IMBRUVICA®

ibrutinib

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

IMBRUVICA® 140 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IMBRUVICA is supplied as white opaque capsules that contain 140 mg ibrutinib as the active ingredient.

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

3. PHARMACEUTICAL FORM

Capsule

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

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 should be swallowed whole with water and should not be opened, broken, or chewed. IMBRUVICA must not be taken with grapefruit juice.

IMBRUVICA should continue until disease progression or no longer tolerated by the patient.

Mantle Cell Lymphoma

The recommended dose of IMBRUVICA for MCL is 560 mg (four 140 mg capsules) once dailyuntil 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 (three 140 mg capsules) once daily until disease progression or no longer tolerated by the patient.

The recommended dose of IMBRUVICA for CLL/SLL when used in combination with bendamustine and rituximab (BR) (administered every 28 days for up to 6 cycles) is 420 mg (three 140 mg capsules) orally once daily until disease progression or no longer tolerated by the patient. For additional information concerning BR, see the corresponding local BR prescribing information.

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 ≥ 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), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue IMBRUVICA.

Recommended dose modifications for these toxicities are described below.

Toxicity occurrence	**MCL dose modification after recovery**	**CLL/SLL/WM dose modification after recovery**
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	

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 capsules 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).

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.

4.4 Special warnings and precautions for use

Bleeding-related events

There have been reports of haemorrhagic events in patients treated with ibrutinib, both with and without thrombocytopenia. These include minor haemorrhagic events such as contusion, epistaxis, and petechiae; and major haemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial haemorrhage, and haematuria.

Patients were excluded from participation in ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed (see section 5.1). Use of ibrutinib in patients requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding.

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 holding ibrutinib. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in patients treated with ibrutinib. Some of these infections have been associated with hospitalisation and death. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in patients treated with ibrutinib. Patients should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

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 events

Atrial fibrillation and atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in patients treated with ibrutinib, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor patients clinically for cardiac arrhythmia. Patients who develop arrhythmic symptoms (e.g., palpitations, light-headedness, syncope, chest discomfort or new onset of dyspnoea) should be evaluated clinically and if indicated have an ECG performed. For cardiac arrhythmias which persists, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines.

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.

Tumour lysis syndrome

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

Non melanoma skin cancer

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

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 1**. 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 1.**

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 1**. 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 1 Recommended dose modifications are described below:

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

[a] Monitor for adverse reactions to IMBRUVICA and interrupt or modify dose as recommended (see 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*. Therefore, it is unlikely that IMBRUVICA has any clinically relevant drug-drug interactions with drugs that may be metabolized by the CYP450 enzymes.

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 B3

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. Those using hormonal methods of birth control must add a second barrier method. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a foetus. The time period following treatment with IMBRUVICA where it is safe to become pregnant is unknown.

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 981 patients treated with IMBRUVICA, 62% were 65 years of age or older. Grade 3 or higher pneumonia occurred more frequently (>5%) among elderly patients treated with IMBRUVICA ≥ 65 years of age versus patients <65 years of age.

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 2**).

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 2** 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 2: 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

		Frequency	
System Organ Class	**Adverse Reaction**	**All grades (%)**	**Grades 3 or 4 (%)**
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 3** 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 3: 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 study (Study PCYC-1102-CA) and three randomized clinical studies (Study PCYC-1115-CA, Study PCYC-1112-CA and Study CLL3001) in patients with CLL/SLL (668).

The most commonly occurring adverse reactions in studies PCYC-1102-CA, PCYC-1112-CA, PCYC-1115-CA and CLL3001 (≥ 20%), were diarrhoea, neutropenia, musculoskeletal pain, haemorrhage (eg. bruising), rash, nausea, pyrexia and thrombocytopenia,.

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

Discontinuation and dose reduction due to AEs

Six percent of patients receiving ibrutinib in studies PCYC-1102-CA, PCYC-1112-CA, PCYC-1115-CA and CLL3001 discontinued treatment due to adverse events. These included

pneumonia, atrial fibrillation, haemorrhage, neutropenia, rash and sepsis. Adverse events leading to dose reduction occurred in approximately 5% of patients.

Patients with previously untreated CLL/SLL

Adverse reactions described below in **Table 4** 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 4: 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

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

Adverse reactions described in **Table 5** 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 5: Adverse reactions reported in patients with CLL/SLL treated with IMBRUVICA as single agent in Study PCYC-1112-CAa,

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
System Organ Class Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Infections and infestations				
Upper respiratory tract infection	16	1	10	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin infection*	7	2	3	1
Sepsis*	4	2	4	3
Blood and lymphatic system disorders				
Anemia	23	5	17	8
Neutropenia	22	16	15	14
Thrombocytopenia	17	6	12	4
Lymphocytosis	4	2	3	1
Leukocytosis	4	3	1	0
Febrile neutropenia	2	2	3	3
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Eye disorders				
Vision blurred	10	0	3	0
Cardiac disorders				
Atrial fibrillation	5	3	1	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	9	0	3	1
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Bruising*	21	0	4	0
Petechiae	14	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
General disorders and administration site conditions				
Pyrexia	24	2	15	1

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
System Organ Class Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
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 6** 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 6: 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.

The most commonly occurring adverse reactions in the WM study (≥ 20%) were neutropenia, thrombocytopenia, diarrhoea, rash, nausea, muscle spasms, and fatigue.

Discontinuation and dose reduction due to ARs

Six percent of patients receiving IMBRUVICA in the WM trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 11% of patients.

Adverse reactions described below in **Table 7** reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM study.

Table 7: 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.

Postmarketing data

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

System Organ Class: Cardiac disorders

Rare: Ventricular tachyarrhythmias*†

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: Skin and subcutaneous tissue disorders

Uncommon: Onychoclasis

Rare: Panniculitis*

Rare: Stevens-Johnson syndrome

Very rare: Angioedema, erythema, urticaria.

System Organ Class: Hepatobiliary disorders

Very rare: Hepatic failure*

System Organ Class: Nervous system disorders

Uncommon: Peripheral neuropathy*

*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: L01XE27

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*.

Lymphocytosis

Upon initiation of treatment, 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 treated with ibrutinib as a single agent. 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 with chemoimmunotherapy, lymphocytosis was infrequent (7% with IMBRUVICA + BR versus 6% with placebo + BR).

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.

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 8**.

Table 8: 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)

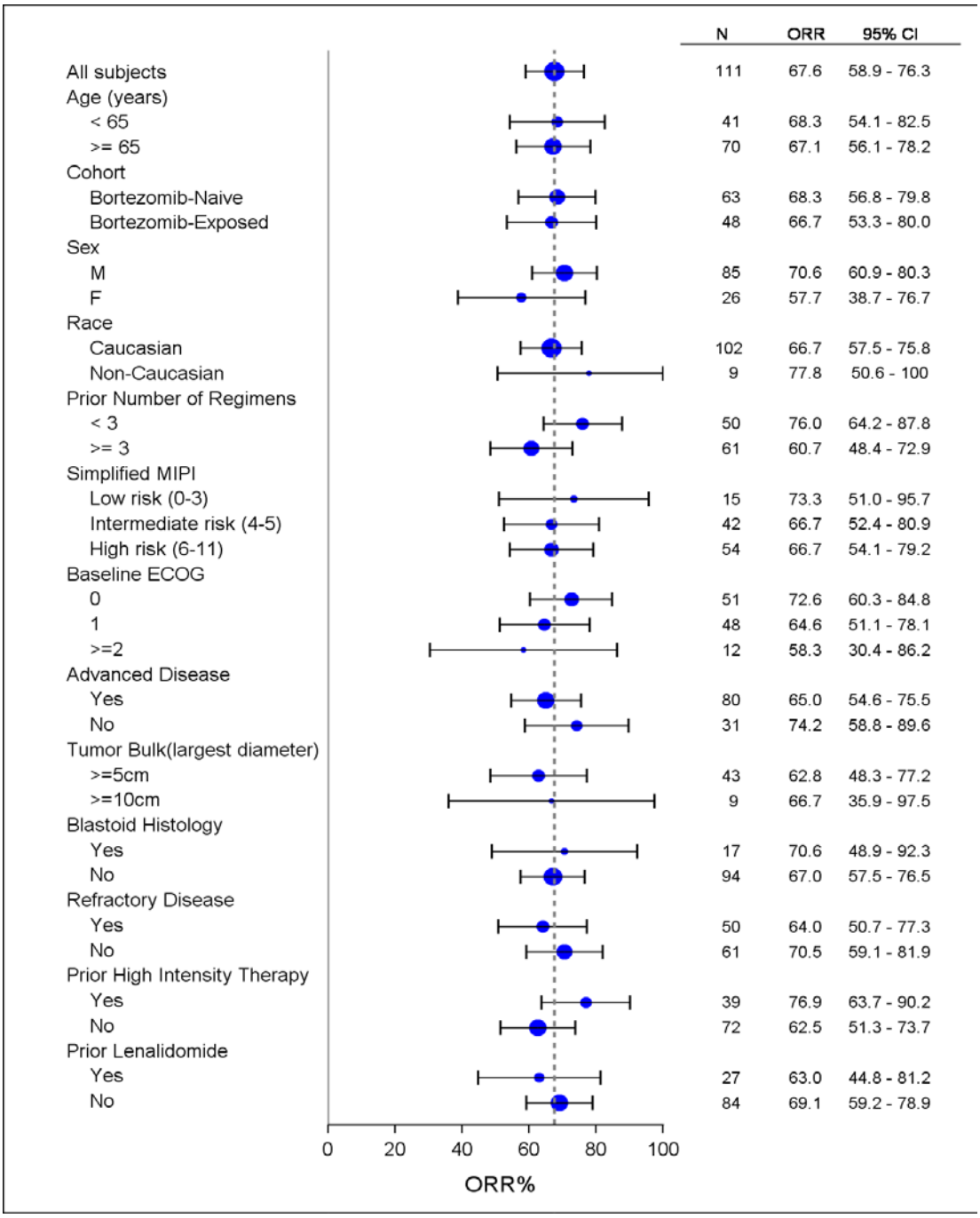
Median Time to Initial Response, months (range)	1.9 (1.4-13.7)
Median Time to CR, months (range)	5.5 (1.7, 11.5)

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 9** and the Kaplan-Meier curve for PFS **Figure 2**.

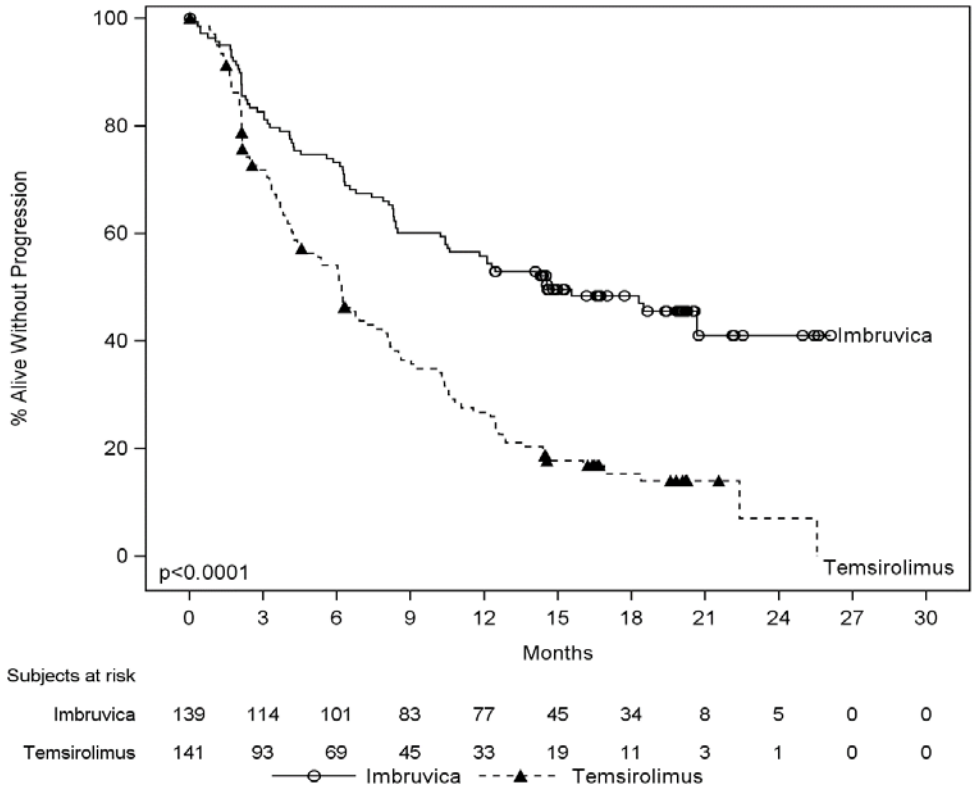
Table 9: Efficacy results in Study MCL3001

Endpoint	**ibrutinib N=139**	**temsirolimus N=141**
Progression Free Survivala		
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	

[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 two randomised, controlled studies.

Single agent

Patients with treatment naïve CLL/SLL

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 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, and 20% of patients presented with del11q.

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%). 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 10** 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 10: 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)
HRb (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

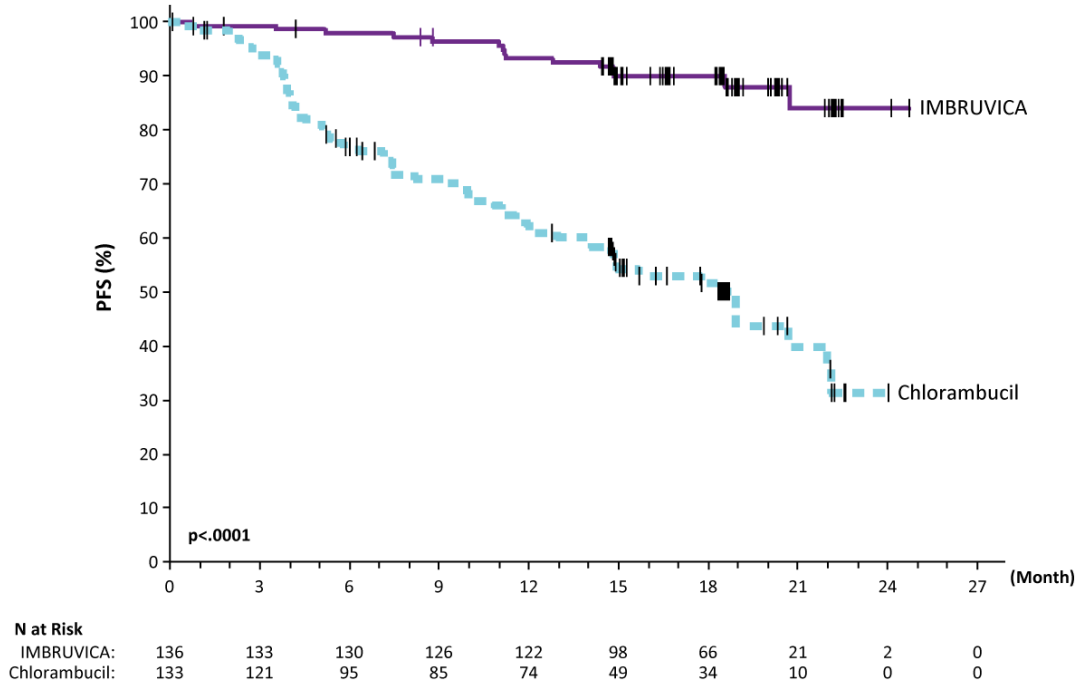
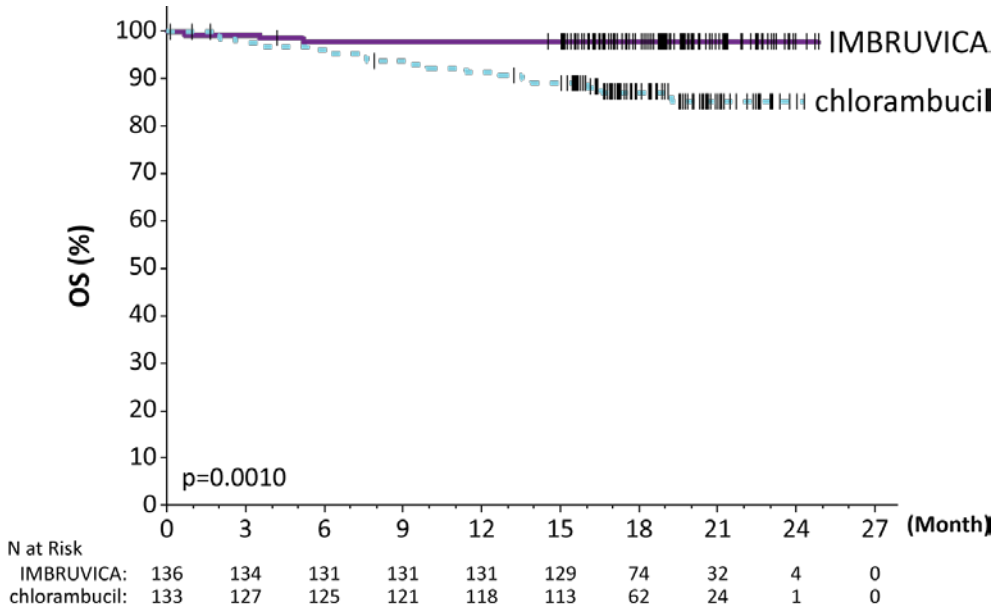


Figure 4: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1115-CA



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

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 11**.

Table 11: 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 and 31% had 11q deletion.

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. Analysis of overall survival (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 12**.

Table 12: 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.

The Kaplan-Meier curves for PFS and OS are shown in **Figure 5** and **Figure 6**, respectively.

Figure 5: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1112-CA

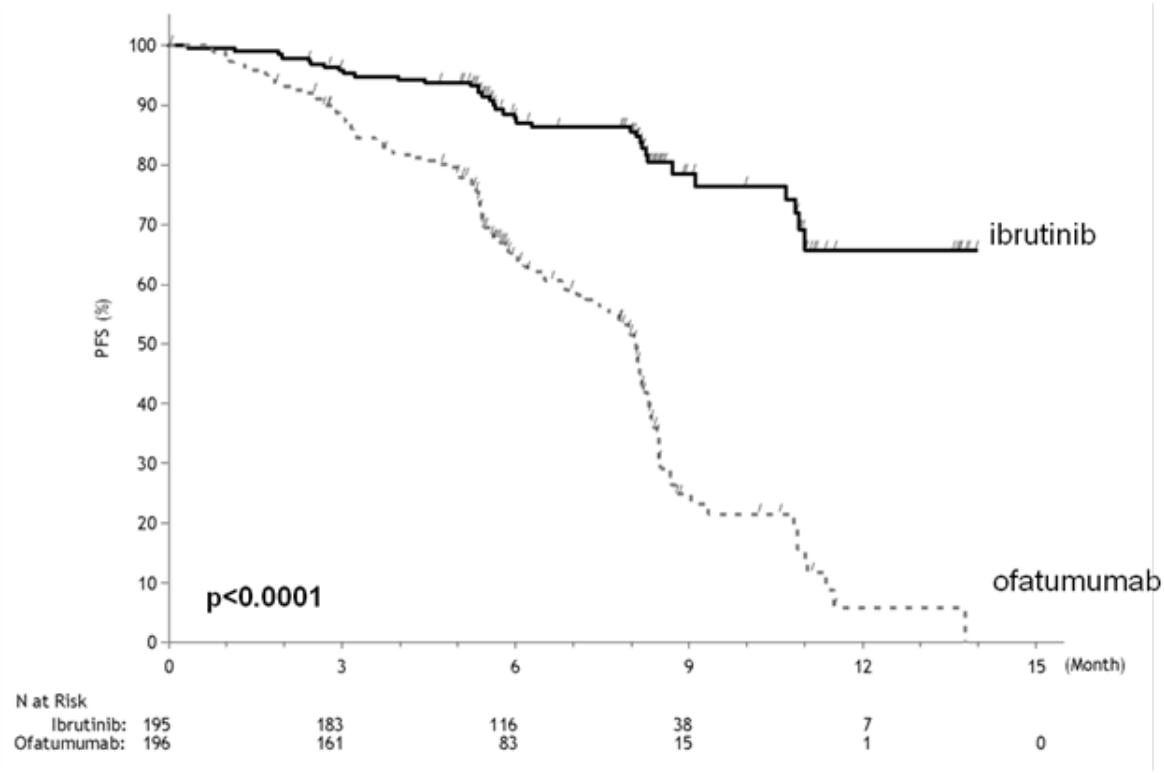
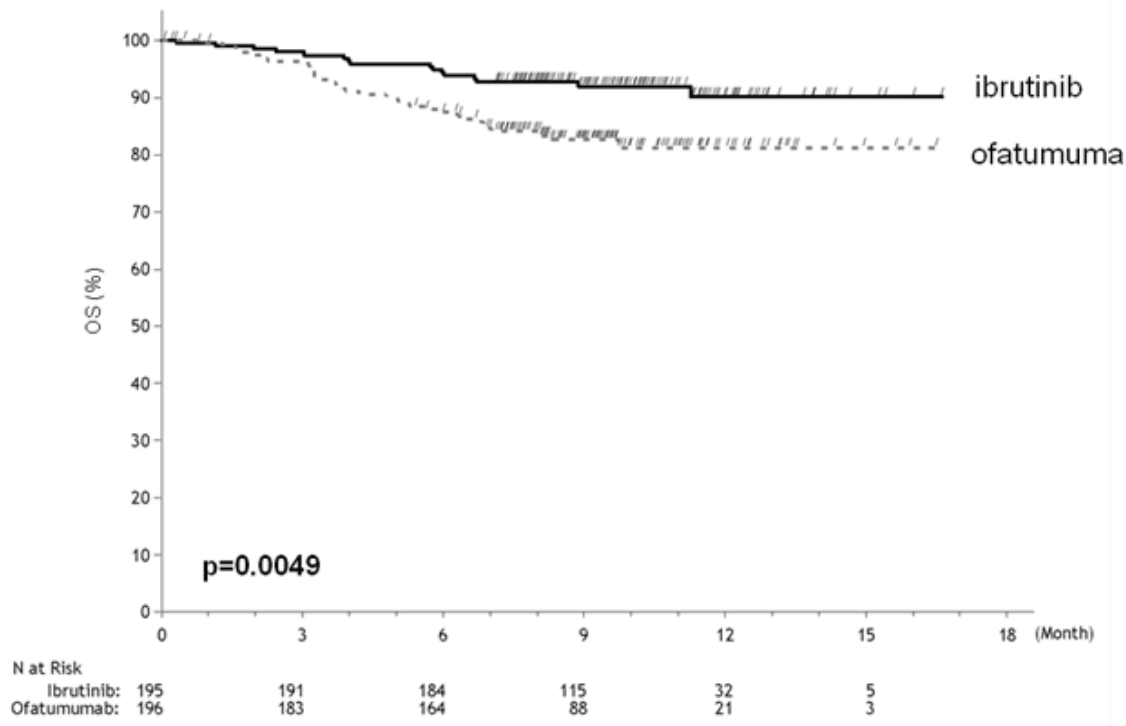
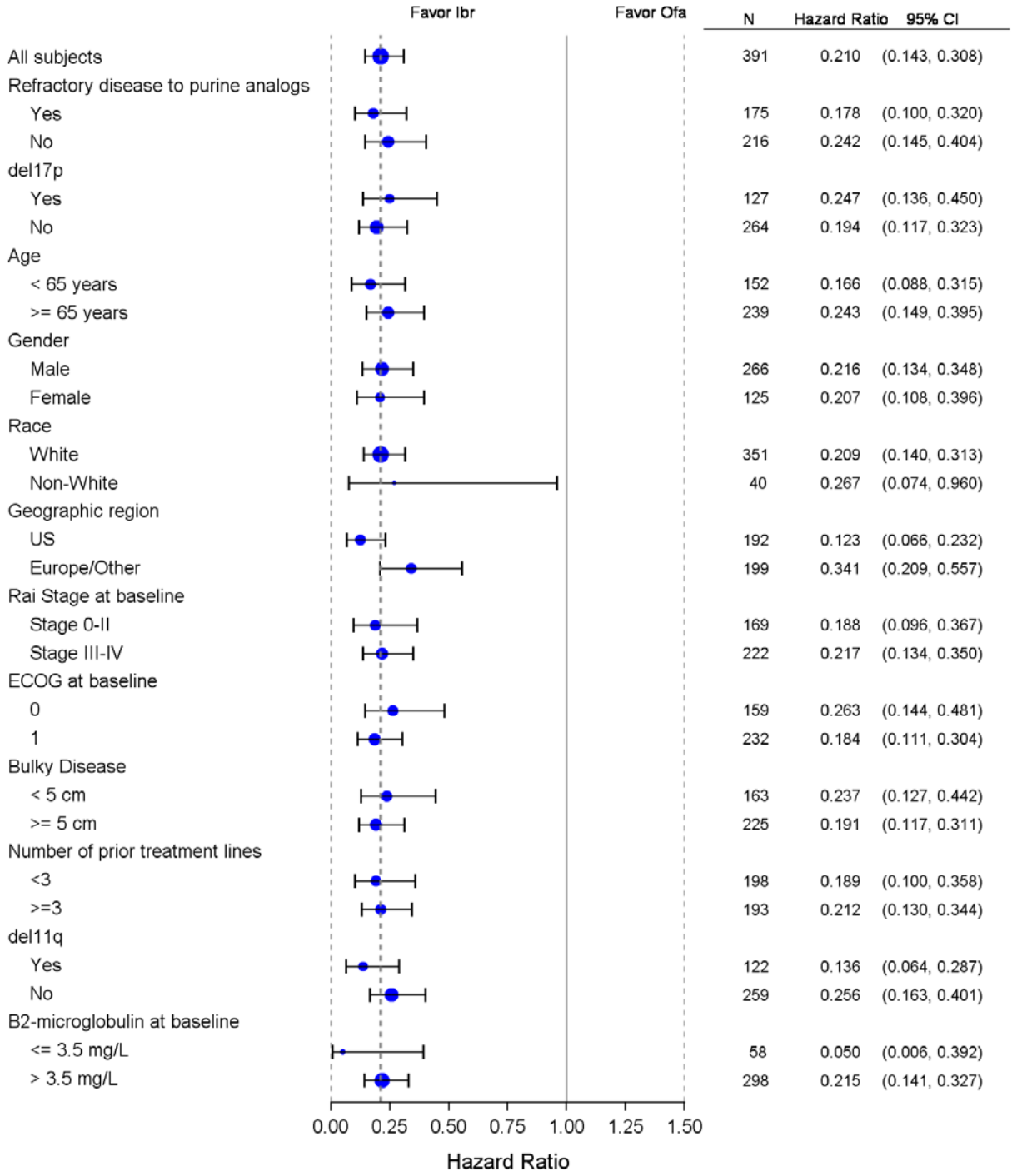


Figure 6: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1112-CA



The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (**Figure 7**).

Figure 7: Subgroup Analysis of Progression Free Survival by IRC (Study PCYC-1112-CA; 420 mg)



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.

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 13** and the Kaplan-Meier curves for PFS are shown in **Figure 8**.

Table 13: 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

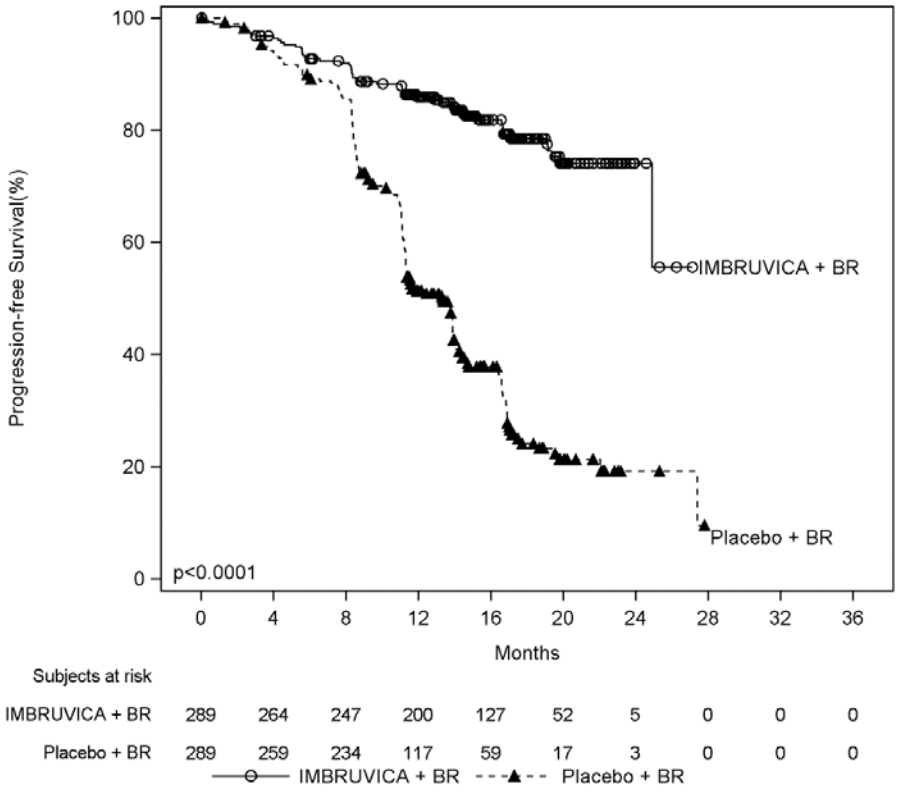
[a] IRC evaluated, ORR (CR, Cri, nPR, PR)

[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 8: 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 14**.

Table 14: Overall response rate (ORR) and duration of response (DOR) based on investigator assessment in patients with WM

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

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.

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

Carcinogenicity studies have not been conducted with ibrutinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium

Magnesium stearate

Microcrystalline cellulose

Sodium lauryl sulfate.

The capsule shell contains:

Gelatin

Titanium dioxide

Black ink.

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 months

6.4 Special precautions for Storage

Store below 30°C.

6.5 Nature and contents of container

IMBRUVICA capsules are supplied in a white HDPE bottle with a child resistant closure.

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

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

7 November 2018

Co-developed with Pharmacyclics

Summary table of changes

Section changes	Summary of new information
4.8 5.1	Addition of 'peripheral neuropathy' as postmarketing adverse reaction Minor editorial changes to Clinical trials section