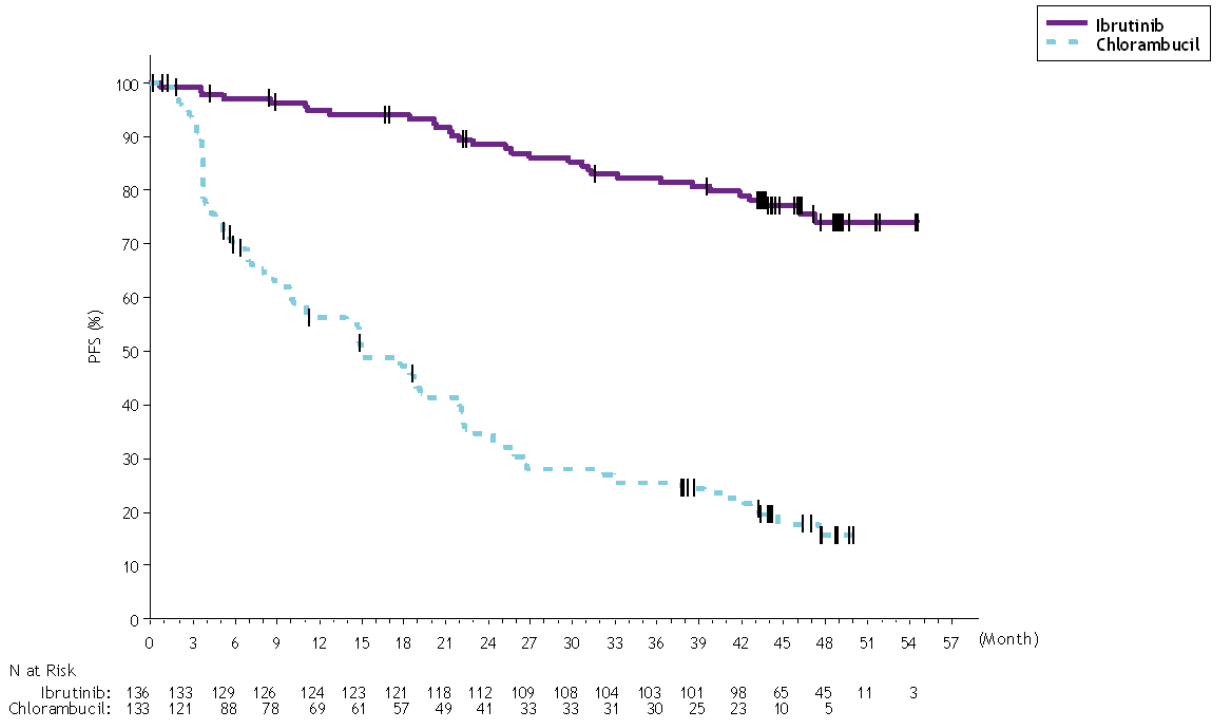
Figure 4: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1115-CA



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-centrer, 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 randomised 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity or chlorambucil at a dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for 6 cycles. In both arms, patients received 100, 900, 1000, and 1000 mg of obinutuzumab on Days 1, 2, 8 and 15 of the first cycle, respectively, followed by treatment of 1000 mg of obinutuzumab on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each).

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 8 and the Kaplan-Meier curve for PFS is shown in Figure 6.

Table 8: Efficacy results in Study PCYC-1130-CA

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

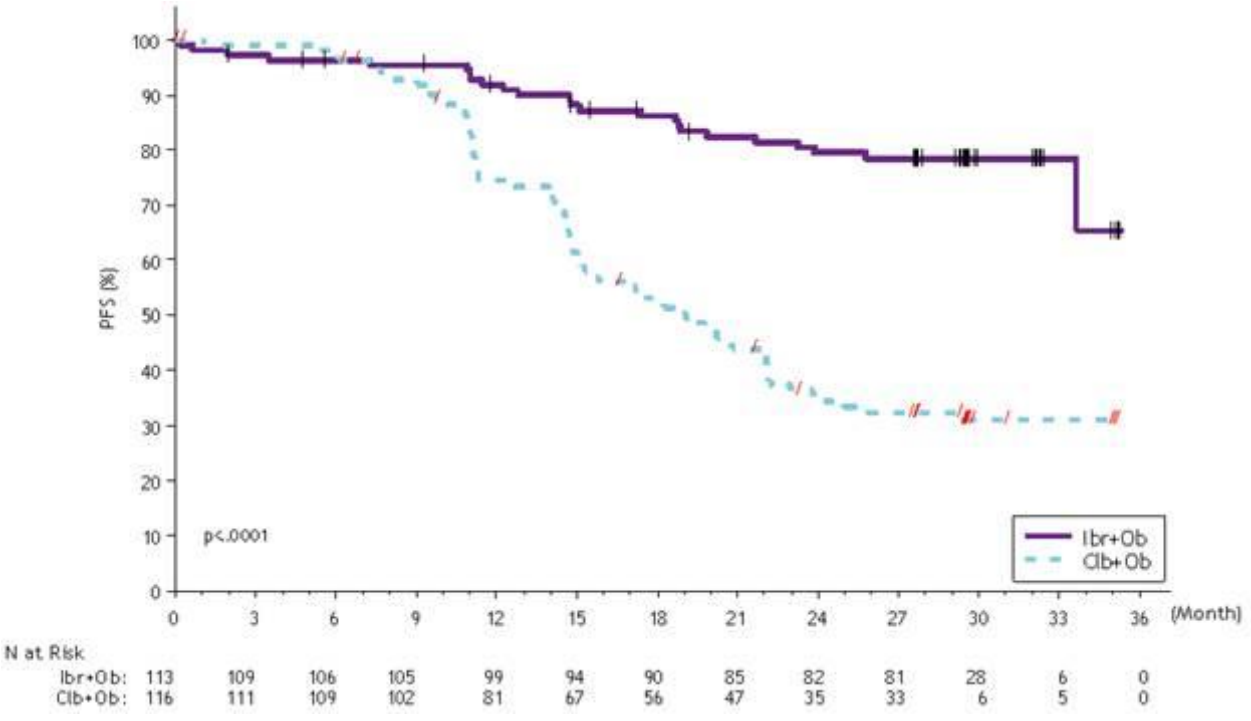
CI = confidence interval; HR = hazard ratio; CR = complete response; PR = partial response; nPR = nodular partial response

[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 9. The 2-year PFS rate estimates for the high-risk CLL/SLL population were 78.8% [95% CI (67.3, 86.7)] and 15.5% [95% CI (8.1, 25.2)] in the IMBRUVICA + obinutuzumab and chlorambucil + obinutuzumab arms, respectively.

Table 9: Subgroup Analysis of PFS (Study PCYC-1130-CA)

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

Hazard ratio based on non-stratified analysis

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

Study E1912/PCYC-1126e-CA

The E1912 study (A Randomized Phase III Study of Ibrutinib based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab [FCR] Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia [CLL]) (NCT02048813) was conducted in adult patients who were 70 years or younger with previously untreated CLL or SLL requiring systemic therapy. All patients had a CLcr > 40 mL/min at baseline. Patients with 17p deletion were excluded. Patients (n =529) were randomized 2:1 to receive either IMBRUVICA plus rituximab (R) 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 IMBRUVICA + R 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, 90% were White and 98% had a ECOG performance status of 0-1. At baseline, 43% of patients were Rai stage 3 or 4 and 59% of patients presented with high risk factors (TP53 mutation [6%], del11q [22%], or unmutated IGHV [53%]).

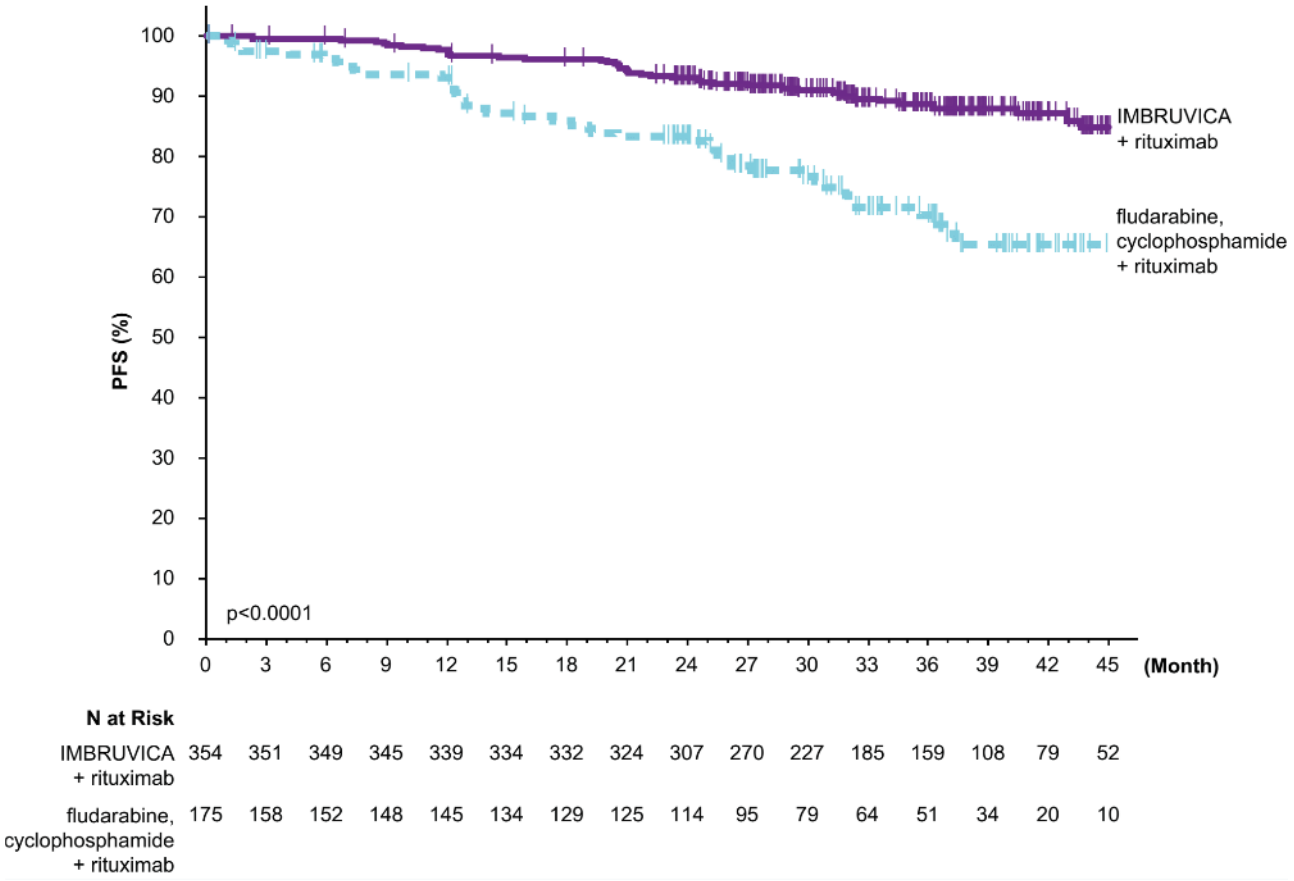
With a median follow-up time on study of 37 months, efficacy results for E1912 are shown in Table 10. The Kaplan-Meier curves for PFS, assessed according to IWCLL criteria is shown in Figure 7.

Table 10: Efficacy Results in Patients with CLL/SLL in E1912

Endpoint	IMBRUVICA + R N=354	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	

[a] P-value is from unstratified log-rank test.
FCR = fludarabine, cyclophosphamide, and rituximab; HR = hazard ratio; R = rituximab; NE = not evaluable

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



With a median follow-up time on study of 49 months, median overall survival was not reached with a total of 23 deaths: 11 (3%) in the IMBRUVICA plus rituximab and 12 (7%) in the FCR treatment arms.

Fixed duration combination therapy

Study CLL3011 (GLOW)
A randomised, 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 randomised 1:1 to receive either IMBRUVICA in combination with venetoclax or chlorambucil in combination with obinutuzumab. Patients in the IMBRUVICA plus venetoclax arm received single agent IMBRUVICA for 3 cycles followed by IMBRUVICA in combination with venetoclax for 12 cycles (including 5-week dose 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: constituitional 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 11, the Kaplan-Meier curve for PFS is shown in Figure 8, and rates of minimal residual disease (MRD) negativity are shown in Table 12.

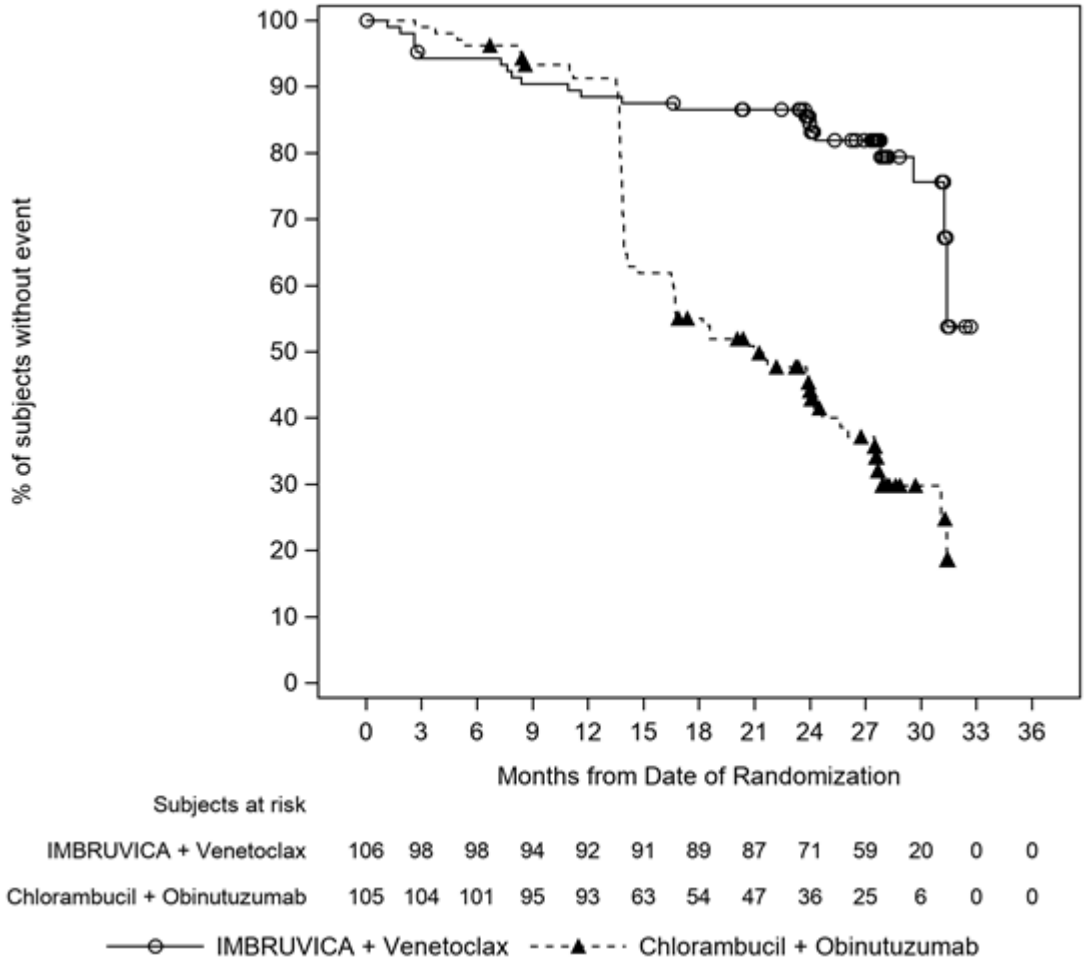
Table 11: Efficacy Results in Study CLL3011

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



Across the high-risk CLL/SLL population (n=123), including TP53 mutation (n=9), del 11q (n=38), or unmutated IGHV (n=109), the treatment effect of IMBRUVICA plus venetoclax was consistent, with a PFS HR of 0.23 [95% CI (0.13, 0.41)].

With a median follow-up of 46.1 months, 15 (out of 106, 14.2%) death events were observed in the Ibr+Ven arm versus 30 (out of 105, 28.6%) death events in the Clb+Ob arm. This corresponds to a HR of 0.487 (95% CI: 0.262, 0.907) and a nominal p=0.0205.

Table 12: Minimal Residual Disease Negativity Rates in Study CLL3011

	NGS Assay[a]		Flow cytometry[b]	
	IMBRUVICA + Venetoclax N=106	**Chlorambucil + Obinutuzumab N=105**	**IMBRUVICA + Venetoclax N=106**	**Chlorambucil + Obinutuzumab N=105**
MRD Negativity Rate				
Bone marrow, n (%)	59 (55.7)	22 (21.0)	72 (67.9)	24 (22.9)
95% CI	(46.2, 65.1)	(13.2, 28.7)	(59.0, 76.8)	(14.8, 30.9)

P-value	<0.0001			
Peripheral Blood, n (%)	63 (59.4)	42 (40.0)	85 (80.2)	49 (46.7)
95% CI	(50.1, 68.8)	(30.6, 49.4)	(72.6, 87.8)	(37.1, 56.2)
P-value				
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			
Peripheral Blood, n (%)	58 (54.7) [c]	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				

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 ($<1\times10^4$).

[c] 56 patients had matched bone marrow specimens; 52 patients were MRD negative in both peripheral blood and bone marrow.

CI = confidence interval; NGS = next-generation sequencing

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

TLS was reported in 6 patients treated with chlorambucil plus obinutuzumab and no TLS was reported in IMBRUVICA in combination with venetoclax as the study protocol included a specific tumour lysis syndrome management strategy.

Study PCYC-1142-CA (CAPTIVATE)

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, and 9 patients received this treatment.

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 ≥25 x 10^9/L.

With a median follow-up time on study of 28 months, efficacy results for PCYC 1142-CA assessed by an IRC according to IWCLL criteria and rates of minimal residual disease (MRD) negativity are described below for patients with or without del17p/TP53 mutation.

CLL/SLL without del 17p/TP53 in PCYC-1142-CA
In patients without del17p/TP53 mutation (n=136) the overall response rate based on IRC assessment was 95.6%; complete response rate was 61.0% and the median duration of complete response was not reached (range, 0.03 to 24.9 months). The MRD negativity rate in patients without del 17p/TP53 mutation 3 months after completion of treatment in bone marrow and peripheral blood was 54.4% and 57.4%, respectively.

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.

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.

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

PCYC-1102-CA
An open label, multi-centre study included 51 CLL/SLL patients with CLL/SLL who had relapsed or refractory disease and received 420 mg of ibrutinib 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 alkylating agent, 39.2% with prior bendamustine and 19.6% with prior ofatumumab. At study entry, 54.9% of patients had Rai Stage III or IV, 45.1% had bulky disease (≥ 5 cm), 35.3% had del 17p, 31.4% had del 11q.

ORR was investigator-assessed according to the 2008 International Workshop on CLL (IWCLL) criteria. At a median duration of follow up of 16.4 months, responses to IMBRUVICA for the 51 patients are shown in Table 13.

Table 13: 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-two percent (32%) 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 14.

Table 14: 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
[e] All PRs achieved. p< 0.0001 for ORR. Repeat CT scans required to confirm response.
Median follow-up time on study = 9 months

The Kaplan-Meier curves for PFS and OS are shown in Figures 9 and 10 respectively.

Figure 9: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1112-CA

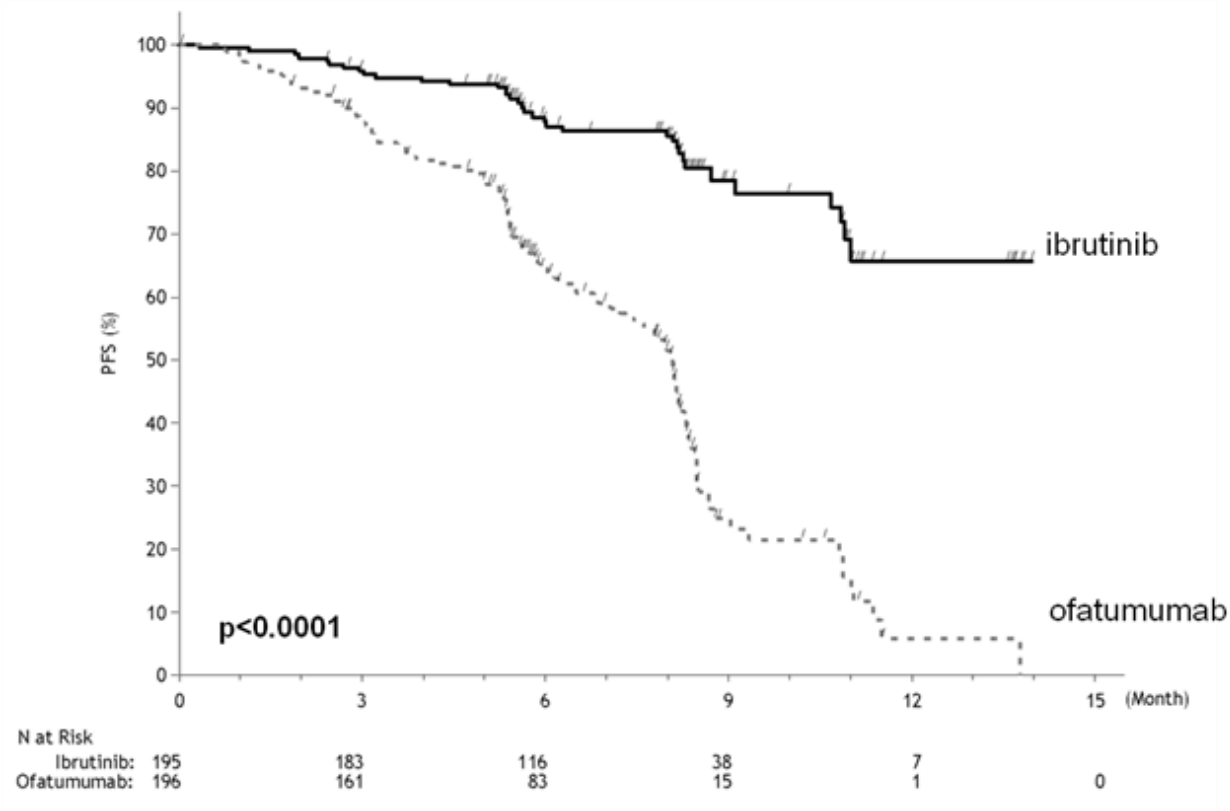
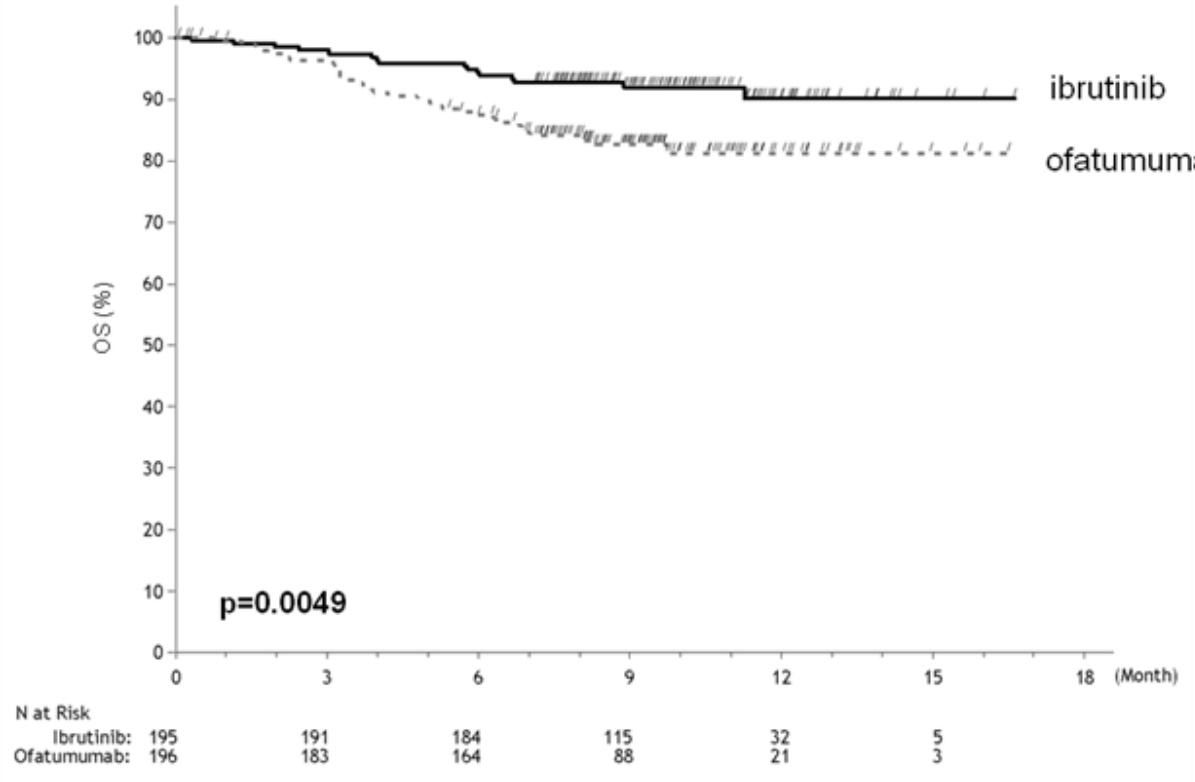
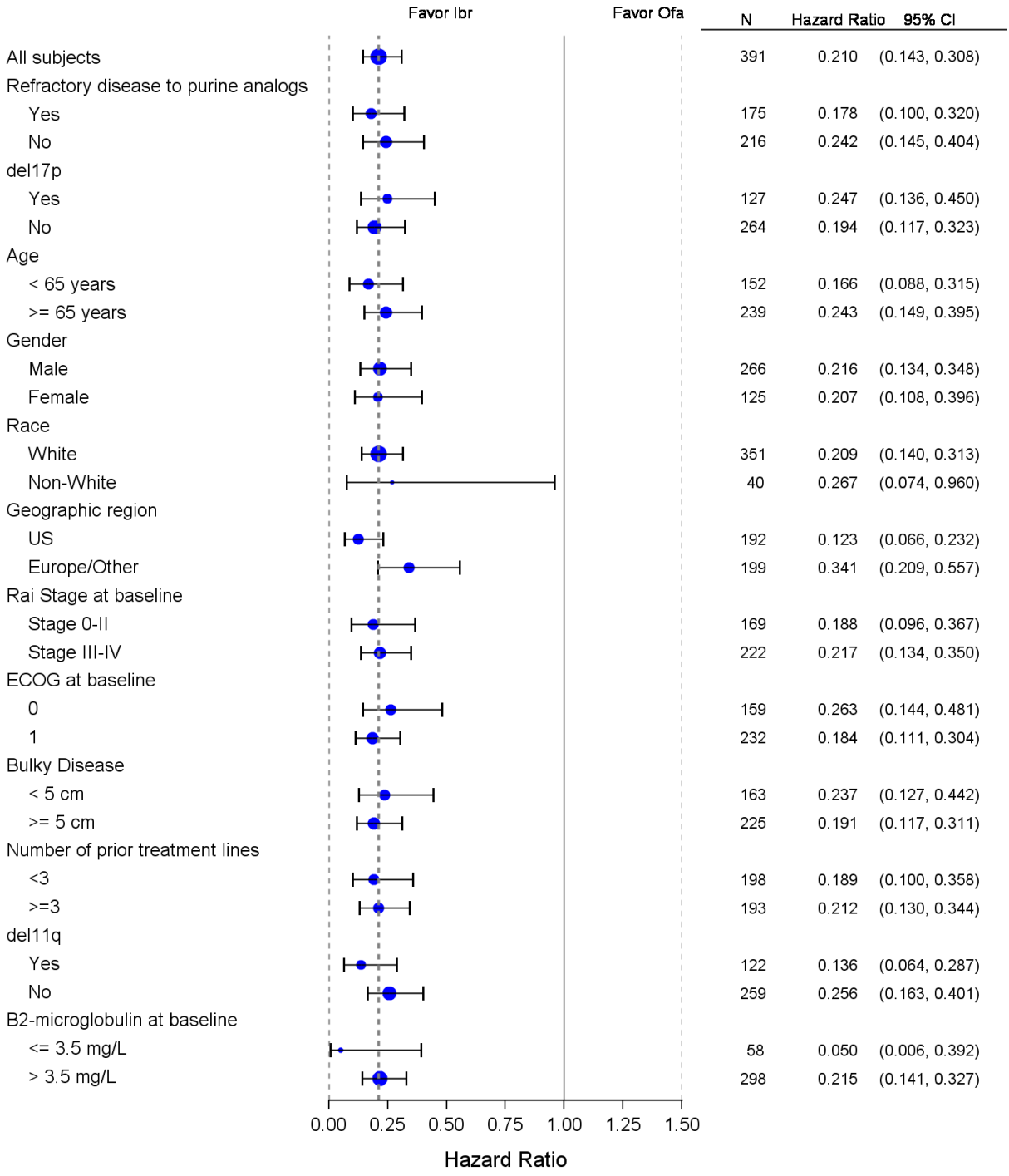


Figure 10: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1112-CA



The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (Figure 11).

Figure 11: Subgroup Analysis of Progression Free Survival by IRC (Study PCYC-1112-CA; 420 mg)

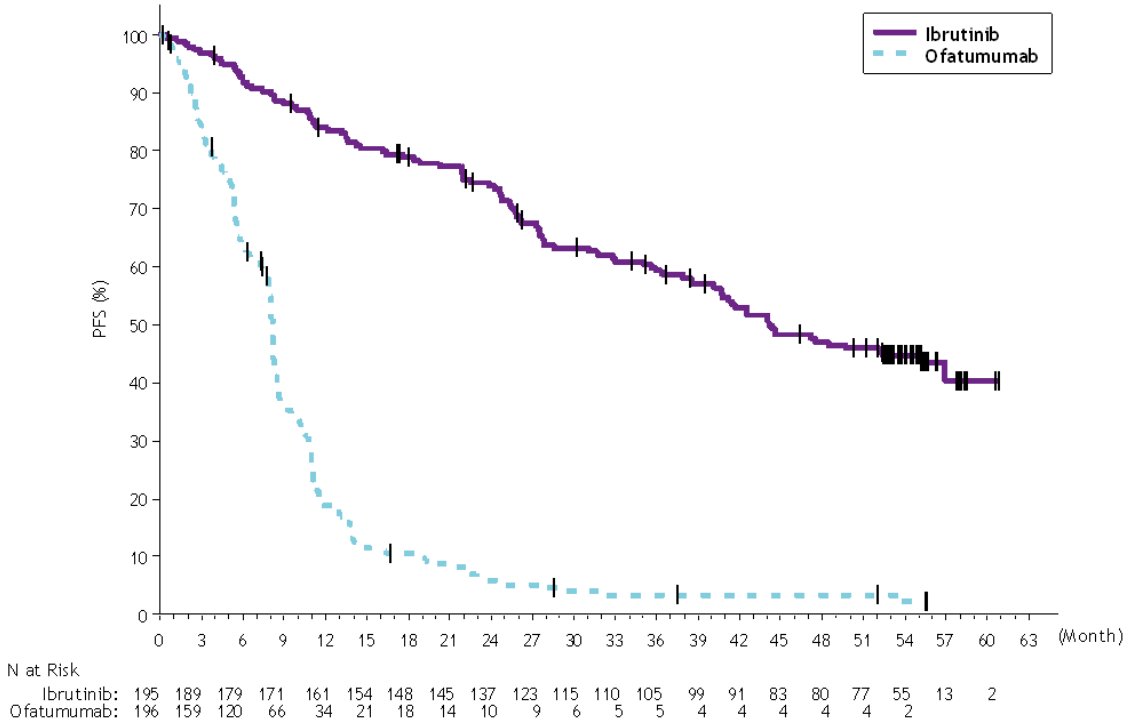


Overall follow-up of 63 months (median of 56 months)

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 12. 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 12: 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.

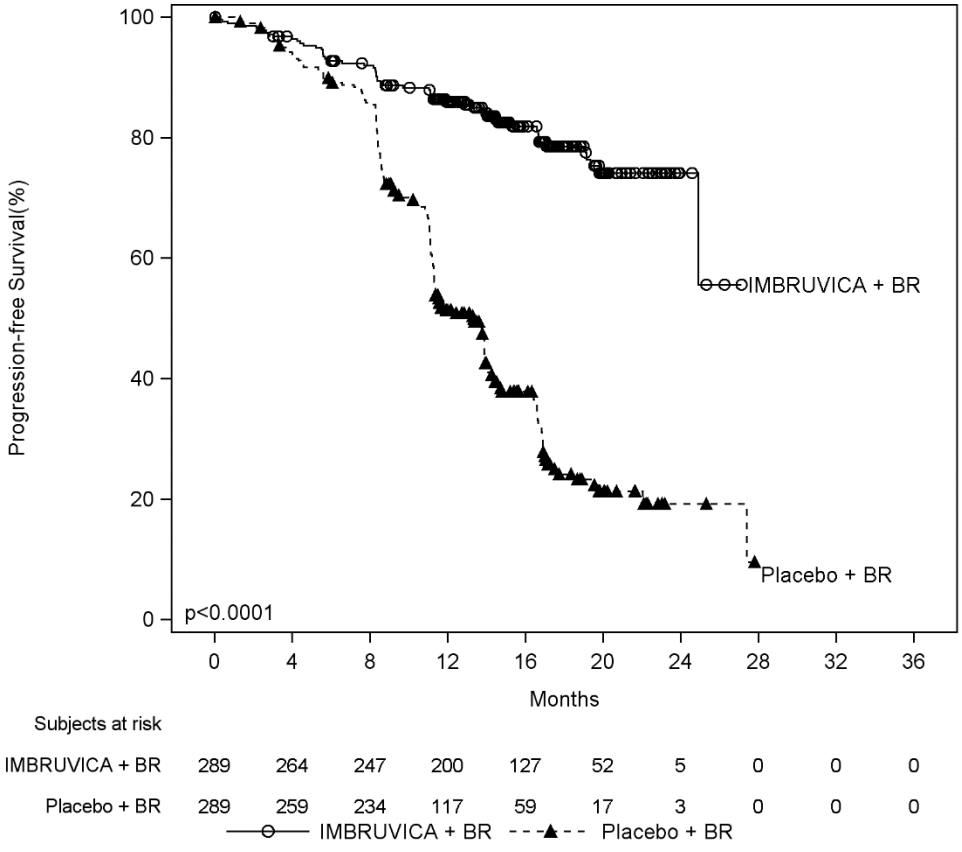
Ninety patients randomized to placebo + BR crossed over to receive IMBRUVICA following IRC confirmed progression. The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis 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 15 and the Kaplan-Meier curves for PFS are shown in Figure 13.

Table 15: 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 13: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study CLL3001



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

PCYC-1118E
An open-label, multicentre, single arm trial (PCYC-1118E) was conducted in 63 previously treated patients. The median age was 63 years (range, 44 to 86 years), 76% were male, and 95% were

Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 74 months, and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL (range, 0.7 to 8.4 g/dL), and 60% of patients were 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 16.

Table 16: 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)
CR (%)	0
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; CR = complete 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 randomised 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with rituximab until disease progression or unacceptable toxicity. Rituximab was administered weekly at a dose of 375 mg/m^2 for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 consecutive weeks (weeks 17-20).

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were Caucasian. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were treatment-naïve, and 55% of patients were previously treated. The median time since diagnosis was 52.6 months (treatment-naïve patients = 6.5 months and previously treated patients = 94.3 months). Among previously treated patients, the median number of prior treatments was 2 (range, 1 to 6 treatments). At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), 63% of patients were anaemic (haemoglobin ≤11 g/dL) 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 17 and the Kaplan-Meier curve for PFS is shown in Figure 14. PFS hazard ratios for treatment-naïve patients, previously treated patients, and patients with or without MYD88 L265P mutations were consistent with the PFS hazard ratio for the ITT population.

Table 17: 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

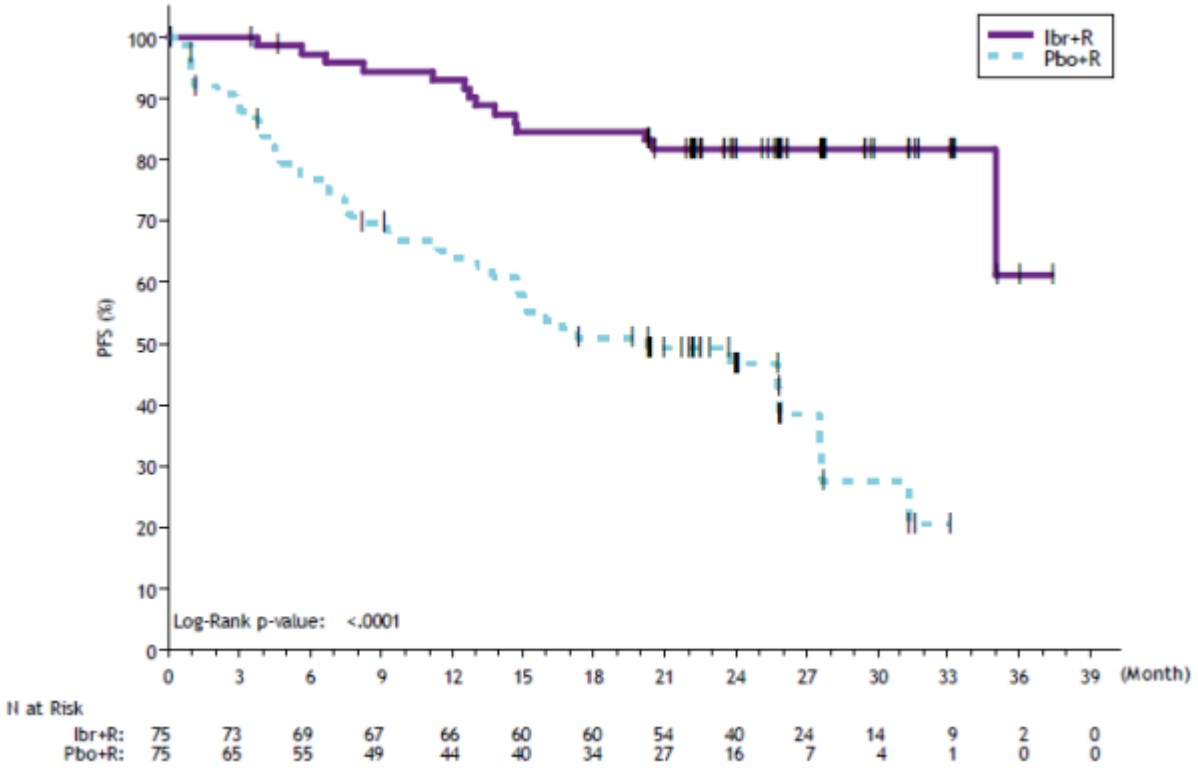
[a] IRC evaluated.

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



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

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. Median PFS per IRC assessment was not reached (95% CI: 27.4, NE); the 30-month landmark estimate was 57.5% (95% CI: 38.2, 72.7).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Ibrutinib is rapidly absorbed after oral administration with a median T_{max} of 1 to 2 hours. Absolute bioavailability in fasted condition (n = 8) was 2.9% (90% CI = 2.1 – 3.9) and doubled when combined with a meal. Pharmacokinetics of ibrutinib does not significantly differ in patients with different B cell malignancies. Ibrutinib exposure increases with doses up to 840 mg. The steady state AUC observed in patients at 560 mg is (mean ± standard deviation) 953 ± 705 ng·h/mL. Administration 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 metabolised primarily by cytochrome P450, CYP3A4, 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, two subjects genotyped as poor metabolisers for CYP2D6, showed a similar pharmacokinetic profile as extensive metabolisers. 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). Hydration should be maintained and serum creatinine levels monitored periodically. 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.

Race

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

Body weight

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

Co-administration with transporter substrates/inhibitors

In vitro studies indicated that ibrutinib is not a substrate of P gp, nor other major transporters, except OCT2. The dihydrodiol metabolite and other metabolites are P gp substrates. Ibrutinib is an *in vitro* inhibitor of OCT2, P gp and BCRP (see **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)**.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ibrutinib has no genotoxic properties when tested for mutagenicity in bacteria or clastogenicity in *in vitro* assays (chromosomal aberration in Chinese hamster ovary cells) or *in vivo* (mouse micronucleus test).

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 based on plasma AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsules

Each ibrutinib capsule also contains the following inactive ingredients:

croscarmellose sodium;

magnesium stearate;

microcrystalline cellulose;

sodium lauryl sulfate.

The capsule shell contains:

gelatin;

OPOACODE monogramming ink S-1-17822 BLACK (ARTG PI No: 12390)

OPACODE monogramming ink S-1-17823 BLACK (ARTG PI No: 12108)

Film-coated tablets

Each ibrutinib tablet also contains the following inactive ingredients:

colloidal anhydrous silica

croscarmellose sodium

lactose monohydrate

magnesium stearate

microcrystalline cellulose

povidone

sodium lauryl sulfate

The film-coating contains:

OPADRY II Complete Film Coating System 85F210036 GREEN (140 mg tablets, 420 mg tablets) (ARTG PI No. 112970)

OPADRY II Complete Film Coating System 85F200011 PURPLE (280 mg tablets) (ARTG PI No. 119906)

OPADRY II Complete Film Coating System 85F32547 YELLOW (560 mg tablets) (ARTG PI No. 119892)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Capsules

IMBRUVICA 140 mg ibrutinib 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 two polyvinyl chloride (PVC) laminated with polychlorotrifluoroethylene (PCTFE) / aluminum push-through blisters of 5 film-coated tablets in a cardboard wallet.

The pack sizes are cartons of 30 film-coated tablets (3 cardboard wallets containing 10 film-coated tablets each).

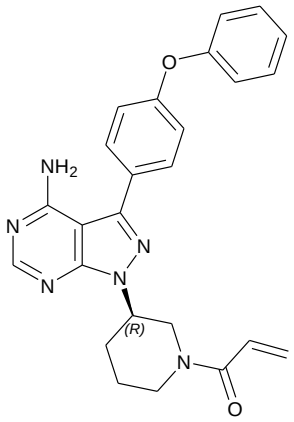
Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



The chemical name of the ibrutinib is 1 [(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4 d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one.

Molecular formula: $C_{25}H_{24}N_6O_2$ Molecular weight: 440.50

CAS number

936563-96-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Janssen-Cilag Pty Ltd,

1-5 Khartoum Road,

Macquarie Park NSW 2113 Australia

NZ Office: Auckland New Zealand

9. DATE OF FIRST APPROVAL

20 April 2015

10. DATE OF REVISION

27 May 2025

Co-developed with Pharmacyclics

Summary table of changes

Section changed	Summary of new information
4.8	Added acute kidney injury and pyogenic granuloma as new adverse reactions