PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrIMBRUVICA®

ibrutinib

tablets 140 mg, 280 mg, 420 mg, 560 mg

capsules 140 mg

Bruton's Tyrosine Kinase (BTK) Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet / 140 mg, 280 mg, 420 mg, 560 mg	Lactose monohydrate. *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*
Oral	Capsule / 140 mg	*For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

IMBRUVICA® (ibrutinib) is indicated for the treatment of patients with previously untreated active chronic lymphocytic leukemia (CLL), including those with 17p deletion.

> Clinical effectiveness of IMBRUVICA® in previously untreated patients with CLL with 17p deletion is based on the benefit observed in patients with CLL with 17p deletion who have received at least one prior therapy. Clinical trial data in previously untreated patients with CLL with 17p deletion are very limited.

IMBRUVICA® (ibrutinib) is indicated for the treatment of patients with CLL who have received at least one prior therapy, including those with 17p deletion.

IMBRUVICA® (ibrutinib) is indicated in combination with bendamustine and rituximab for the treatment of patients with CLL who have received at least one prior therapy.

> Clinical trial data with IMBRUVICA® in combination with bendamustine and rituximab in patients with CLL with 17p deletion are limited.

IMBRUVICA® (ibrutinib) is indicated for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL).

IMBRUVICA® (ibrutinib) is indicated for the treatment of patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

IMBRUVICA® (ibrutinib) is indicated for the treatment of patients with Waldenström's macroglobulinemia (WM).

Clinical effectiveness of IMBRUVICA® is based on response rates demonstrated in a single-arm study in patients who had received at least one prior therapy.

IMBRUVICA® (ibrutinib) is indicated in combination with rituximab for the treatment of patients with WM.

IMBRUVICA® (ibrutinib) is indicated for the treatment of patients with steroid dependent or refractory chronic graft versus host disease (cGVHD).

Geriatrics (≥65 years of age):
In studies of patients with B-cell malignancies treated with IMBRUVICA®, approximately 60% were ≥65 years of age. No overall differences in the efficacy of IMBRUVICA® treatment were observed between these patients and younger patients. Grade 3 or higher adverse events, serious adverse events, adverse events leading to drug discontinuation, and fatal adverse events occurred more frequently among elderly patients treated with IMBRUVICA® than among younger patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

A study of 42 patients with cGVHD treated with IMBRUVICA® did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.

Pediatrics (<18 years of age):
The safety and efficacy of IMBRUVICA® in children and adolescents have not been evaluated.

CONTRAINDICATIONS

IMBRUVICA® is contraindicated in patients who have known hypersensitivity to ibrutinib or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

IMBRUVICA® should only be prescribed by a qualified physician who is experienced in the use of anti-cancer agents.

- Major bleeding events, some fatal, have been reported (see **Hemorrhage**, below)
- IMBRUVICA® should not be used in patients with moderate or severe hepatic impairment (see **Special Populations**, below)
- Concomitant use of IMBRUVICA® with a strong CYP3A inhibitor should be avoided (see **Drug Interactions**)

General

Effects on Ability to Drive and Use Machines

Fatigue, dizziness and asthenia have been reported very commonly in patients taking IMBRUVICA® and should be considered when assessing a patient's ability to drive or operate machines.

Carcinogenesis and Mutagenesis

Second Primary Malignancies

In the pooled safety database, non-melanoma skin cancers occurred in 6% of patients treated with IMBRUVICA® (see **ADVERSE REACTIONS, Non-melanoma skin cancer**). Non-skin related malignancies occurred in 2% of patients in the pooled safety database. Monitor patients for the appearance of non-melanoma skin cancers. No carcinogenicity studies have been done.

Cardiovascular

Cardiac Arrhythmias

Patients treated with IMBRUVICA® reported events of atrial fibrillation (including Grade ≥3 events), atrial flutter, and ventricular tachyarrhythmia (including some fatal events), particularly patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**).

Periodically monitor all patients clinically for cardiac arrhythmia. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed. Cardiac arrhythmias should be managed appropriately, and if they persist, consider the benefits and risks of IMBRUVICA® treatment (including a potential increase in the risk of hemorrhage with concomitant use of anticoagulant or antiplatelet agents; see **WARNINGS AND PRECAUTIONS, Hemorrhage**) and follow the dose modification guidelines (see **DOSAGE AND ADMINISTRATION**).

PR Interval Prolongation

IMBRUVICA® causes a dose- and concentration-dependent prolongation of the PR interval of the electrocardiogram (see **DRUG INTERACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**). Caution should be observed in patients with pre-existing conduction system abnormalities (e.g., marked first-degree AV block or second- or third-degree AV block, sinoatrial block) or a history of rhythm disturbances (e.g., tachyarrhythmias).

Hypertension

In the pooled safety database, hypertension occurred in 12% of the patients treated with IMBRUVICA®, with Grade 3 or 4 hypertension in 4.7% of patients. An increase in the prevalence of hypertension has been observed over time on treatment with IMBRUVICA®; see **ADVERSE REACTIONS, Long-term safety** for additional information. Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Drug Interactions

Concomitant use of IMBRUVICA® and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure significantly. Strong CYP3A inhibitors should be avoided (see **DRUG INTERACTIONS**). Grapefruit and Seville oranges must not be consumed during IMBRUVICA® treatment, as they contain moderate inhibitors of CYP3A. If a strong or moderate CYP3A inhibitor must be used, refer to the section on concomitant use of CYP3A inhibitors for IMBRUVICA® dosing recommendations (see **DRUG INTERACTIONS** and **DOSAGE AND ADMINISTRATION**).

Concomitant use of IMBRUVICA® and drugs that strongly induce CYP3A decreases ibrutinib exposure and should be avoided (see **DRUG INTERACTIONS**).

IMBRUVICA® may increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin. Dose reduction of these concomitant drugs may be necessary (see **DRUG INTERACTIONS**).

IMBRUVICA® may increase the absorption of BCRP and P-gp substrates. Therefore, narrow therapeutic range BCRP and P-gp substrates, such as methotrexate and digoxin, respectively, should be taken at least 6 hours before or after IMBRUVICA® to avoid a potential interaction in the GI tract (see **DRUG INTERACTIONS)**.

Endocrine and metabolism

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.

Gastrointestinal

Diarrhea

In the pooled safety database, diarrhea occurred in approximately 40% of the patients with B-cell malignancies treated with IMBRUVICA®, with Grade 3 or 4 diarrhea in 3% of patients (see **ADVERSE REACTIONS**). In a study of 42 patients with cGVHD treated with IMBRUVICA®, diarrhea occurred in 36% of patients, with Grade 3 or 4 diarrhea in 10% of patients.

To prevent dehydration, administer fluid and electrolyte replacement and antidiarrheal medications as needed. Follow IMBRUVICA® dose modification guidance as needed (see **DOSAGE AND ADMINISTRATION**).

Hematologic

Cytopenias

In the pooled safety database of patients treated with IMBRUVICA® as a single agent, treatment-emergent Grade 3 or 4 cytopenias, including neutropenia (14%), thrombocytopenia (6%) and anemia (6%) were reported (see **ADVERSE REACTIONS**). Patients should have their complete blood counts monitored monthly and their doses modified as necessary (see **DOSAGE AND ADMINISTRATION**).

Lymphocytosis

Upon initiation of IMBRUVICA® as a single agent in controlled CLL clinical studies, a temporary increase in lymphocyte counts (≥50% increase from baseline and above absolute lymphocyte count of 5000/μL) occurred in a majority (57% to 69%) of patients; a majority (77% to 95%) of these patients achieved resolution. The median time to treatment-emergent lymphocytosis was 1 to 2 weeks, with a median time to resolution of 12 to 14 weeks. In a study of patients with CLL receiving IMBRUVICA® in combination with bendamustine and rituximab (BR), lymphocytosis occurred in 7% of patients; median time to treatment-emergent lymphocytosis was approximately 1 week, and median time to resolution was approximately 2 weeks; 95% of these patients achieved resolution. In the MCL clinical study, lymphocytosis occurred in 35% of patients; 68% of these patients achieved resolution. The median time to treatment-emergent lymphocytosis was 1.1 weeks, with a median time to resolution of 8 weeks. In the MZL clinical study, lymphocytosis occurred in 11% of patients; all of these patients achieved resolution. The median time to treatment-emergent lymphocytosis was 1.1 week, with a median time to resolution of 11 weeks. Lymphocytosis may be a pharmacodynamic effect of the inhibition of Bruton Tyrosine Kinase (BTK)-mediated cellular homing and adhesion, and should not be considered progressive disease in the absence of other clinical findings.

Lymphocytosis was observed in less than 1% of patients with WM treated with IMBRUVICA®.

Leukostasis

Isolated cases of leukostasis have been reported in patients treated with IMBRUVICA®. Cases were typically reported within two to three weeks of ibrutinib initiation, and included cases of intracranial hemorrhage, lethargy, gait instability, and headache. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk. In patients with high number of circulating lymphocytes (>400,000/μL), consider temporarily holding IMBRUVICA® treatment, and monitor patients closely for signs of leukostasis, particularly in patients who experience a rapid increase of lymphocyte count to above 400,000/μL. Administer supportive care including hydration and/or cytoreduction as indicated.

Hemorrhage

In the pooled safety database, major hemorrhagic events (Grade ≥3), including intracranial hemorrhage (subdural hematoma, cerebral hemorrhage, subarachnoid hemorrhage), gastrointestinal bleeding, hematuria, and post-procedural hemorrhage, occurred in 3% of patients. Some events were fatal. Bleeding events of any grade, including contusion, epistaxis, and petechiae, occurred in 44% of patients treated with IMBRUVICA®, both with and without thrombocytopenia. BTK is expressed in platelets; however, the mechanism for the bleeding events is not well understood. Based on the reports of major bleeding events from the ibrutinib global safety database of clinical trials and post-marketing exposure, a numerically increased risk of bleeding was observed in patients of older age (>65 years), patients with a history of bleeding disorders, decreased baseline thrombocyte count, increased baseline lymphocyte count, and the use of anticoagulant and/or antiplatelet agents. Fatal bleeding events were due to CNS hemorrhage in most cases.

In an *in vitro* human platelet function study, ibrutinib was shown to have an inhibitory effect on collagen-induced platelet aggregation.

In clinical studies, IMBRUVICA®-treated patients using concomitant antiplatelet or anticoagulant agents had more minor bleeding events compared to those without these concomitant drugs. Patients were excluded from participation in IMBRUVICA® studies if they required warfarin or other vitamin K antagonists, or if they had a recent history of stroke or intracranial hemorrhage. Patients with congenital bleeding diathesis have not been studied.

Warfarin or other vitamin K antagonists should not be administered concomitantly with IMBRUVICA®. IMBRUVICA® should be used with caution in patients requiring other anticoagulants or medications that inhibit platelet function. If therapeutic anticoagulation is required, consider temporarily withholding IMBRUVICA® treatment until stable anticoagulation is achieved. Supplements that may have an inhibitory effect on platelet aggregation, such as fish oil, flaxseed, and vitamin E preparations, should be avoided.

IMBRUVICA® should be held at least 3 to 7 days pre and post-surgery, and reinitiated at the discretion of the physician, depending upon the type of surgery and the risk of bleeding.

Immune

Infections

In the pooled safety database, infections (including sepsis, bacterial, viral, or fungal infections) occurred in approximately 70% of patients with B-cell malignancies treated with IMBRUVICA®, with Grade 3 or 4 infections in approximately 25% of patients, and fatal infections in 2% of patients. In a study of 42 patients with cGVHD treated with IMBRUVICA®, infections occurred in 69% of patients, with Grade 3 or 4 infections in 31% of patients, and fatal infections in 5% of patients.

Most patients reporting infections, including those with fatal infections, also had neutropenia. Patients should be monitored for fever, neutropenia, and infection, 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. As ibrutinib exposure may be

affected by CYP3A inducers and inhibitors, follow IMBRUVICA® dose modification guidance as needed during anti-infective treatment (see **DRUG INTERACTIONS** and **DOSAGE AND ADMINISTRATION**).

Progressive multifocal leukoencephalopathy
Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®, although causality has not been established. Patients should be monitored for symptoms (chills, weakness, confusion), and appropriate therapy should be instituted as indicated.

Hepatitis B virus reactivation
Cases of hepatitis B reactivation have occurred in patients treated with IMBRUVICA®, although causality has not been established. Patients should be monitored for signs and symptoms (jaundice, abdominal pain, weakness, fatigue, nausea and vomiting), and appropriate therapy should be instituted as indicated.

Interstitial Lung Disease

Cases of interstitial lung disease (ILD), including cases confirmed by biopsy, have been reported in patients treated with IMBRUVICA® (see **ADVERSE REACTIONS, Overview** and **Post-Market Adverse Drug Reactions**).

Monitor patients for pulmonary symptoms indicative of ILD. Advise patients to report promptly any new or worsening respiratory symptoms. If symptoms develop, interrupt IMBRUVICA®, manage appropriately, consider the risks and benefits of IMBRUVICA® before resuming treatment, and follow the dose modification guidance (see **DOSAGE AND ADMINISTRATION**). If ILD is confirmed, discontinue IMBRUVICA®. In confirmed cases of ILD, recovery with medical management and discontinuation of IMBRUVICA® has been reported.

Peri-Operative Considerations

IMBRUVICA® should be held at least 3 to 7 days pre and post-surgery depending on the type of surgery and the risk of bleeding (see **WARNINGS AND PRECAUTIONS, Hemorrhage**).

Sexual Function/Reproduction

No human data on the effects of IMBRUVICA® on fertility are available. No effects of ibrutinib on fertility or reproductive capacities were observed in male or female rats (see **TOXICOLOGY, Reproductive and Developmental Toxicity**).

It is not known whether ibrutinib or its metabolites are present in semen. Men should be advised to not father a child or donate sperm while receiving IMBRUVICA®, and for 3 months following completion of treatment.

Special Populations

Pregnant Women

There are no adequate and well controlled studies of IMBRUVICA® in pregnant women. In studies with pregnant rats, ibrutinib was associated with increased post-implantation loss, increased visceral malformations (heart and major vessels), and decreased fetal weights. In studies with pregnant rabbits, ibrutinib was associated with increased post-implantation loss and skeletal malformations (fused sternebrae) (see **TOXICOLOGY, Reproductive and Developmental Toxicity**). Based on these findings, IMBRUVICA® 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® and for at least 3 months after ending treatment. Women who use hormonal methods of birth control must add a barrier method. If IMBRUVICA® is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA®, the patient should be apprised of the potential hazard to a fetus.

It is not known whether ibrutinib or its metabolites are present in semen. Male patients should use a condom if engaging in sexual activity with a pregnant woman while receiving IMBRUVICA® and for 3 months after treatment has stopped.

Nursing Women

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 to IMBRUVICA® in nursing infants, breastfeeding should be discontinued during IMBRUVICA® treatment.

Pediatrics (<18 years of age)

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

Geriatrics (≥65 years of age)

In patients with B-cell malignancies, no overall differences in the efficacy of IMBRUVICA® treatment were observed between patients ≥65 years of age and younger patients. Patients ≥65 years of age had higher steady-state systemic exposures of ibrutinib and the dihydrodiol metabolite compared to patients <65 years of age (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

In the pooled safety database, approximately 60% of patients with B-cell malignancies were ≥65 years of age. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA® (73% of patients age ≥65 versus 64% of younger patients). Grade ≥3 serious adverse events were also reported more frequently in elderly patients than in younger patients (45% versus 34%, respectively), as were adverse events leading to drug discontinuation (13% versus 8%, respectively) and fatal adverse events (7% versus 4%, respectively). Events reported more frequently in patients ≥65 years compared to younger patients included thrombocytopenia, pneumonia, hypertension, atrial fibrillation, and hyponatraemia.

A study of 42 patients with cGVHD treated with IMBRUVICA® did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.

Hepatic Impairment

Ibrutinib is metabolized in the liver. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥3.0x upper limit of normal (ULN) were excluded from IMBRUVICA® clinical trials. In a study in patients with hepatic impairment, data showed a significant increase in ibrutinib exposure (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**). As hepatic impairment can lead to coagulopathy, the risk of bleeding associated with IMBRUVICA® may be increased in patients with moderate or severe hepatic impairment. IMBRUVICA® should not be used in patients with moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C). Pharmacokinetic data showed comparable exposures of the unbound ibrutinib in patients with mild hepatic impairment (Child-Pugh class A) administered a 140 mg dose and patients without hepatic impairment administered a 420 mg daily dose. If the benefit is considered to outweigh the risk in a patient with mild hepatic impairment, a dose reduction to 140 mg should be considered. Monitor patients for signs of toxicity (see **DOSAGE AND ADMINISTRATION**).

Renal Impairment

Ibrutinib has minimal renal clearance. Clinical pharmacokinetic studies have not been conducted in patients with renal impairment. Patients with mild or moderate renal impairment (creatinine clearance >30 mL/min) were treated in clinical studies without adjustment of the starting dose. Hydration should be maintained and serum creatinine levels monitored periodically. There are no data in patients with severe renal impairment or patients on dialysis (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Monitoring and Laboratory Tests

Patients should have their baseline renal function and hepatic status, and coagulation status measured prior to IMBRUVICA® initiation. Patients with cardiac risk factors or a history of atrial fibrillation, or with acute infections should have their baseline ECG assessed prior to IMBRUVICA® initiation.

Patients treated with IMBRUVICA® should be monitored for symptoms of atrial fibrillation, infection, hepatitis B reactivation, fever, tumour lysis syndrome, new onset hypertension or hypertension that is not adequately controlled, and have their complete blood counts monitored monthly. Patients with renal impairment should have their serum creatinine levels monitored periodically.

ADVERSE REACTIONS

Overview

The safety of IMBRUVICA® has been assessed in completed clinical development studies as well as in the post-marketing setting.

Chronic Lymphocytic Leukemia (CLL) studies

The data described below reflect exposure to IMBRUVICA® in three controlled, randomized clinical studies (Study PCYC-1115-CA, Study PCYC-1112-CA, and Study CLL3001) and one single-arm study (Study PCYC-1102-CA) that included patients with CLL treated with 420 mg IMBRUVICA® daily, as a single agent or in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in the studies (≥20%) were diarrhea, neutropenia, musculoskeletal pain, nausea, fatigue, rash, pyrexia, anemia, bruising and thrombocytopenia. The most common Grade 3/4 adverse reactions (≥5%) were neutropenia, pneumonia, thrombocytopenia, and febrile neutropenia.

Approximately 6% of patients receiving IMBRUVICA® in the studies discontinued treatment due to adverse reactions. These adverse reactions included pneumonia, atrial fibrillation, neutropenia, rash, subdural hematoma, and diarrhea. Adverse reactions leading to dose reduction occurred in approximately 5% of patients.

Mantle Cell Lymphoma (MCL) study

The data described below reflect exposure to IMBRUVICA® in a single-arm clinical study (Study PCYC-1104-CA) that included patients with relapsed or refractory MCL treated with 560 mg IMBRUVICA® daily.

The most commonly occurring adverse reactions (≥20%) were diarrhea, fatigue, nausea, dyspnea, constipation, upper respiratory tract infection, oedema peripheral, vomiting, decreased appetite, cough and thrombocytopenia. The most common Grade 3/4 adverse reactions (≥5%) were neutropenia, thrombocytopenia, anemia, pneumonia, atrial fibrillation, abdominal pain, and diarrhea.

Approximately 11% of patients receiving IMBRUVICA® in the Study PCYC-1104-CA discontinued treatment due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in approximately 16% of patients.

Marginal zone lymphoma (MZL) study

The data described below reflect exposure to IMBRUVICA® in a single-arm clinical study (Study PCYC-1121-CA) that included 63 patients with MZL who had received at least one prior line of systemic therapy.

The most commonly occurring adverse reactions (≥ 20%) were fatigue, diarrhea, bruising, musculoskeletal pain, anemia, hemorrhage, rash, nausea, thrombocytopenia, arthralgia, edema

peripheral, cough, dyspnea and upper respiratory tract infection (see Table 9). The most commonly occurring Grade 3/4 adverse reactions (≥ 5%) were anemia, pneumonia, and fatigue.

Thirteen percent of patients discontinued treatment due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were diarrhea, ILD (i.e. pneumonitis, eosinophilic pneumonia), and rash. Adverse reactions leading to dose reduction occurred in approximately 10% of patients.

Waldenström's Macroglobulinemia (WM) studies

The data described below reflect exposure to 420 mg IMBRUVICA® daily in patients with WM, as a single agent or in combination with rituximab in an open-label, single-arm clinical study (Study PCYC-1118E) and a randomized, double-blind, controlled phase 3 study with a non-randomized substudy arm (Study PCYC-1127-CA).

The most commonly occurring adverse reactions in the WM studies (≥20%) were hemorrhage (e.g., bruising), diarrhea, musculoskeletal pain, rash, nausea, and neutropenia. The most common Grade 3/4 adverse reactions (≥5%) were neutropenia, pneumonia, hypertension, atrial fibrillation, and thrombocytopenia.

Five percent of patients receiving IMBRUVICA® in Studies PCYC-1118E and PCYC-1127-CA discontinued IMBRUVICA® treatment due to adverse reactions. Adverse reactions leading to IMBRUVICA® dose reduction occurred in 14% of patients.

Chronic graft versus host disease (cGVHD) study

The data described below reflect exposure to IMBRUVICA® in an open-label clinical study (Study PCYC-1129-CA) that included patients with cGVHD who failed first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD study (≥ 20%) were fatigue, bruising, diarrhea, stomatitis, muscle spasms, nausea, hemorrhage, and pneumonia. Grade 3/4 adverse reactions were experienced by 45% of patients. The most common Grade 3/4 adverse reactions (≥5%) were fatigue, diarrhea, pneumonia, sepsis, and hypokalemia. Atrial fibrillation occurred in one patient (2%), which was Grade 3. Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions (2 or more patients) were pneumonia, sepsis (septic shock), cellulitis, headache, and pyrexia. There were two fatal events, one case of pneumonia and one case of pulmonary aspergillosis.

Adverse reactions leading to treatment discontinuation occurred in 24% of patients, the most common being fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Non-melanoma skin cancer

The incidence of non-melanoma skin cancer in IMBRUVICA®-treated patients was approximately 6% across the following studies: PCYC-1102-CA, PCYC-1104-CA, PCYC-1112-CA, PCYC-1118E, PCYC-1115-CA, CLL3001, PCYC-1129-CA, PCYC-1121-CA and PCYC-1127-CA.

Interstitial Lung Disease

The incidence of interstitial lung disease in IMBRUVICA®-treated patients was 2% (0.3% were considered as Grade 3 or 4 in severity and a single fatal case (0.1%) was reported) across pivotal phase 2 and 3 studies in patients with CLL, MCL, MZL, WM, and cGVHD.

Atrial fibrillation

In the randomized clinical trials in patients with CLL, atrial fibrillation was reported more frequently in patients treated with 420 mg daily IMBRUVICA® (6%; Grade 3+4, 3%) than in the comparator arms (1%; Grade 3+4, 0%).

In a single-arm phase 2 clinical trial in patients with MCL (Study PCYC-1104), atrial fibrillation was reported in 10% (Grade 3+4, 6%) of patients treated with 560 mg daily IMBRUVICA®.

In the randomized clinical trial in patients with WM (Study PCYC-1127-CA), atrial fibrillation was reported more frequently in patients treated with 420 mg daily IMBRUVICA® in combination with rituximab (15%; Grade 3+4, 12%) than in the placebo + rituximab comparator arm (3%; Grade 3+4, 1%). In the single arm trials in patients with WM (Study PCYC1118E and the single-agent therapy arm of Study PCYC-1127-CA), atrial fibrillation was reported in 5% (Grade 3+4, 2%) of patients treated with 420 mg daily IMBRUVICA® as a single agent.

Long-term safety

Long-term safety data for patients with B-cell malignancies treated with IMBRUVICA® as a single agent for a median of approximately 18.3 to 24.1 months (range, 0.2 to 52.5 months) indicate that there is generally no cumulative or unique late-onset toxicity with continued IMBRUVICA® treatment. For patients treated with IMBRUVICA® in Study PCYC-1112-CA, the prevalence rate of hypertension increased from the first exposure period analyzed (>0-1 year: all grades, 8%; Grade 3, 4%) to the second exposure period (>1-2 years: all grades, 14%; Grade 3, 8%); no Grade 4 or 5 events were observed.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Adverse reactions presented in this section 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.

Previously Untreated Chronic Lymphocytic Leukemia

Adverse reactions described in Table 1 below 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. Hematologic laboratory abnormalities are described in Table 2.

Table 1: Adverse reactions† reported from Study PCYC-1115-CA

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

System Organ Class Adverse reaction	IMBRUVICA® (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)

* Includes multiple adverse reaction terms

† Adverse reactions meeting the following criteria are presented: ≥10% incidence in the IMBRUVICA® arm and ≥5% higher incidence compared to the chlorambucil arm, or serious reactions reported in ≥2% of patients in the IMBRUVICA® arm and >2% higher incidence compared to the chlorambucil arm, or biological plausibility. 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.

Less common adverse events reported in patients treated with IMBRUVICA® included:
Major hemorrhage events (4%)**:** cerebral hemorrhage (<1%), hyphema (<1%), post-procedural hemorrhage (<1%), subarachnoid hemorrhage (<1%), subdural hematoma (<1%), traumatic hematoma (<1%), vitreous hemorrhage (<1%);
Non-melanoma skin cancer: squamous cell carcinoma (4%);
Eye disorders: eye pain (6%), vitreous floaters (6%), cataract (5%), blindness unilateral (1%).

Abnormal Hematologic and Clinical Chemistry Findings (Previously Untreated CLL)

Table 2: Hematologic laboratory abnormalities (per IWCLL criteria) from Study PCYC-1115-CA

Laboratory Parameter	IMBRUVICA® N=135		Chlorambucil N=132	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hemoglobin decreased[a]	36%	0%	39%	2%
Neutrophils decreased[b]	55%	28%	67%	31%
Platelets decreased[c]	47%	7%	58%	14%

[a] Grade 1: decreased ≥10.5% to <24.5% and <lower limit of normal (LLN); Grade 2: decreased ≥24.5% to <49.5% and <LLN; Grade 3: decreased ≥49.5% to <74.5% and <LLN; Grade 4: decreased ≥74.5% and <LLN.
[b] Units=$x10^9$/L; Grade 1: ≥1.5 to <2.0; Grade 2: ≥1.0 to <1.5; Grade 3: ≥0.5 to <1.0; Grade 4: <0.5.
[c] Grade 1: decreased ≥10.5% to <24.5% and <LLN; Grade 2: decreased ≥24.5% to <49.5% and <LLN; Grade 3: decreased ≥49.5% to <74.5% and <LLN; Grade 4: decreased ≥74.5% and <LLN, or <$20x10^9$/L.

Previously Treated Chronic Lymphocytic Leukemia

Single-agent therapy

Adverse reactions described in Table 3 below reflect exposure to IMBRUVICA® 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. Hematologic laboratory abnormalities are described in Table 4.

Table 3: Adverse reactions† reported from Study PCYC-1112-CA

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

	IMBRUVICA® (N=195)		Ofatumumab (N=191)	
System Organ Class Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Leukocytosis	4	3	1	0
Febrile neutropenia	2	2	3	3
Cardiac disorders				
Atrial fibrillation	5	3	1	0
Eye disorders				
Vision blurred	10	0	3	0
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
General disorders and administration site conditions				
Pyrexia	24	2	15	1
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
Injury, poisoning and procedural complications				
Subdural hematoma	1	0	0	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	9	0	3	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Bruising*	21	0	4	0
Petechiae	14	0	1	0

* Includes multiple adverse reaction terms.

† Adverse reactions 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 that are biologically plausible are presented. 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.

Isolated cases of leukostasis have been observed (see **WARNINGS AND PRECAUTIONS, Hematologic**).

Long-term safety data for patients treated with IMBRUVICA® in Study PCYC-1112-CA indicate a generally consistent safety profile with no cumulative or late-onset toxicity after a median duration of exposure of 18.3 months compared with 8.6 months. The prevalence rate of hypertension increased from the first exposure period analyzed (>0-1 year: all grades, 8%; Grade 3, 4%) to the second exposure period (>1-2 years: all grades, 14%; Grade 3, 8%); no Grade 4 or 5 events were observed.

Abnormal Hematologic and Clinical Chemistry Findings (Previously Treated CLL, single agent therapy)

Table 4: Hematologic laboratory abnormalities (per IWCLL criteria) from Study PCYC-1112-CA

Laboratory Parameter	IMBRUVICA® N=195		Ofatumumab N=191	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hemoglobin decreased[a]	36	0	21	0
Neutrophils decreased[b]	51	23	57	26
Platelets decreased[c]	52	5	45	10

[a] Grade 1: decreased ≥10.5% to <24.5% and <lower limit of normal (LLN); Grade 2: decreased ≥24.5% to <49.5% and <LLN; Grade 3: decreased ≥49.5% to <74.5% and <LLN; Grade 4: decreased ≥74.5% and <LLN.
[b] Units=x10^9/L; Grade 1: ≥1.5 to <2.0; Grade 2: ≥1.0 to <1.5; Grade 3: ≥0.5 to <1.0; Grade 4: <0.5.
[c] Grade 1: decreased ≥10.5% to <24.5% and <LLN; Grade 2: decreased ≥24.5% to <49.5% and <LLN; Grade 3: decreased ≥49.5% to <74.5% and <LLN; Grade 4: decreased ≥74.5% and <LLN, or <20x10^9/L.

Combination therapy

Adverse reactions described in Table 5 below reflect exposure to IMBRUVICA® in combination with bendamustine and rituximab (BR) with a median duration of 14.7 months and exposure to placebo in combination with BR with a median duration of 12.8 months in Study CLL3001. Bendamustine and rituximab were administered for up to 6 cycles, while IMBRUVICA® or placebo were administered daily for the duration of the study. Hematologic laboratory abnormalities are described in Table 6.

Table 5: Adverse reactions† reported from Study CLL3001

System Organ Class Adverse Reaction Term	IMBRUVICA®+BR (N=287)		Placebo+BR (N=287)	
	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				
Diarrhea	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	12	<1	5	0

Events are sorted by system organ class and by decreasing frequency of adverse reaction term in the IMBRUVICA®+BR arm.
†Adverse reactions meeting the following criteria are presented: TEAE with ≥10% incidence and ≥5% greater in the IMBRUVICA®+BR arm when compared to the placebo+BR arm; Serious TEAE with ≥2% incidence and ≥2% greater in the IMBRUVICA®+BR arm when compared to the placebo+BR arm.
* Includes multiple adverse reaction terms
<1 used for frequency below 0.5%

Abnormal Hematologic and Clinical Chemistry Findings (CLL, combination therapy)

Table 6: Hematologic laboratory abnormalities (per IWCLL criteria) from Study CLL3001

Laboratory Parameter	IMBRUVICA®+BR (N=287)		Placebo+BR (N=287)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hemoglobin decreased[a]	54	2	61	3
Neutrophils decreased[b]	90	72	88	70
Platelets decreased[c]	83	33	82	27

[a] Grade 1: decreased ≥10.5% to <24.5% and <lower limit of normal (LLN); Grade 2: decreased ≥24.5% to <49.5% and <LLN; Grade 3: decreased ≥49.5% to <74.5% and <LLN; Grade 4: decreased ≥74.5% and <LLN.
[b] Units=$x10^9$/L; Grade 1: ≥1.5 to <2.0; Grade 2: ≥1.0 to <1.5; Grade 3: ≥0.5 to <1.0; Grade 4: <0.5.
[c] Grade 1: decreased ≥10.5% to <24.5% and <LLN; Grade 2: decreased ≥24.5% to <49.5% and <LLN; Grade 3: decreased ≥49.5% to <74.5% and <LLN; Grade 4: decreased ≥74.5% and <LLN, or <$20x10^9$/L.

Mantle Cell Lymphoma

Adverse reactions described in Table 7 below reflect exposure to IMBRUVICA® (560 mg daily) with a median treatment duration of 8.3 months in Study PCYC-1104-CA. Patients received IMBRUVICA® until disease progression or unacceptable toxicity. Hematologic laboratory abnormalities are described in Table 8.

Table 7: Adverse reactions† reported from Study PCYC-1104-CA (N=111)

		Frequency	
System Organ Class	**Adverse Reaction**	**All grades (%)**	**Grades 3 or 4 (%)**
Blood and lymphatic system disorders	Thrombocytopenia	22	13
	Neutropenia	19	17
	Anemia	18	11
	Febrile neutropenia	4	4
Cardiac disorders	Atrial fibrillation	11	6
Gastrointestinal disorders	Diarrhea	54	5
	Nausea	33	1
	Constipation	29	0
	Vomiting	25	0
	Abdominal pain	20	5
	Stomatitis	14	1
	Dyspepsia	12	0
General disorders and administration site conditions	Fatigue	50	5
	Edema peripheral	26	2
	Pyrexia	19	1
	Asthenia	14	3
Infections and infestations	Upper respiratory tract infection	28	0
	Urinary tract infection	16	4
	Sinusitis	15	1
	Pneumonia	14	7
Injury, poisoning and procedural complications	Contusion	18	0
	Subdural hematoma	4	2
Metabolism and nutrition disorders	Decreased appetite	24	2
	Hyperuricemia	17	5
	Dehydration	14	4
Musculoskeletal and connective tissue disorders	Back pain	15	1
	Arthralgia	18	0
	Muscle spasms	14	0
	Myalgia	16	0
	Pain in extremity	14	0
Nervous system disorders	Dizziness	14	0
	Headache	14	0
Psychiatric disorders	Insomnia	11	0
Renal and urinary disorders	Renal failure acute	5	2
Respiratory, thoracic and mediastinal disorders	Dyspnea	32	4
	Cough	22	0
	Epistaxis	11	0
Skin and subcutaneous tissue disorders	Rash	18	2
	Pruritus	11	0
Vascular disorders	Hypertension	11	5

† Adverse reactions occurring at ≥10% incidence or serious adverse reactions ≥2% incidence are presented.

Serious adverse reactions were reported in approximately 60% of patients (treatment-emergent frequencies).

Isolated cases of leukostasis have been observed (see **WARNINGS AND PRECAUTIONS, Hematologic**).

Abnormal Hematologic and Clinical Chemistry Findings (MCL)

Table 8: Hematologic laboratory abnormalities (per CTCAE criteria) from Study PCYC-1104-CA

Laboratory Parameter	IMBRUVICA® (N=111)	
	All Grades (%)	Grades 3 or 4 (%)
Hemoglobin decreased[a]	39	4
Neutrophils decreased[b]	46	24
Platelets decreased[c]	57	14

[a] Units=g/L; grade 1: ≥100 to <lower limit of normal; grade 2: ≥80 to <100; grade 3: <80.
[b] Units=x10^9/L; grade 1: ≥1.5 to <lower limit of normal; grade 2: ≥1.0 to <1.5; grade 3: ≥0.5 to <1.0; grade 4: <0.5.
[c] Units=10^9/L; grade 1: ≥75.0 to <lower limit of normal; grade 2: ≥50.0 to <75.0; grade 3: ≥25.0 to <50.0; grade 4: <25.0.

Marginal zone lymphoma

Adverse reactions described in Table 9 below reflect exposure to IMBRUVICA® with a median treatment duration of 11.6 months in study PCYC-1121-CA. Patients received IMBRUVICA® until disease progression or unacceptable toxicity. Hematologic laboratory abnormalities are described in Table 10.

Table 9: Adverse reactions reported in ≥10% of patients with MZL treated with 560 mg IMBRUVICA® - Study PCYC-1121-CA (N=63)

System Organ Class	Adverse Reaction	All Grades (%)	Grades 3-4 (%)
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Blood and lymphatic system disorders	Anemia	33	14
	Thrombocytopenia*	25	2
	Neutropenia*	8	8
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Psychiatric disorders	Anxiety	16	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Vascular disorders	Hemorrhage*	30	0
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
Skin and subcutaneous tissue disorders	Bruising*	41	0
	Rash*	29	5
	Pruritus	14	0

Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
General disorders and administration site conditions	Fatigue	44	6
	Edema peripheral	24	2
	Pyrexia	17	2

* Includes multiple adverse reaction terms.

Table 10: Hematologic laboratory abnormalities (per CTCAE criteria) from Study PCYC-1121

	IMBRUVICA® (N=63)	
Laboratory Parameter	**All Grades (%)**	**Grades 3 or 4 (%)**
Hemoglobin decreased[a]	43	13
Neutrophils decreased[b]	22	13
Platelets decreased[c]	49	6

[a] Units=g/L; grade 1: ≥100 to <lower limit of normal; grade 2: ≥80 to <100; grade 3: <80.
[b] Units=$x10^9$/L; grade 1: ≥1.5 to <lower limit of normal; grade 2: ≥1.0 to <1.5; grade 3: ≥0.5 to <1.0; grade 4: <0.5.
[c] Units=10^9/L; grade 1: ≥75.0 to <lower limit of normal; grade 2: ≥50.0 to <75.0; grade 3: ≥25.0 to <50.0; grade 4: <25.0.

Waldenström's Macroglobulinemia

Single-agent therapy

Adverse reactions described in Table 11 below reflect exposure to IMBRUVICA® (420 mg daily) with a median duration of 11.7 months in Study PCYC-1118E. Patients received IMBRUVICA® until disease progression or unacceptable toxicity. Hematologic laboratory abnormalities are described in Table 12.

Table 11: Adverse reactions† reported from Study PCYC-1118E (N=63)

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

		Frequency	
System Organ Class	**Adverse Reaction**	**All grades (%)**	**Grades 3 or 4 (%)**
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0

***** Includes multiple adverse reaction terms.
† Adverse reactions occurring at ≥10% incidence or that are biologically plausible are presented.

Abnormal Hematologic and Clinical Chemistry Findings (WM, single-agent therapy)

Table 12: Hematologic laboratory abnormalities (per CTCAE criteria) from Study PCYC-1118E

	IMBRUVICA® (N=63)	
Laboratory Parameter	**All Grades (%)**	**Grades 3 or 4 (%)**
Hemoglobin decreased[a]	13	8
Neutrophils decreased[b]	44	19
Platelets decreased[c]	43	13

[a] Units=g/L; grade 1: ≥100 to <lower limit of normal; grade 2: ≥80 to <100; grade 3: <80.
[b] Units=$x10^9$/L; grade 1: ≥1.5 to <lower limit of normal; grade 2: ≥1.0 to <1.5; grade 3: ≥0.5 to <1.0; grade 4: <0.5.
[c] Units=10^9/L; grade 1: ≥75.0 to <lower limit of normal; grade 2: ≥50.0 to <75.0; grade 3: ≥25.0 to <50.0; grade 4: <25.0.

The safety profile of IMBRUVICA® in patients with previously treated WM who failed prior rituximab-containing therapy in the PCYC-1127-CA non-randomized single-agent therapy substudy arm (N=31) was consistent with the safety profile for IMBRUVICA® in Study PCYC-1118E.

Combination therapy

Adverse reactions described in Table 13 below reflect exposure to IMBRUVICA® + rituximab with a median duration of 25.8 months and exposure to placebo + rituximab with a median duration of 15.5 months in patients with WM in Study PCYC-1127-CA. Rituximab was administered weekly for 4 consecutive weeks over two courses (weeks 1-4 and 17-20), and IMBRUVICA® or placebo was administered daily until disease progression or unacceptable toxicity. Hematologic laboratory abnormalities are described in Table 14.

Table 13: Adverse reactions reported from Study PCYC-1127-CA[a]

	IMBRUVICA® + Rituximab (N=75)		Placebo + Rituximab (N=75)	
System Organ Class **Adverse Reaction Term**	**All Grades %**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
Blood and lymphatic system disorders				
Anemia	19	11	29	17
Neutropenia*	16	12	11	4
Cardiac disorders				
Atrial fibrillation	15	12	3	1
Cardiac failure congestive	3	3	0	0
Myocardial ischemia	3	1	0	0
Gastrointestinal disorders				
Diarrhea	28	0	15	1
Nausea	21	0	12	0
Dyspepsia	16	0	1	0
General disorders and administration site conditions				
Peripheral edema	17	0	12	1

System Organ Class Adverse Reaction Term	IMBRUVICA® + Rituximab (N=75)		Placebo + Rituximab (N=75)	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Infections and infestations				
Pneumonia*	19	13	5	3
Skin infection*	17	3	3	0
Urinary tract infection	13	0	0	0
Bronchitis	12	3	7	0
Influenza	12	0	7	1
Gastroenteritis	7	3	1	0
Respiratory tract infection	7	3	3	0
Injury, poisoning and procedural complications				
Fall	4	3	4	0
Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	35	4	21	3
Arthralgia	24	3	11	1
Muscle spasms	17	0	12	1
Psychiatric disorders				
Insomnia	11	0	4	0
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	11	0
Skin and subcutaneous tissue disorders				
Bruising*	37	1	5	0
Rash*	24	1	11	0
Vascular disorders				
Hemorrhage*	32	3	17	3
Hypertension*	20	13	5	4

[a] Occurring at ≥10% incidence and ≥5% greater in the IMBRUVICA® + rituximab arm when compared to the placebo + rituximab arm or serious adverse events ≥2% incidence and ≥2% greater in the IMBRUVICA® + rituximab arm when compared to the placebo + rituximab arm or that are biologically plausible.

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

* Includes multiple adverse reaction terms

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

Abnormal Hematologic and Clinical Chemistry Findings (WM, IMBRUVICA® + rituximab Therapy)

Table 14: Hematologic laboratory abnormalities (per CTCAE criteria) from Study PCYC-1127-CA

Laboratory Parameter	IMBRUVICA®+Rituximab (N=75) n (%)		Placebo+Rituximab (N=75) n (%)	
	Any Grade	Grade 3+4	Any Grade	Grade 3+4
Hemoglobin decreased[a]	12 (16.0)	1 (1.3)	18 (24.0)	8 (10.7)
Neutrophils decreased[b]	19 (25.3)	7 (9.3)	16 (21.3)	5 (6.7)
Platelets decreased[c]	17 (22.7)	1 (1.3)	13 (17.3)	4 (5.3)

N: number of patients who received at least 1 dose of ibrutinib in each analysis population; R: rituximab.

[a] Units=g/L; grade 1: ≥100 to <lower limit of normal; grade 2: ≥80 to <100; grade 3: <80.

[b] Units=$x10^9$/L; grade 1: ≥1.5 to <lower limit of normal; grade 2: ≥1.0 to <1.5; grade 3: ≥0.5 to <1.0; grade 4: <0.5.

[c] Units=10^9/L; grade 1: ≥75.0 to <lower limit of normal; grade 2: ≥50.0 to <75.0; grade 3: ≥25.0 to <50.0; grade 4: <25.0.

Abnormalities worsened after first dose of study treatment up to 30 days after the last dose of study drug were included in this table.

Chronic graft versus host disease

Adverse reactions described below in Table 15 reflect exposure to IMBRUVICA® (420 mg daily) with a median duration of 4.4 months in the cGVHD study. Hematologic laboratory abnormalities are described in Table 16.

Table 15: Adverse reactions reported in ≥10% of patients with cGVHD treated with 420 mg IMBRUVICA® - Study 1129 (N=42)

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

* Includes multiple adverse reaction terms.

Table 16: Hematologic laboratory abnormalities (per CTCAE criteria) from Study PCYC-1129-CA

Laboratory Parameter	IMBRUVICA® (N=42)	
	All Grades (%)	Grades 3 or 4 (%)
Hemoglobin decreased[a]	24	2
Neutrophils decreased[b]	10	10
Platelets decreased[c]	33	0

[a] Units=g/L; grade 1: ≥100 to <lower limit of normal; grade 2: ≥80 to <100; grade 3: <80.
[b] Units=$x10^9$/L; grade 1: ≥1.5 to <lower limit of normal; grade 2: ≥1.0 to <1.5; grade 3: ≥0.5 to <1.0; grade 4: <0.5.
[c] Units=10^9/L; grade 1: ≥75.0 to <lower limit of normal; grade 2: ≥50.0 to <75.0; grade 3: ≥25.0 to <50.0; grade 4: <25.0.

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported during post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

Cardiac disorders: ventricular tachyarrhythmias (see **WARNINGS AND PRECAUTIONS**)

Hepatobiliary disorders: hepatic failure including acute and/or fatal events (including cases that lacked clear alternative explanation and in which a positive de-challenge/re-challenge was observed), hepatic cirrhosis
Immune system disorders: hypersensitivity reaction, interstitial lung disease (ILD) (see **WARNINGS AND PRECAUTIONS**)
Infections and infestations: progressive multifocal leukoencephalopathy (PML), hepatitis B reactivation (see **WARNINGS AND PRECAUTIONS**)
Metabolism and nutrition disorders: tumour lysis syndrome (see **WARNINGS AND PRECAUTIONS**)
Nervous system disorders: peripheral neuropathy
Skin and subcutaneous tissue disorders: angioedema, erythema, onychoclasis (commonly reported in clinical trials), panniculitis, Stevens-Johnson syndrome, urticaria
Vascular disorders: hemorrhage (see **WARNINGS AND PRECAUTIONS**)

DRUG INTERACTIONS

Serious Drug Interactions

Concomitant use of IMBRUVICA® with a strong CYP3A inhibitor should be avoided (see **DOSAGE AND ADMINISTRATION, Concomitant use of CYP3A Inhibitors**).

Overview

Ibrutinib is metabolized primarily by cytochrome P450 enzyme 3A. Ibrutinib is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*. IMBRUVICA® should not be used concomitantly with strong inhibitors or inducers of CYP3A.

Drug-Drug Interactions

Agents that may increase ibrutinib plasma concentrations

Co-administration of ketoconazole, a strong CYP3A inhibitor, in healthy subjects increased exposure (C_{max} and AUC_{∞}) of ibrutinib by 29- and 26-fold, respectively. Simulations under fed conditions suggest that posaconazole (a strong CYP3A inhibitor) may increase the AUC of ibrutinib 7-fold to 10-fold.

In patients with B-cell malignancies, concomitant use of strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, itraconazole, cobicistat, and posaconazole) should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If a strong CYP3A inhibitor must be used short term (7 days or less), withhold IMBRUVICA® treatment temporarily for the duration of the CYP3A inhibitor treatment.

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 CYP3A inhibitor (e.g., erythromycin, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib,

verapamil, amiodarone, dronedarone) is indicated, reduce IMBRUVICA® dose to 280 mg for the duration of the CYP3A inhibitor use. If voriconazole is indicated, reduce IMBRUVICA® dose to 140 mg for the duration of the CYP3A inhibitor use. No dose adjustment is required in combination with mild CYP3A inhibitors.

In patients with cGVHD, if used concomitantly with voriconazole, or posaconazole at doses less than or equal to 200 mg BID (suspension), reduce the IMBRUVICA® dose to 280 mg for the duration of the CYP3A inhibitor use. If used concomitantly with posaconazole at 300 mg QD (delayed release tablet), reduce the IMBRUVICA® dose to 140 mg for the duration of the CYP3A inhibitor use. Concomitant use with posaconazole at higher doses or with other strong CYP3A inhibitors should be avoided; if used short term (7 days or less), withhold IMBRUVICA® treatment temporarily for the duration of the CYP3A inhibitor treatment. No dose adjustment is required in combination with moderate CYP3A inhibitors, or with mild CYP3A inhibitors.

Patients should be monitored closely for toxicity. Follow dose modification guidelines as needed (see **DOSAGE AND ADMINISTRATION**).

Agents that may decrease ibrutinib plasma concentrations

Administration of IMBRUVICA® with strong inducers of CYP3A (e.g., rifampin) decreases ibrutinib plasma exposures by approximately 10-fold and the dihydrodiol metabolite by 2.5-fold. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction. IMBRUVICA® can be administered concomitantly with mild inducers.

Drugs that may have their plasma concentrations altered by ibrutinib

Ibrutinib is an inhibitor of P-glycoprotein (P-gp) *in vitro.* Ibrutinib may inhibit intestinal P-gp after a therapeutic dose and alter the absorption of co-dosed drugs that are P-gp substrates (e.g., aliskiren, digoxin, fexofenadine). There are no clinical data available.

In vitro studies have also demonstrated that ibrutinib inhibits the breast cancer resistance protein (BCRP). *In vivo* studies to confirm the transporter-based interaction have not been conducted. Ibrutinib may inhibit intestinal BCRP after a therapeutic dose and alter the absorption of co-dosed drugs that are BCRP substrates (e.g., methotrexate, topotecan, imatinib). Ibrutinib may also inhibit BCRP in the liver and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

To avoid a potential interaction in the GI tract, narrow therapeutic range BCRP and P-gp substrates should be taken at least 6 hours before or after IMBRUVICA®. Dose reduction of concomitant drugs that undergo BCRP-mediated hepatic efflux may be needed to avoid increased exposure and to reduce the risk of serious adverse reactions.

Anticoagulant and antiplatelet agents

Warfarin or other vitamin K antagonists should not be administered concomitantly with IMBRUVICA®. Use of IMBRUVICA® in patients requiring other anticoagulants or medications

that inhibit platelet function may increase the risk of bleeding and should be used with caution (see **WARNINGS AND PRECAUTIONS, Hemorrhage**).

Drugs that Prolong the PR Interval

IMBRUVICA® causes an increase in the PR interval (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**). The concomitant use of IMBRUVICA® with other drugs that prolong the PR interval, including, but not limited to, beta blockers, non-dihydropyridine calcium channel blockers, and digitalis glycosides, as well as certain antiarrhythmics and HIV protease inhibitors, should be undertaken with caution.

Drug-Food Interactions

Co-administration of grapefruit juice in non-fasted healthy subjects increased exposure (C_{max} and AUC_{last}) of ibrutinib by approximately 4 and 2-fold, respectively. Grapefruit and Seville oranges must not be consumed during IMBRUVICA® treatment as they contain moderate inhibitors of CYP3A (see **DOSAGE AND ADMINISTRATION**).

Supplements such as fish oil, flaxseed, and vitamin E preparations should be avoided as they may increase the risk of bleeding associated with IMBRUVICA® (see **WARNINGS AND PRECAUTIONS, Hemorrhage**).

Administration with food increases AUC of ibrutinib by approximately 2-fold and C_{max} by up to 4.5-fold as compared to overnight fasting. Administration with food increases the exposure of the dihydrodiol metabolite by approximately 2-fold as compared to overnight fasting (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). IMBRUVICA® can be taken with or without food.

Drug-Herb Interactions

Avoid concomitant use of St. John's Wort, as this herb is a strong inducer of CYP3A.

Drug-Lifestyle Interactions

Fatigue, dizziness and asthenia have been reported very commonly in patients taking IMBRUVICA® and should be considered when assessing a patient's ability to drive or operate machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

IMBRUVICA® should be administered orally, with or without food, with a glass of water once daily, at approximately the same time each day. IMBRUVICA® should be swallowed whole with water and should not be opened, broken, or chewed. IMBRUVICA® must not be taken with grapefruit juice.

Upon initiation of treatment with IMBRUVICA®, a reversible increase in lymphocyte counts, often associated with reduction of lymphadenopathy, has been observed in a majority of patients with CLL and some patients with MCL. This observed lymphocytosis may be a pharmacodynamic effect of the inhibition of BTK-mediated cellular homing and adhesion, and should not be considered progressive disease in the absence of other clinical findings (see **ACTION AND CLINICAL PHARMACOLOGY**).

Recommended Dose and Dosage Adjustment

The recommended dose of IMBRUVICA® for CLL or WM is 420 mg once daily until disease progression or no longer tolerated by the patient.

In patients with previously treated CLL, IMBRUVICA® can also be used in combination with bendamustine and rituximab. For information on dosing of bendamustine and rituximab, consult the corresponding Product Monographs.

In patients with WM, IMBRUVICA® can also be used in combination with rituximab. For information on dosing and administration of rituximab, consult the Product Monograph. For rituximab dosing used in the pivotal clinical study, see **CLINICAL TRIALS**, **Waldenström's Macroglobulinemia (WM)**, *Combination Therapy*.

When administering IMBRUVICA® in combination with rituximab, consider administering IMBRUVICA® prior to rituximab when given on the same day.

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

The recommended dose of IMBRUVICA® for cGVHD is 420 mg once daily until cGVHD progression, recurrence of an underlying malignancy, or until no longer tolerated by the patient. When a patient no longer requires therapy for the treatment of cGVHD, IMBRUVICA® should be discontinued considering the medical assessment of the individual patient.

IMBRUVICA® therapy should be withheld for any new onset or worsening Grade ≥3 non-hematological toxicities, Grade ≥3 neutropenia with infection or fever, or Grade 4 hematological 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 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	CLL/WM/cGVHD dose modification after recovery	MCL/MZL dose modification after recovery
First	restart at 420 mg daily	restart at 560 mg daily
Second	restart at 280 mg daily	restart at 420 mg daily
Third	restart at 140 mg daily	restart at 280 mg daily
Fourth	discontinue IMBRUVICA®	discontinue IMBRUVICA®

Patients with Hepatic Impairment

IMBRUVICA® should not be used in patients with moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C) (see **WARNINGS AND PRECAUTIONS, Special Populations**). If the benefit is considered to outweigh the risk in a patient with mild hepatic impairment (Child Pugh class A), a dose reduction to 140 mg should be considered. Monitor patients for signs of toxicity.

Concomitant use of CYP3A Inhibitors

Concomitant use of moderate and strong CYP3A inhibitors increases the exposure of ibrutinib (see **DRUG INTERACTIONS**). Avoid concomitant use with strong CYP3A inhibitors. If a strong or moderate CYP3A inhibitor must be used, refer to the dosing recommendations in the table below. After discontinuation of the strong or moderate CYP3A inhibitor, resume the previous dose of IMBRUVICA® if it had been adjusted or withheld. No dose adjustment is required in combination with mild inhibitors. Patients should be monitored closely for toxicity. Follow dose modification guidelines as needed.

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 for the duration of the CYP3A inhibitor use.
	• Voriconazole	140 mg once daily for the duration of the CYP3A inhibitor use.
	• Strong CYP3A inhibitors	Concomitant use should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If a strong CYP3A inhibitor must be used short term (7 days or less), withhold IMBRUVICA® treatment temporarily for the duration of the CYP3A inhibitor treatment.
Chronic Graft versus Host Disease	• Mild CYP3A inhibitors	420 mg once daily. No dose adjustment required.
	• Moderate CYP3A inhibitors	420 mg once daily. No dose adjustment required.
	• Voriconazole • Posaconazole at doses less than or equal to 200 mg BID (suspension)	280 mg once daily for the duration of the CYP3A inhibitor use.
	• Posaconazole at 300 mg QD (delayed-release tablet)	140 mg once daily for the duration of the CYP3A inhibitor use.
	• Strong CYP3A inhibitors • Posaconazole at doses higher than 200 mg BID (suspension) or 300 mg QD (delayed-release tablet)*	Concomitant use should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If a strong CYP3A inhibitor must be used short term (7 days or less), withhold IMBRUVICA® treatment temporarily for the duration of the CYP3A inhibitor treatment.

*Posaconazole at higher doses includes posaconazole suspension 200 mg three times daily or 400 mg twice daily, and posaconazole IV injection 300 mg once daily.

[a] Based on a combination of observed data and physiologically based pharmacokinetics simulations

Missed Dose

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

OVERDOSAGE

There are limited data on the effects of IMBRUVICA® overdose. No Maximum Tolerated Dose was reached in the phase 1 study in which a small number of 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 ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ibrutinib is a small-molecule, targeted 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 inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is a signaling molecule of the B-cell antigen receptor (BCR) pathway. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies including CLL. In addition to its roles in antigen mediated BCR signaling, BTK is involved in signaling of chemokine receptors such as CXCR4 and CXCR5 that play roles in B-cell trafficking and tissue homing. Nonclinical studies have shown that ibrutinib inhibits malignant B-cell proliferation and survival as well as cell migration and substrate adhesion.

Pharmacodynamics

Lymphocytosis

Upon initiation of IMBRUVICA® as a single agent in controlled CLL clinical studies, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/μL), often associated with reduction of lymphadenopathy, occurred in a majority (57% to 69%) of patients. In a study of patients receiving IMBRUVICA® in combination with BR, lymphocytosis occurred in 7% of patients. In the MCL clinical study, this effect occurred in some patients (35%) treated with IMBRUVICA®. This observed lymphocytosis may be a pharmacodynamic effect of the inhibition of BTK-mediated cellular homing and adhesion, and should not be considered progressive disease in the absence of other clinical findings. Lymphocytosis typically occurs during the first few weeks of IMBRUVICA® therapy (median time 1 to 2 weeks) and typically resolves within a median 12 to 14 weeks in patients with CLL, and within a median 8 weeks in patients with MCL.

A large increase in the number of circulating lymphocytes (e.g., to above 400,000/μL) has been observed in some patients and may confer increased risk of leukostasis.

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

Cardiac Electrophysiology

A randomized, double-blind, placebo- and positive-controlled, single-dose, four-way 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 of whom 9 received ibrutinib (either 840 or 1680 mg), the negative control (placebo), and the positive control (moxifloxacin).

Ibrutinib caused a dose- and concentration-dependent prolongation of the PR interval. The maximum difference from placebo in the mean change from baseline PR interval was 3.9 ms (90% CI: 0.17, 7.70) at the 840 mg dose and 7.6 ms (90% CI: 3.04, 12.10) at the 1680 mg dose.

Ibrutinib was also observed to decrease heart rate. The maximum difference from placebo in the mean change from baseline heart rate was -4.8 bpm (90% CI: -9.08, -0.54) at the 840 mg dose and -5.9 bpm (90% CI: -9.49, -2.28) at the 1680 mg dose.

In this study, mean C_{max} values of 304 ng/mL (range 60-670 ng/mL) and 719 ng/mL (range 261-1890 ng/mL) were reported following single dose administration of the 840 mg and 1680 mg doses, respectively. The mean steady-state C_{max} observed in subjects who received daily doses of 560 mg was 164 ng/mL (range 5.23-956 ng/mL).

Based on an exposure-response analysis using data from this study, a concentration dependent shortening in the QTcF interval was predicted, with an estimated change in QTcF of -3.8 ms [90% CI -5.88, -1.80] and -7.1 ms [90% CI -10.2, -3.94] at the 840 and 1680 mg supratherapeutic doses, respectively.

Pharmacokinetics

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 when combined with a meal was 7.6% (90% CI: 6.4; 9.0). Population pharmacokinetic modeling suggests that the pharmacokinetics of ibrutinib does not differ significantly in patients with different B-cell malignancies. Ibrutinib exposure increases with doses up to 840 mg. The pharmacokinetic parameters of ibrutinib as a single agent at steady-state are shown in Table 17. High intersubject variability of exposures was observed in patients.

Table 17: Ibrutinib pharmacokinetic parameters at steady-state in patients with B-cell malignancies

	AUC_{0-24h}				C_{max}			
	n	**Mean (SD) (ng.h/mL)**	**Range (ng.h/mL)**	**CV (%)**	**n**	**Mean (SD) (ng/mL)**	**Range (ng/mL)**	**CV (%)**
420 mg	71	732 (521)	102 - 2333	71.1	73	137 (118)	11.2 - 609	86.1
560 mg	43	953 (705)	115 - 3372	74.0	45	164 (164)	5.23 - 956	99.9

Ibrutinib exposure was consistent between patients with WM on combination therapy of ibrutinib 420 mg/day with rituximab, and patients with B-cell malignancies on single agent ibrutinib at 420 mg/day.

In patients at 420 mg with cGVHD, the steady state AUC observed was (mean ± standard deviation) 1159 ± 583 ng·h/mL.

Administration of ibrutinib with a high-fat breakfast resulted in approximately 2.0-fold higher AUC_{last} and up to 4.5-fold higher C_{max} as compared to overnight fasting. Administration with food increases the exposure of the dihydrodiol metabolite by approximately two-fold compared to administration after overnight fasting. A delay in T_{max} (from ~2 to 4 hours) was also observed with food.

Distribution

Binding of ibrutinib to human plasma proteins *in vitro* was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution (V_d) was 683 L and the apparent volume of distribution at steady state ($V_{d,ss}/F$) is approximately 10,000 L. Binding of the dihydrodiol metabolite to human plasma protein *in vitro* is 91% at 475 ng/mL.

The proportion of unbound ibrutinib is inversely related to the plasma levels of α1-acid glycoprotein and albumin in humans. Approximately 12% C_{max} and 51% AUC_{0-72h} of total radioactivity were accounted for by covalent binding in the plasma of healthy male volunteers administered a single dose of 140 mg ibrutinib admixed with ^{14}C-ibrutinib. *In vitro*, ibrutinib binds both reversibly and covalently to human serum albumin and, to a lesser extent, to α1-acid glycoprotein.

Metabolism

Ibrutinib is extensively metabolized, primarily by cytochrome P450, CYP3A, 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 2.5-fold that of the parent drug in patients administered 420 mg daily dose. Other main circulating metabolites include M25 (oxidative opening of the piperidine with further oxidation to a carboxylic acid), M34 (oxidative opening of the piperidine with further reduction to a primary alcohol), M23 (resulting from amide hydrolysis) and M21 (hydroxylation of the phenyl moiety followed by sulfation). M23, M25 and M34 have low to negligible activity towards BTK and activity of M21 has not been studied. Steady-state exposure of these metabolites is not known.

In vitro studies suggest that CYP2D6 involvement in ibrutinib oxidative metabolism is minor. *In vitro* enzyme kinetic studies demonstrated that the rate of metabolism of ibrutinib to its dihydrodiol metabolite by human recombinant CYP2D6 was lower with the poor metabolizer phenotype compared to that of wildtype. As part of the human mass balance study, two subjects genotyped as poor metabolizers for CYP2D6, showed a similar pharmacokinetic profile as four extensive metabolizers.

Elimination

Intravenous clearance was 62 and 76 L/h in fasted and fed condition, respectively. In line with the high first-pass effect, the apparent oral clearance is approximately 2000 and 1000 L/h in fasted and fed condition, respectively.

The half-life of ibrutinib is 4 to 6 hours. The half-life of the dihydrodiol metabolite is 6 to 11 hours. Compared to when a single dose of ibrutinib was given, accumulation of less than two-fold of both parent compound and the dihydrodiol metabolite following daily dose regimen was observed.

After a single oral administration of 140 mg ibrutinib admixed with [^{14}C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib

accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

Drug-drug interactions

In a sequential design trial of 18 healthy volunteers, a single dose of 120 mg of IMBRUVICA® was administered alone on Day 1 and a single dose of 40 mg of IMBRUVICA® was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 to 9). Ketoconazole increased ibrutinib dose-normalized C_{max} and AUC_{last} 29-fold and 24-fold, respectively. The corresponding decrease in dose-normalized C_{max} and AUC_{last} of the dihydrodiol metabolite was 2.6-fold and 1.2-fold, respectively. Drug-drug interaction studies of ibrutinib with moderate or mild inhibitors of CYP3A have not been conducted. Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that moderate CYP3A inhibitors (diltiazem and erythromycin) may increase the AUC of ibrutinib 5 to 8-fold in fasted condition, and that mild CYP3A inhibitors (fluvoxamine and azithromycin) may increase the AUC of ibrutinib less than 2-fold in fasted condition.

In a sequential design trial of 18 healthy volunteers, a single dose of 560 mg of IMBRUVICA® was administered alone on Day 1 and on Day 11 in combination with 600 mg of rifampin (given daily on Days 4 to 13). Rifampin (a strong CYP3A inducer) decreased ibrutinib C_{max} and AUC_{last} 13-and 10-fold, respectively. The corresponding decrease in C_{max} and AUC_{last} of the dihydrodiol metabolite was 1.4- and 2.5-fold, respectively. Drug-drug interaction studies of ibrutinib with moderate or mild inducers of CYP3A have not been conducted. Simulations using PBPK models suggested that a moderate CYP3A inducer (efavirenz) and a strong CYP3A inducer (carbamazepine) may decrease the AUC of ibrutinib by up to 3 and 6-fold, respectively.

Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. In 20 fasted healthy subjects, a single dose of 560 mg IMBRUVICA® was administered after taking omeprazole (a proton pump inhibitor) at 40 mg once daily for 5 days. Compared with ibrutinib alone, repeated administration of omeprazole at 40 mg (once daily) minimally affected AUC of ibrutinib while C_{max} was reduced by 62.50%. There is no evidence that the lower C_{max} would have clinical significance, and medicinal products that increase stomach pH (e.g., proton pump inhibitors) have been used without restrictions in the pivotal clinical trials.

Ibrutinib did not significantly affect the *in vitro* plasma protein binding of warfarin (bound predominantly to albumin).

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*. Inhibition or induction of CYP450 enzymes by ibrutinib, the dihydrodiol metabolite, and other metabolites is unlikely to lead to a clinically relevant drug interaction with drugs that are CYP450 substrates.

In vitro studies indicated that ibrutinib is not a substrate of P-gp nor BCRP, MRP1, OATP1B1, OATP1B3, OATP2B1, OCT1, OAT1 or OAT3, but is a substrate of OCT2. The dihydrodiol metabolite and other metabolites are P-gp substrates. Administration of ibrutinib with inhibitors of P-gp or other major transporters is unlikely to lead to clinically relevant drug interactions.

Drug-food interactions

In a cross-over design trial of 8 healthy volunteers, 240 mL of grapefruit juice was given the evening before and again 30 minutes before a single dose of 140 mg of IMBRUVICA®, followed by a standard breakfast 30 minutes after dosing. Grapefruit juice increased ibrutinib dose-normalized C_{max} and AUC_{last} 4 and 2-fold, respectively.

Special Populations and Conditions

Pediatrics (<18 years of age)

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

Geriatrics (≥65 years of age)

Pharmacokinetic data in patients administered 420 mg daily dose showed higher systemic exposures of ibrutinib (25% higher AUC and 50% higher C_{max}) and the dihydrodiol metabolite (48% higher AUC and 56% higher C_{max}) at steady state in patients ≥65 years of age when compared with those <65 years.

Gender

Pharmacokinetic data in patients administered 420 mg daily dose showed approximately 34% higher steady state exposure of the dihydrodiol metabolite in female patients when compared with males whereas ibrutinib exposures were comparable. Population pharmacokinetics data indicated that gender does not significantly affect ibrutinib clearance from the circulation.

Hepatic Impairment

Ibrutinib is metabolized in the liver. In a hepatic impairment trial in non-cancer patients administered a single dose of 140 mg of IMBRUVICA®, data showed up to 9- and 13-fold increase in exposure of total ibrutinib and unbound ibrutinib, respectively, in subjects with hepatic impairment.

Renal Impairment

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

STORAGE AND STABILITY

Store at room temperature between 15°C-30°C. Keep out of reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

IMBRUVICA® tablets and capsules are formulated for oral administration.

IMBRUVICA® (ibrutinib) tablets

140 mg tablets
Yellow-green to green round film-coated tablet debossed with "ibr" on one side and "140" on the other, containing 140 mg of ibrutinib.

280 mg tablets
Purple oblong film-coated tablet debossed with "ibr" on one side and "280" on the other, containing 280 mg of ibrutinib.

420 mg tablets
Yellow-green to green oblong film-coated tablet debossed with "ibr" on one side and "420" on the other, containing 420 mg of ibrutinib.

560 mg tablets
Yellow to orange oblong film-coated tablet debossed with "ibr" on one side and "560" on the other, containing 560 mg of ibrutinib.

Each tablet also contains the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. The tablet film coatings contain black iron oxide (140 mg, 280 mg and 420 mg tablets), polyethylene glycol, polyvinyl alcohol, red iron oxide (280 mg and 560 mg tablets), talc, titanium dioxide, and yellow iron oxide (140 mg, 420 mg and 560 mg tablets).

All strengths of IMBRUVICA® tablets are packaged in push-through blisters composed of polyvinyl chloride (PVC) laminated with polychlorotrifluoroethylene (PCTFE) with aluminium foil backing, and are available in cartons of 30 tablets (each carton contains 3 wallets of 10 tablets).

IMBRUVICA® (ibrutinib) capsules

140 mg capsules
White hard gelatin capsules marked with "ibr 140 mg" in black ink, containing 140 mg ibrutinib.

Each capsule also contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The white capsule shell contains gelatin and titanium dioxide (E171). Capsules are printed with ink containing iron oxide black (E172) and shellac.

IMBRUVICA® capsules are packaged in high-density polyethylene (HDPE) bottles of 90 or 120 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

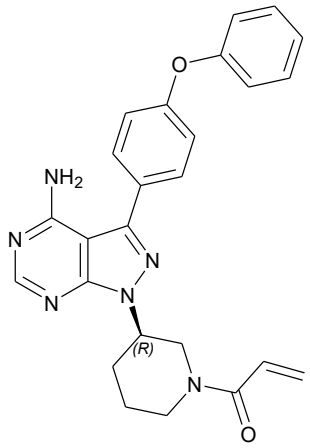
Drug Substance

Common name: ibrutinib

Chemical name: 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one

Molecular formula and molecular mass: $C_{25}H_{24}N_6O_2$ and 440.50 g/mol

Structural formula:



Physicochemical properties:

Appearance: Ibrutinib is a crystalline white to off-white solid.

Solubility: Ibrutinib is practically insoluble in water over a wide pH range (pH 3 to 8).

Dissociation Constant: The drug substance has one ionizable group, the protonated pyrimidine moiety, with a pKa of 3.74.

CLINICAL TRIALS

Previously Untreated Chronic Lymphocytic Leukemia (CLL)

The efficacy and safety of IMBRUVICA® were demonstrated in a multi-center, randomized, controlled, open-label phase 3 trial in patients with previously untreated CLL, including 20 patients with clinical presentation of SLL (PCYC-1115-CA). Patients were eligible for the study if they were 65 years of age or older. Patients between age 65 and 70 years were required to have at least one of the following comorbidities that could preclude the use of chemoimmunotherapy

with fludarabine, cyclophosphamide, and rituximab: creatinine clearance <70 mL/min, platelet count <100,000/µL or hemoglobin <100 g/L, clinical apparent autoimmune cytopenia, or ECOG performance status score of 1 or 2. 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 primary endpoint was progression-free survival (PFS) as assessed by independent review committee (IRC). Secondary endpoints included overall response rate (ORR) as assessed by the IRC, overall survival (OS), rate of sustained platelet improvement, and rate of sustained hemoglobin improvement.

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. At baseline, 45% of patients had advanced clinical stage (Rai Stage III or IV), 35% had at least one tumour ≥5 cm, 39% had baseline anemia, 23% had baseline thrombocytopenia, 65% had elevated β2 microglobulin >3500 µg/L, 47% had creatinine clearance <60 mL/min, and 20% had 11q deletion.

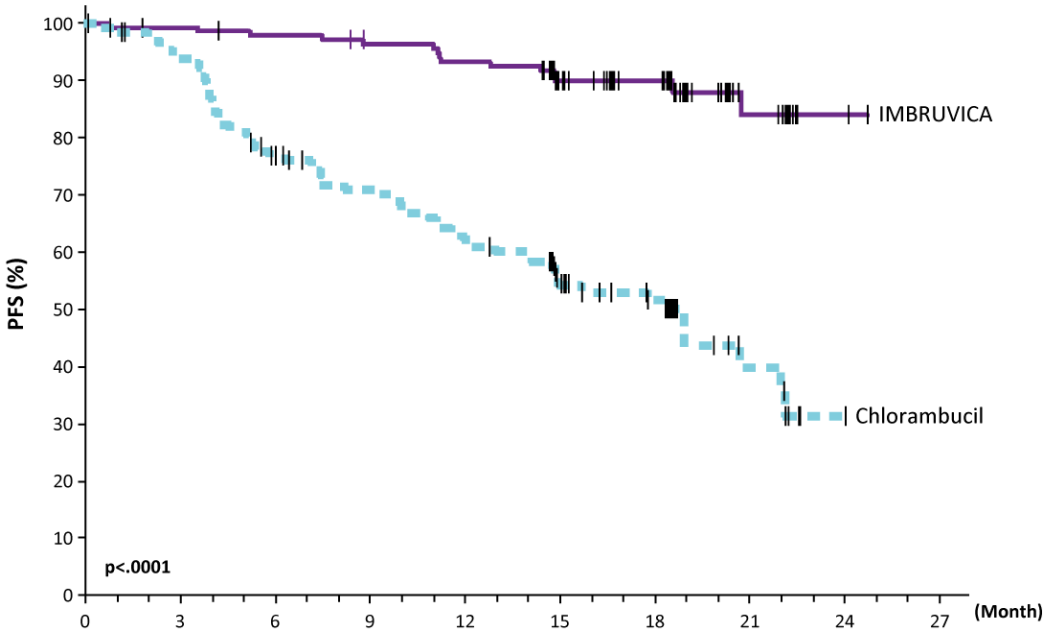
At a median follow-up of 18.4 months, PFS as assessed by IRC according to International Workshop on CLL (IWCLL) criteria indicated an 84% statistically significant reduction in the risk of death or progression in the IMBRUVICA® arm. Analysis of OS demonstrated an 84% statistically significant reduction in the risk of death for patients in the IMBRUVICA® arm. Efficacy results are shown in Table 18 and the Kaplan-Meier curves for PFS and OS are shown in Figure 1 and Figure 2, respectively.

Table 18: Efficacy Results in Study PCYC-1115-CA

Endpoint	**IMBRUVICA® N=136**	**Chlorambucil N=133**
Progression-Free Survival[a]		
Median	Not reached	18.9 months (95% CI: 14.1, 22.0)
Hazard Ratio (HR)	0.16 (95% CI: 0.091, 0.28); p<0.0001	
Overall Response Rate[a,b]		
CR+PR	82.4%	35.3%
P-value	p<0.0001	
Overall Survival		
Median	Not reached	Not reached
HR	0.16 (95% CI: 0.048, 0.56); p<0.005	

[a] Per IRC.
[b] Repeat CT scans required to confirm response.

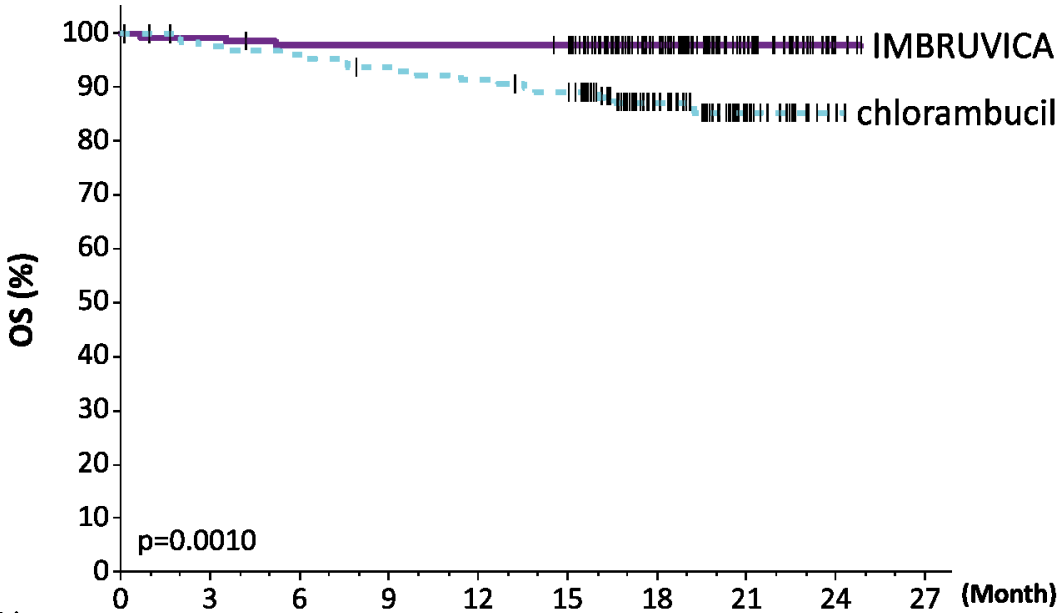
Figure 1: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1115-CA



N at Risk

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

Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1115-CA



N at Risk

IMBRUVICA:	136	134	131	131	131	129	74	32	4	0
chlorambucil:	133	127	125	121	118	113	62	24	1	0

The PFS was similar across subgroups examined, including in patients with and without advanced disease (Rai stage 0-II and stage III-IV; a pre-specified stratification factor), patients with ECOG performance status 0-1 and 2; a pre-specified stratification factor), patients age <70

years and ≥70 years, patients with and without bulky lymphadenopathy (<5 cm and ≥5 cm), patients with and without cytopenias at baseline, patients with and without deletion 11q, and patients with baseline β2-microglobulin ≤3.5 mg/mL and >3.5 mg/mL.

In the intent-to-treat population, a significantly greater proportion of patients exhibited sustained improvement in platelets or hemoglobin in the IMBRUVICA® arm than in the chlorambucil arm (platelets, 27% versus 11%, p=0.0009; hemoglobin, 46% versus 20%, p<0.0001). In patients with baseline cytopenias, a significantly greater proportion of patients in the IMBRUVICA® arm exhibited sustained hematologic improvement than in the chlorambucil arm (platelets, 77% versus 43%, p=0.0054; hemoglobin, 84% versus 46%, p<0.0001).

Previously Treated Chronic Lymphocytic Leukemia (CLL)

Single-agent therapy

The safety and efficacy of IMBRUVICA® in patients with CLL who have received at least one prior therapy were demonstrated in one randomized, controlled trial (PCYC-1112-CA), and one uncontrolled trial (PCYC-1102-CA).

Study PCYC-1112-CA was a randomized, multi-center, open-label phase 3 study of IMBRUVICA® versus ofatumumab conducted in patients with previously treated CLL, including 18 patients with clinical presentation of SLL. Patients were eligible for the study if they failed to respond to prior therapy, relapsed following a response to prior therapy, or otherwise met the 2008 IWCLL criteria for active disease requiring treatment following at least one prior therapy, and were not appropriate for treatment or retreatment with purine analog. Patients (n=391) were randomized 1:1 to receive either IMBRUVICA® 420 mg daily until disease progression or unacceptable toxicity, or ofatumumab for up to 12 doses (300/2000 mg). Fifty-seven patients randomized to ofatumumab crossed over following progression to receive IMBRUVICA®. The median age was 67 years (range, 30 to 88 years), 68% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range, 1 to 13 treatments). At baseline, 58% of patients had at least one tumour ≥5 cm. Thirty-two percent of patients had 17p deletion and 31% had 11q deletion.

At a median duration of follow-up of 9.6 months in the ibrutinib arm and 9.2 months in the ofatumumab arm, PFS as assessed by IRC according to 2008 IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the IMBRUVICA® arm. Analysis of OS demonstrated a 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA® arm. Efficacy results are shown in Table 19 and the Kaplan-Meier curves for PFS and OS are shown in Figure 4 and Figure 5, respectively.

Table 19: Efficacy results in patients with Chronic Lymphocytic Leukemia (Study PCYC-1112-CA)

Endpoint	IMBRUVICA® N=195	Ofatumumab N=196
Median Progression Free Survival	Not reached	8.1 months
	HR=0.22 [95% CI: 0.15; 0.32]	
Overall Survival[a]	HR=0.43 [95% CI: 0.24; 0.79][b] HR=0.39 [95% CI: 0.22; 0.70][c]	
Overall Response Rate[d,e]	42.6%	4.1%
Overall Response Rate with PRL[d]	62.6%	4.1%

[a] Median OS not reached for both arms.
[b] Patients randomized 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 IMBRUVICA®.
[d] Per IRC. Repeat CT scans required to confirm response.
[e] All PRs achieved; none of the patients achieved a CR. $p<0.0001$ for ORR.

The efficacy was similar across all of the subgroups examined, including in patients with and without 17p deletion (a pre-specified stratification factor), patients with and without deletion 11q, patients refractory and not refractory to prior purine analog treatment, patients with and without advanced disease (Rai stage 0-II and stage III-IV), and patients with and without bulky lymphadenopathy (<5 cm and ≥5 cm) (Figure 3).

Figure 3: Subgroup Analysis of Progression-Free Survival by IRC (Study PCYC-1112-CA; 420 mg)

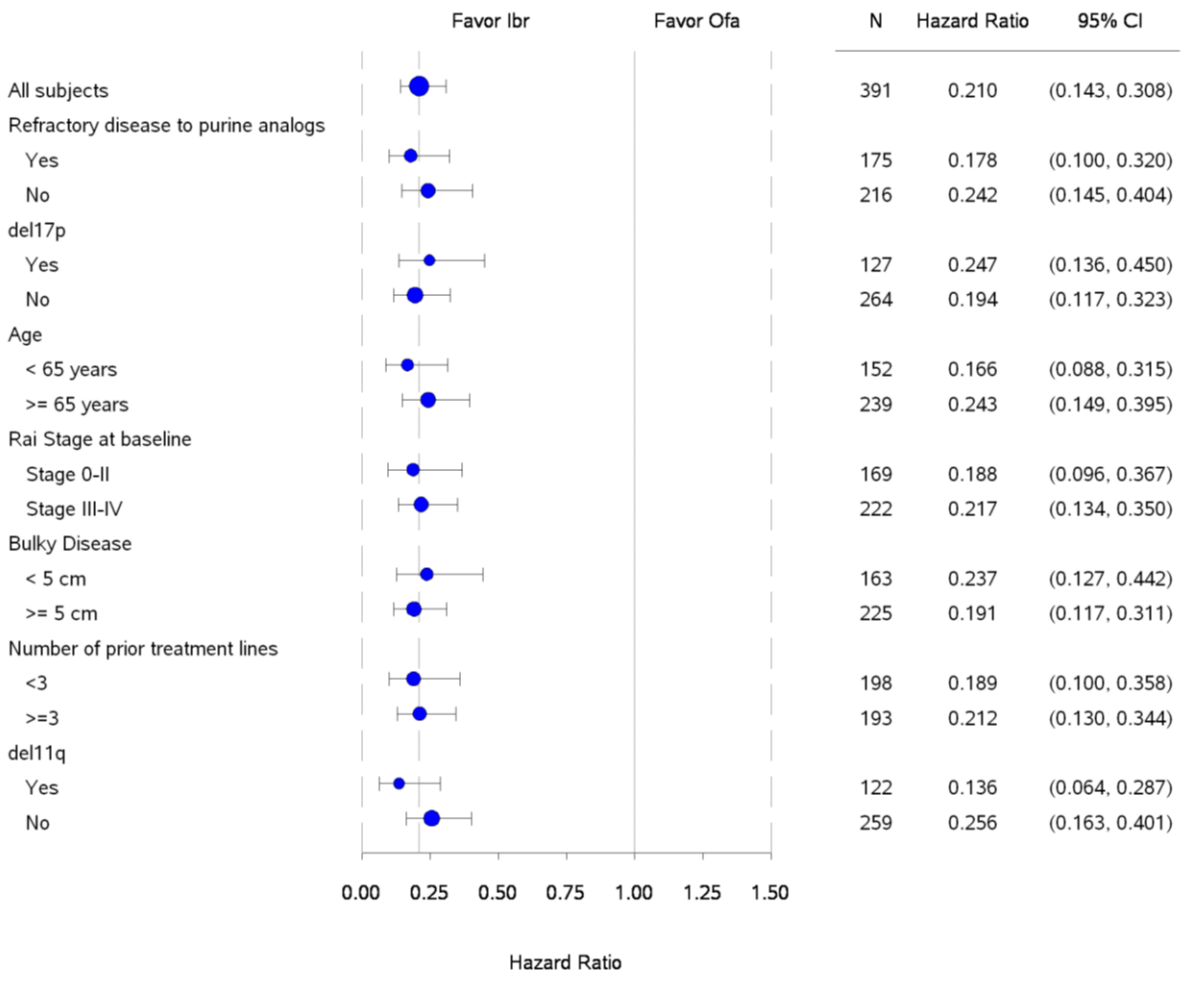


Figure 4: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1112-CA

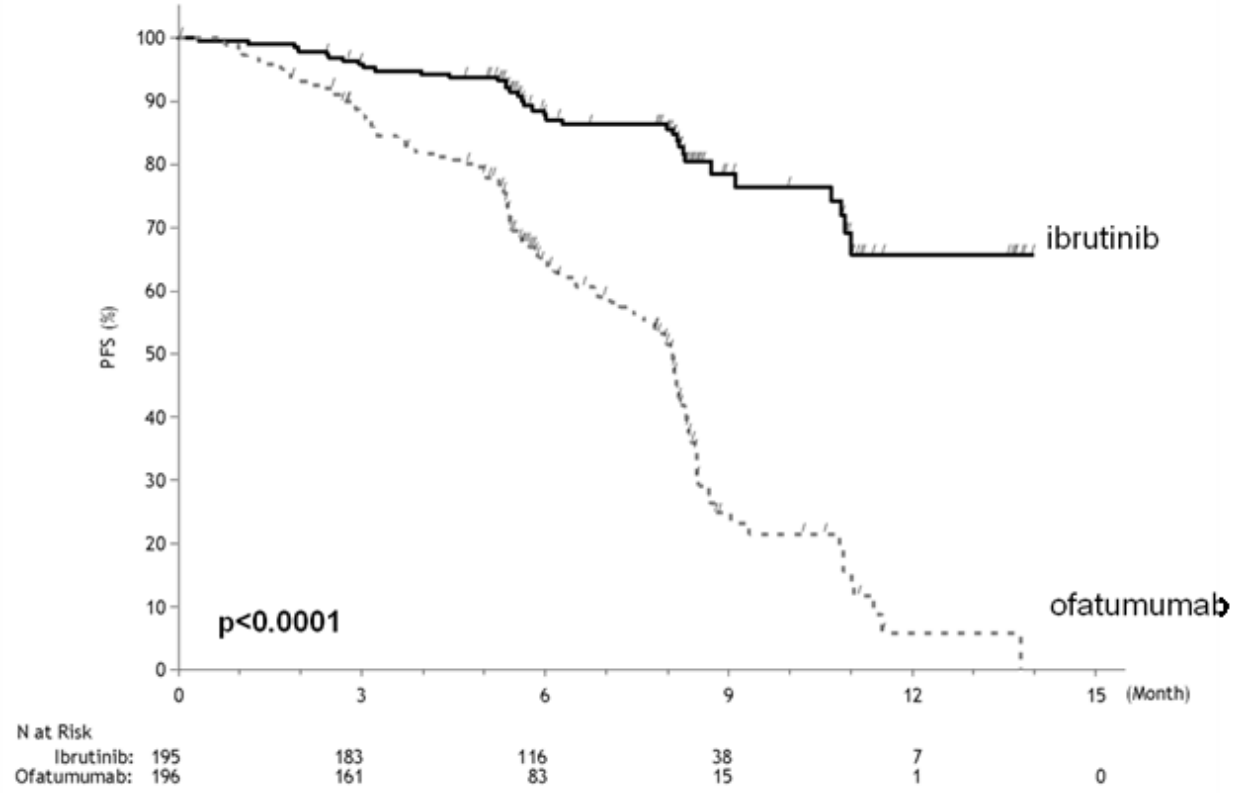
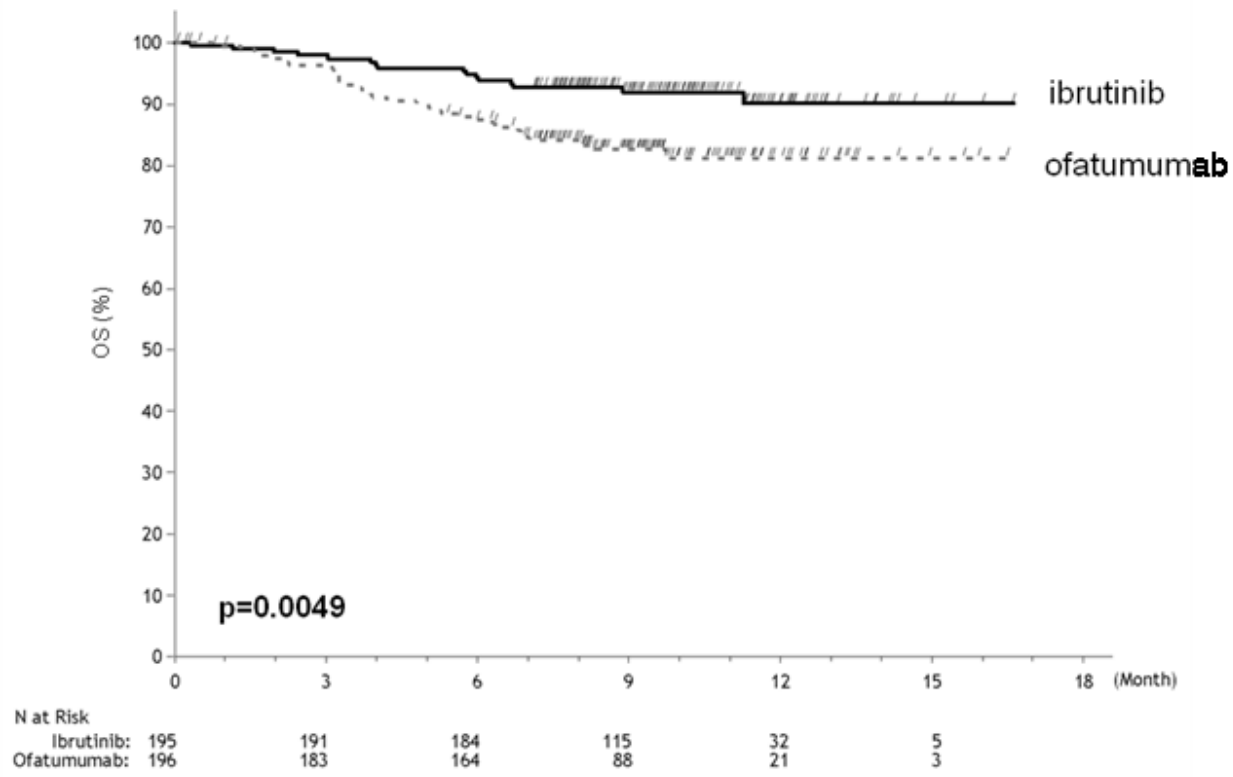


Figure 5: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1112-CA



At a median duration of treatment in the IMBRUVICA® arm of 18.3 months, PFS as assessed by investigators indicated an 89% reduction in the risk of death or progression for patients in the IMBRUVICA® arm (HR=0.11; 95% CI: 0.075, 0.15). Analysis of OS demonstrated a 48% reduction in the risk of death for patients in the IMBRUVICA® arm, irrespective of 63% of patients who crossed over from the ofatumumab arm to the IMBRUVICA® arm (HR=0.52; 95% CI: 0.32, 0.84). In the IMBRUVICA® arm, the ORR and ORR with PRL (per investigator) were 83% and 90%, respectively.

Study PCYC-1102-CA was an open-label, multi-center study conducted in 51 patients with relapsed or refractory CLL who have failed at least 1 prior therapy, including 3 patients with clinical presentation of SLL. Patient demographics and baseline characteristics were similar to those of patients in Study PCYC-1112-CA. At a median duration of follow-up of 16.4 months, response rates (ORR and ORR with PRL) were similar to response rates observed in Study PCYC-1112-CA. Median (range) time to initial response was 1.8 months (1.4 to 12.2 months).

Study PCYC-1112-CA included 127 patients with CLL with 17p deletion. The median age was 67 years (range, 30 to 84 years), 62% were male, and 88% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. PFS and ORR were assessed by IRC. Efficacy results for CLL with 17p deletion are shown in Table 20.

Table 20: Efficacy results in patients with CLL with 17p deletion (Study PCYC-1112-CA)

Endpoint	**IMBRUVICA® N=63**	**Ofatumumab N=64**
Median Progression Free Survival	Not reached	5.8 months
	HR=0.25 [95% CI: 0.14; 0.45]	
Overall Response Rate[a]	47.6%	4.7%
Overall Response Rate with PRL	66.7%	4.7%

[a] IRC evaluated. All partial responses achieved; none of the patients achieved a complete response. HR=hazard ratio.

Combination therapy

The safety and efficacy of IMBRUVICA® in combination with BR in patients with previously treated CLL were demonstrated in a randomized, controlled trial (CLL3001).

CLL3001 was a randomized, multi-center, double-blind, placebo-controlled phase 3 study of IMBRUVICA® in combination with BR versus placebo in combination with BR was conducted in patients with previously treated CLL without 17p deletion, including 64 patients with clinical presentation of SLL. 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. 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 in combination with BR crossed over to receive IMBRUVICA® following IRC-confirmed disease 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, and 26% had del11q.

At a median duration of treatment of 14.7 months in the IMBRUVICA® in combination with BR arm, and 12.8 months in the placebo in combination with BR arm, PFS as assessed by IRC according to IWCLL criteria indicated a statistically significant, 80% reduction in the risk of death or progression. Efficacy results for Study CLL3001 are shown in Table 21 and the Kaplan-Meier curve for PFS is shown in Figure 6.

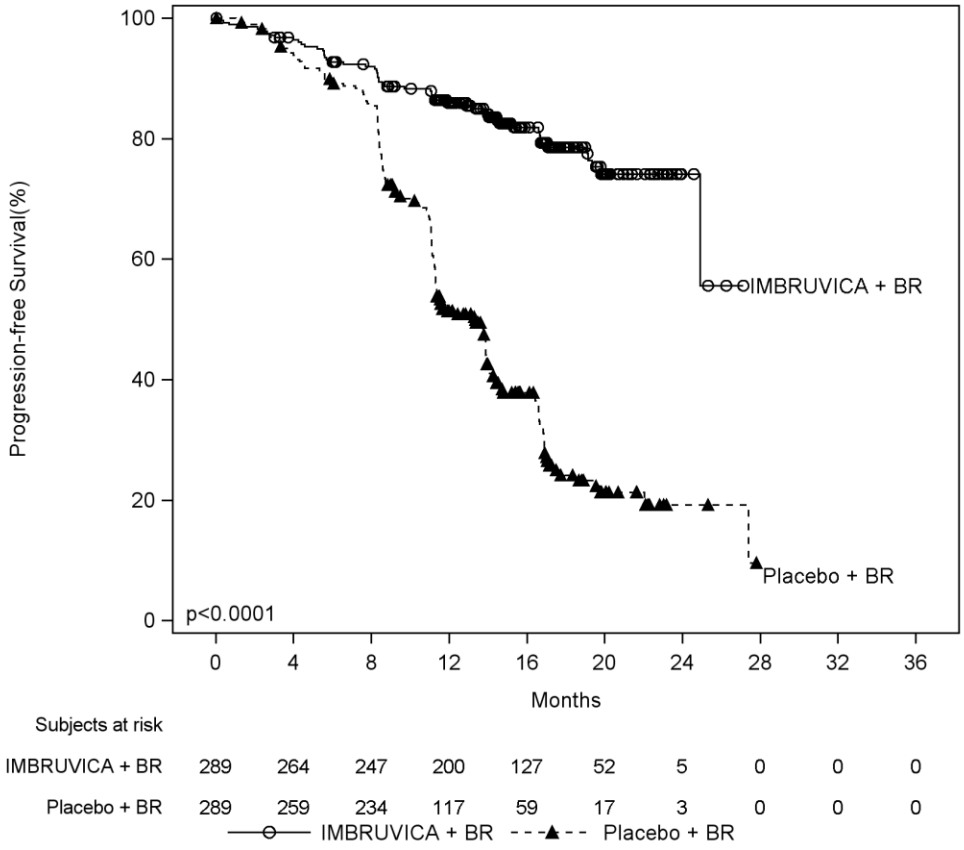
Table 21: Efficacy results in patients with CLL treated with IMBRUVICA® in combination with BR (Study CLL3001)

Endpoint	**IMBRUVICA®+BR N=289**	**Placebo+BR N=289**
Median Progression Free Survival	Not reached	13.3 months
	HR=0.20 [95% CI: 0.15; 0.28]	
Overall Response Rate*	82.7%	67.8%
Overall Response Rate with PRL	83.4%	67.8%

* Per IRC, ORR (CR, CRi, nPR, PR)

The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 11q, patients refractory and not refractory to prior purine analog treatment, patients with and without advanced disease (Rai stage 0-II and stage III-IV), patients with and without bulky lymphadenopathy (<5 cm and ≥5 cm), patients <65 or ≥65 years of age, and patients with 1 or >1 prior lines of therapy.

Figure 6: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study CLL3001



Mantle Cell Lymphoma (MCL)

The safety and efficacy of IMBRUVICA® in patients with relapsed or refractory MCL were demonstrated in a single-arm, multicenter phase 2 trial (PCYC-1104-CA). The patients studied received at least 1, but no more than 5, prior treatment regimens for MCL, and had documented failure to achieve at least partial response with, or documented disease progression after, the most recent treatment regimen. 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). At baseline, 39% of patients had bulky disease (≥5 cm), 49% had high-risk score by Simplified MCL International Prognostic Index (MIPI), 72% had advanced disease (extranodal and/or bone marrow involvement), and 15% had blastoid histology at screening.

IMBRUVICA® was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumour response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). At a median duration of follow up of 26.7 months, responses to IMBRUVICA® are shown in Table 22.

Table 22: Overall Response Rate (ORR) Based on Investigator Assessment in Patients with Mantle Cell Lymphoma (Study PCYC-1104-CA; n=111)

ORR (CR+PR) (95% CI)	66.7% (57.1%, 75.3%)
CR	22.5%
PR	44.1%

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

The median time to initial response was 1.9 months, and the median duration of response (DOR) was estimated to be 17.5 months. The efficacy data were further evaluated by an IRC demonstrating an ORR of 69%, with a 25% CR rate and a 43% PR rate.

The overall response to IMBRUVICA® appears to be independent of prior treatment (bortezomib, lenalidomide), prognostic factors, bulky disease, blastoid histology, gender, and age.

Marginal zone lymphoma (MZL)

The safety and efficacy of IMBRUVICA® were evaluated in a multicenter, single arm phase 2 study (PCYC-1121) of patients with MZL who received at least one prior line of systemic therapy, including an anti-CD20-based therapy. The efficacy analysis included 60 patients with 3 sub types of MZL: mucosa-associated lymphoid tissue (MALT; n=30), nodal (n=17), and splenic (n=13). The median age was 66 years (range, 30 to 92 years), 57% were female, and 85% were Caucasian. Ninety two percent of patients had a baseline ECOG performance status of 0 or 1 and 8% had a status of 2. The median time since diagnosis was 3.7 years and the median number of prior treatments was 2 (range, 1 to 9 treatments).

IMBRUVICA® was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. The primary endpoint in this study was overall response rate (ORR) per independent review committee (IRC) assessment according to revised International Working Group (IWG) criteria for non-Hodgkin's lymphoma (NHL). Responses to IMBRUVICA® are shown in Table 23.

Table 23: Overall response rate (ORR) and duration of response (DOR) based on IRC assessment in patients with MZL

	Total (N=60)*
ORR (CR +PR) (%)	48.3
95% CI (%)	(35.3, 61.7)
Complete Response (CR) (%)	3.3
Partial Response (PR) (%)	45.0
Median DOR, months (range)	NR (16.7, NR)

*Efficacy Population: all patients who had measurable disease at baseline per IRC assessment, received at least 1 dose of IMBRUVICA®, and had at least 1 adequate post-baseline disease assessment
CI = confidence interval; NR = not reached
Median follow up of 19.4 months.

The median time to initial response was 4.5 months (range, 2.3 to 16.4 months). Per IRC assessment, the median DOR was not reached (range, 16.7 to not reached), with 62% of all responders alive and progression-free at 18 months. The overall response to IMBRUVICA® appears to be consistent among the subgroups examined, including MZL subtypes, number of

prior regimens (1, 2, >=3), presence or absence of extranodal disease, bone marrow involvement (positive, negative), baseline ECOG (0, >=1), gender and age.

Waldenström's Macroglobulinemia (WM)

Single-Agent Therapy

The safety and efficacy of IMBRUVICA® in patients with WM (IgM-excreting lymphoplasmacytic lymphoma) were evaluated in a single arm trial (PCYC-1118E) and a non-randomized single-agent therapy substudy arm (Study PCYC-1127-CA).

Study PCYC-1118E was an open-label, multi-center, single-arm trial of 63 previously treated patients with WM. 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 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), the median β2 microglobulin value was 3.9 mg/L (range, 1.4 to 14.2 mg/L), and 60% of patients were anemic (hemoglobin ≤110 g/L).

IMBRUVICA® was administered orally as a single-agent therapy at 420 mg once daily until disease progression or unacceptable toxicity. The primary endpoint in this study was ORR, defined as minor response or better (where minor response was categorized by ≥25-49% reduction in serum monoclonal IgM levels), per investigator assessment. The ORR and duration of response were assessed using criteria adopted from the Third International Workshop of Waldenström's Macroglobulinemia (IWWM). At a median duration of follow-up of 14.8 months, the ORR per investigator assessment was 87.3% (Table 24). Efficacy results were also assessed by an IRC demonstrating an ORR of 82.5% (Table 24).

Table 24: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator and IRC Assessment in Patients with Waldenström's Macroglobulinemia (Study PCYC-1118E; n=63)

Endpoint	Investigator	IRC
ORR (95% CI)	87.3% (76.5%, 94.4%)[a]	82.5% (70.9%, 90.9%)
CR	0%	0%
VGPR	14.3%	11.1%
PR	55.6%	50.8%
MR	17.5%	20.6%
Median DOR, months (range)	NR (0.03+, 18.8+)[b]	NR (2.43, 18.8+)
Median time to response, months (range)	1.0 (0.7, 13.4)[b]	1.0 (0.7, 13.4)

[a] primary endpoint; [b] secondary endpoint. CI = confidence interval; MR = minor response; NR = not reached; PR = partial response; VGPR = very good partial response; ORR = MR+PR+VGPR.

The overall response to IMBRUVICA® was consistent among all subgroups examined, including number of prior regimens (1-2 and >2), baseline ECOG, hemoglobin level at baseline (≤110 g/L and >110 g/L), IgM level at baseline (<40 g/L and ≥40 g/L), and β2-microglobulin level at baseline (≤3 mg/L and >3 mg/L), gender and age.

The non-randomized single-agent therapy substudy arm of Study PCYC-1127-CA included 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 overall response rate appeared to be consistent with PCYC-1118E.

Combination Therapy

The safety and efficacy of IMBRUVICA® in combination with rituximab were evaluated in a randomized, double-blind, multi-center, controlled phase 3 study (PCYC-1127-CA) in patients with previously untreated and previously treated WM. Patients (n=150) were randomized 1:1 to receive either IMBRUVICA® 420 mg once daily in combination with rituximab or placebo plus rituximab until disease progression or unacceptable toxicity. Intravenous 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 previously untreated, and 55% of patients were previously treated. The median time since diagnosis was 52.6 months (previously untreated 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), the median β2 microglobulin value was 3.7 mg/L (range, 1.4 to 27.9 mg/L), 63% of patients were anemic (hemoglobin ≤11 g/dL), MYD88 L265P mutations were present in 77% of patients and absent in 13% of patients, CXCR4 WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) mutations were present in 33% of patients and absent in 58% of patients, and 9% of patients were not evaluable for MYD88 or CXCR4 mutation status. Both MYD88 L265P and CXCR4 WHIM mutations were absent in 13% of patients.

The primary endpoint was PFS as assessed by an IRC, and efficacy evaluations were based on the modified Consensus Response Criteria from the Sixth IWWM. Efficacy results for Study PCYC-1127-CA at a median time on study of 26.5 months are shown in Table 25 and the Kaplan-Meier curve for PFS is shown in Figure 7.

Table 25: Efficacy results of Overall Population of patients with WM based on IRC assessment (Study PCYC-1127-CA)

Endpoint	IMBRUVICA® + Rituximab N=75	Placebo + Rituximab N=75
Progression Free Survival[a]		
Number of events	14 (18.7%)	42 (56.0%)
Median, months	Not reached (35.0, NE)	20.3 (95% CI: 13.7, 27.6)
HR	0.20 (95% CI: 0.11, 0.38) p < 0.0001	
Response Rate (CR, VGPR, PR)[b]	54 (72.0%)	24 (32.0%)
Rate Ratio	2.299 (95% CI: 1.592, 3.319) p<0.0001	

Median duration of response, months (range)	Not reached (1.9+, 36.4+)	21.2 (4.6, 25.8)
Clinical Response Rate (CR, VGPR, PR, MR)[b]	69 (92.0%)	35 (46.7%)
Rate ratio	2.001 (95% CI: 1.554, 2.576) p<0.0001	
CR	2 (2.7%)	1 (1.3%)
VGPR	17 (22.7%)	3 (4.0%)
PR	35 (46.7%)	20 (26.7%)
MR	15 (20.0%)	11 (14.7%)

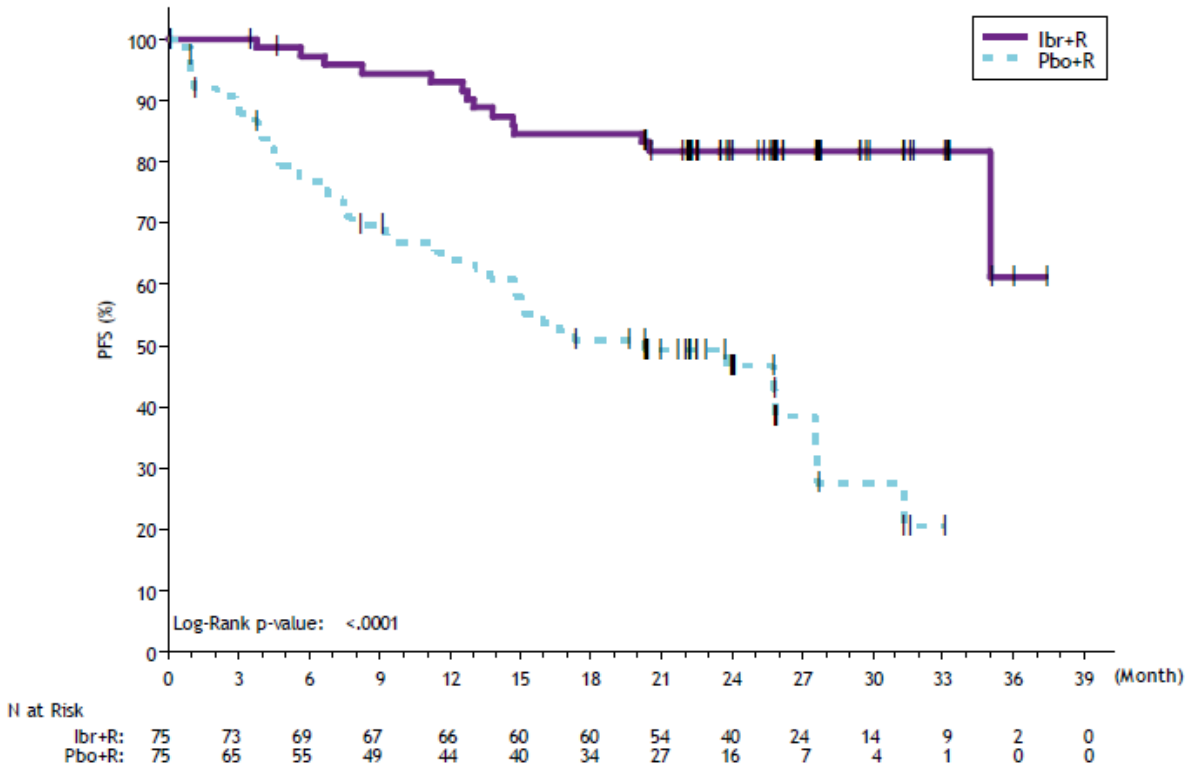
CI = confidence interval; CR = complete response; HR = hazard ratio; MR = minor response; NE = not estimable; PR = partial response; VGPR = very good partial response

[a] Per IRC.

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

The median duration of clinical response was not reached in the IMBRUVICA®+rituximab arm, and was 24.8 months in the placebo + rituximab arm. The proportion of patients with sustained hemoglobin improvement (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) was 73.3% in the IMBRUVICA®+rituximab arm, and 41.3% in the placebo +rituximab arm, rate ratio = 1.774 (95% CI: 1.311, 2.400), p < 0.0001.

Figure 7: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1127-CA



Tumour flare in the form of IgM increase occurred in 8.0% of patients in the IMBRUVICA® + rituximab arm and 46.7% of patients in the placebo + rituximab arm.

The PFS hazard ratios for previously untreated and previously treated patients were 0.337 (95% CI: 0.120, 0.948) and 0.165 (95% CI: 0.075, 0.363), respectively. A treatment effect in favour of the IMBRUVICA® + rituximab arm was observed for subgroups examined, including patients with and without MYD88 L265P mutations, gender, and age (<65 and ≥65).

Chronic graft versus host disease (cGVHD)

The safety and efficacy of IMBRUVICA® in cGVHD were evaluated in an open-label, multi-center, single-arm trial of 42 patients with cGVHD who required additional therapy after failure of first line corticosteroid therapy (Study PCYC-1129-CA). The median age was 56 years (range, 19 to 74 years), 52% were male, 93% were Caucasian, and 60% of patients had a Karnofsky performance score of ≤ 80. The most common underlying malignancies leading to transplant were acute lymphocytic leukemia, acute myeloid leukemia, and CLL. The median time since diagnosis was 14 months and the median number of prior cGVHD treatments was 2 (range, 1 to 3 treatments). The majority of patients (88%) had at least 2 organs involved at baseline, with the most commonly involved organs being mouth (86%), skin (81%), and gastrointestinal tract (33%). The median daily steroid dose per body weight at baseline was 0.3 mg/kg/day and 52% of patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Median duration of exposure was 4.4 months (range 0.2 to 14.9; mean 6.6 months) and 12 patients (28.6%) remained on treatment at the time of analysis.

IMBRUVICA® was administered orally at 420 mg once daily until disease progression, unacceptable toxicity or recurrence of underlying malignancy. The primary endpoint in this study was best ORR per investigator assessment using the 2005 National Institutes of Health (NIH) Consensus Panel Response Criteria, with two modifications based on the updated 2014 NIH Consensus Panel Response Criteria. At a median duration of follow-up of 13.9 months the best ORR was 66.7%. Responses were seen across involved organs for cGVHD (skin, mouth, gastrointestinal tract, and liver). The rate of sustained response for ≥ 20 weeks was 71% for responders. The median steroid dose was reduced over time for the all-treated population, from 0.31 mg/kg/day at baseline to 0.14 mg/kg/day at week 48, and 5 patients were able to completely discontinue corticosteroids while in response. Two patients who responded discontinued ibrutinib treatment because their condition no longer required treatment. Exploratory analyses of patient-reported symptom bother showed a decrease of at least 7 points in the Lee Chronic GVHD Symptom Scale total summary score in 43% (18/42) of patients, and in 24% (10/42) of patients on at least 2 consecutive visits. Efficacy results are shown in Table 26.

Table 26: Best overall response rate (ORR), sustained response rate, based on investigator assessment in patients with cGVHD

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

CI = confidence interval

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

Comparative Bioavailability Studies

IMBRUVICA® tablets were evaluated in bioavailability studies. Ibrutinib exposure (C_{max} and AUC_{last}) is comparable following a single 1 x 140 mg dose of IMBRUVICA® as either tablets or capsules. In a similar study comparing 560 mg doses of ibrutinib as either 1 x 560 mg tablets or 4 x 140 mg capsules, AUC_{last} was comparable for the two dosage forms and C_{max} was 28% lower for IMBRUVICA® 560 mg tablets as compared with the capsules. The difference in C_{max} seen with the 560 mg doses is considered not to be clinically meaningful.

DETAILED PHARMACOLOGY

Pharmacodynamics

The effects of ibrutinib and the dihydrodiol metabolite on hERG channel-mediated ion current were evaluated in voltage-clamped HEK293 cells that stably express hERG potassium channels. The IC_{50} for inhibitory effect of ibrutinib on hERG channel current was 970 nM (427 ng/mL). The IC_{50} for inhibitory effect of the dihydrodiol metabolite on hERG channel current was 9600 nM (4555 ng/mL).

The acute effects of ibrutinib treatment on cardiovascular function were also assessed in dogs up to doses of 150 mg/kg. Lowered heart rate and increased blood pressure were observed at doses ≥24 mg/kg (≥7.2 times human exposure at the dose of 420 mg daily based on C_{max}). There was no treatment-related prolongation of QT_c intervals observed at any dose level. Shortening of the QTc interval was observed at a dose of 150 mg/kg (≥5.6 times human exposure at the dose of 420 mg daily based on C_{max}).

There were no ibrutinib-related acute effects on CNS or respiratory function in rats at doses up to 150 mg/kg (approximately 22 times human exposure at the dose of 420 mg daily based on C_{max}).

TOXICOLOGY

Carcinogenicity and Mutagenicity

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not genotoxic *in vitro* in bacterial reverse mutation (Ames) and chromosomal aberrations assays. Ibrutinib was also non-clastogenic *in vivo* in the mouse bone marrow erythrocyte micronucleus assay.

Chronic Toxicity

In rats and dogs, lymphoid organs and the gastrointestinal tract were identified as target organs/tissues of toxicity. Additional histopathological changes were noted in the pancreas and bone in rats, but were not observed in dogs.

The following adverse effects were seen in studies up to 13-weeks duration in rats and dogs. Ibrutinib was found to induce gastrointestinal effects (soft feces/diarrhea and/or inflammation) in

rats at human equivalent doses (HEDs) ≥16 mg/kg/day and in dogs at HEDs ≥32 mg/kg/day (≥4 times human clinical exposure at the dose of 420 mg daily based on AUC). Effects on lymphoid tissue (lymphoid depletion) were also induced at HEDs ≥28 mg/kg/day in rats and ≥32 mg/kg/day in dogs (≥4 times human clinical exposure at the dose of 420 mg daily based on AUC). In rats, moderate pancreatic acinar cell atrophy was observed after 13 weeks of administration at HEDs ≥16 mg/kg/day (≥8 times human clinical exposure at the dose of 420 mg daily based on AUC). Mildly decreased trabecular and cortical bone was seen in female rats administered HEDs ≥16 mg/kg/day for 13 weeks (≥8 times human clinical exposure at the dose of 420 mg daily based on AUC). All notable findings in rats and dogs fully or partially reversed following recovery periods of 6 to 13 weeks.

In a 6-month repeat dose toxicity study in rats, effects on the pancreas (minimal to mild acinar atrophy or hemorrhage) were observed at HEDs ≥4 mg/kg/day (≥2.4 times human clinical exposure at the dose of 420 mg daily based on AUC). These effects were considered non-adverse due to lack of corresponding evidence of functional perturbation. In a 9-month repeat dose toxicity study in dogs, effects on lymphoid tissue (minimal lymphoid depletion in Peyer's patches and/or minimal to mild lymphoid depletion with sinus congestion in the peripheral lymph nodes) were observed at HEDs ≥16 mg/kg/day (≥0.3 times human clinical exposure at the dose of 420 mg daily based on AUC). These findings in rats and dogs fully or partially reversed following a 1-month recovery period.

Reproductive and Developmental Toxicity

In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

In a study of fertility and early embryonic development in rats, ibrutinib administered orally before cohabitation and through mating and implantation had no effects on fertility or reproductive capacities in males or females up to the maximum dose tested, 100 mg/kg/day (approximately 8 times in males and 30 times in females of the clinical dose of 420 mg daily based on AUC).

Ibrutinib was studied for effects on embryo-fetal development in pregnant rats given oral doses of 10, 40 and 80 mg/kg/day during organogenesis. At a dose of 80 mg/kg/day (approximately 18 times the AUC of ibrutinib and 9.1 times the AUC of the dihydrodiol metabolite compared to patients at the dose of 420 mg daily), ibrutinib was associated with increased post-implantation loss and increased visceral malformations (heart and major vessels). At a dose of ≥40 mg/kg/day (≥ approximately 7.3 times the AUC of ibrutinib and 3.9 times the AUC of the dihydrodiol metabolite compared to patients at a dose of 420 mg daily), ibrutinib was associated with decreased fetal weights. The no-observed-adverse-effect level (NOAEL) for rat embryo-fetal development was 10 mg/kg/day (1.9 times the AUC of ibrutinib and 1.0 times the AUC of the dihydrodiol metabolite in patients receiving 420 mg daily).

Ibrutinib was administered orally to pregnant rabbits during the period of organogenesis at oral doses of 5, 15, and 45 mg/kg/day. At a dose of ≥15 mg/kg/day (≥2.8 times the AUC of ibrutinib and ≥1.4 times the AUC of the dihydrodiol metabolite in patients receiving 420 mg daily), ibrutinib was associated with skeletal malformations (fused sternebrae). At a dose of 45 mg/kg/day (6.9 times the AUC of ibrutinib and 4.6 times the AUC of the dihydrodiol metabolite in patients receiving 420 mg daily), ibrutinib was associated with increased

post-implantation loss. Maternal toxicity (i.e., reduced food consumption and body weights) was evident at 45 mg/kg/day. The NOAEL for rabbit embryo-fetal development was 5 mg/kg/day (1.1 times the AUC of ibrutinib and 0.4 times the AUC of the dihydrodiol metabolite in patients receiving 420 mg daily).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrIMBRUVICA®
ibrutinib tablets
ibrutinib capsules

Read this carefully before you start taking **IMBRUVICA®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IMBRUVICA®**.

Serious Warnings and Precautions

IMBRUVICA® should only be prescribed by a qualified doctor who is experienced in the use of anti-cancer drugs.

- Major bleeding events, some fatal, have been reported (see below)
- IMBRUVICA® should not be used in patients with moderate or severe liver problems (see below)
- IMBRUVICA® should not be used with certain medications that can increase the blood level of IMBRUVICA® (see below)

What is IMBRUVICA® used for?

IMBRUVICA® is used in adults to treat:

- **Chronic Lymphocytic Leukemia (CLL):** IMBRUVICA® is used to treat patients with active CLL who have not had prior therapy, including those with a deletion of the "TP53" gene (17p deletion). IMBRUVICA® is also used to treat patients with CLL who have received at least one prior therapy, including those with a deletion of the "TP53" gene (17p deletion). In patients with CLL who have received at least one prior therapy, IMBRUVICA® can also be used in combination with bendamustine and rituximab.
- **Mantle Cell Lymphoma (MCL):** IMBRUVICA® is used to treat patients with previously treated MCL when the disease has come back or has not responded to treatment.
- **Marginal Zone Lymphoma (MZL):** IMBRUVICA® is used to treat patients with MZL. It is used when they need medicine and not radiation or surgery. It is for patients who have received at least one prior therapy including an antibody that acts against their cancer. This antibody is called anti-CD20.
- **Waldenström's Macroglobulinemia (WM):** IMBRUVICA® is used to treat patients with WM, and can also be used in combination with rituximab.
- **Chronic graft versus host disease (cGVHD):** IMBRUVICA® is used to treat patients with cGVHD after failure of first line corticosteroid therapy and who need additional therapy.
- It is not known if IMBRUVICA® is safe and effective in children under the age of 18 years.

How does IMBRUVICA® work?

IMBRUVICA® blocks a specific protein in the body that helps cancer cells live and grow. This protein is called "Bruton's Tyrosine Kinase." By blocking this protein, IMBRUVICA® may help kill and reduce the number of cancer cells and slow the spread of the cancer.

What are the ingredients in IMBRUVICA®?
Medicinal ingredient: ibrutinib
Non-medicinal ingredients:
Tablets: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. The tablet film coatings contain black iron oxide (140 mg, 280 mg, 420 mg tablets), polyethylene glycol, polyvinyl alcohol, red iron oxide (280 mg, 560 mg tablets), talc, titanium dioxide, and yellow iron oxide (140 mg, 420 mg, 560 mg tablets).

Capsules: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The white capsule shell contains gelatin and titanium dioxide. Capsules are printed with ink containing iron oxide black and shellac.

IMBRUVICA® comes in the following dosage forms:
Tablets: 140 mg, 280 mg, 420 mg, 560 mg
Capsules: 140 mg

Do not use IMBRUVICA® if you:
- are allergic to ibrutinib or any of the other ingredients in this medicine or components of the container. If you are not sure about this, talk to your healthcare professional before taking IMBRUVICA®.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IMBRUVICA®. Talk about any health conditions or problems you may have, including if you:
- have ever had unusual bleeding or bruising or are on any medicines that increase your risk of bleeding such as aspirin, anti-inflammatories (e.g., ibuprofen, naproxen, and others), warfarin, heparin, other medications to prevent or treat blood clots (e.g., dabigatran, rivaroxaban, apixaban), or any supplements that increase your risk of bleeding such as fish oil, flaxseed, or vitamin E. You should not take warfarin (COUMADIN®) with IMBRUVICA®.
- have or have had heart rhythm problems or severe heart failure, or if you have any of the following: fast and irregular heartbeat, lightheadedness, dizziness, shortness of breath, chest discomfort, swollen legs, or if you faint.
- have or are at increased risk of heart disease.
- have high blood pressure.
- have any infection.
- have had a hepatitis B infection (a viral infection of the liver).
- have liver or kidney problems. You should not take this drug if you have certain liver problems.
- are planning to have any medical, surgical or dental procedure. Your doctor may ask you to stop taking IMBRUVICA® for a short time.

Other warnings you should know about:

Tests and check-ups before and during treatment
Laboratory tests may show that your blood count contains more white blood cells (called "lymphocytes") in the first few weeks of treatment. This is expected and may last for a few

weeks or months. This does not necessarily mean that your blood cancer is getting worse. Your doctor will check your blood counts before and during the treatment. In rare cases your doctor may need to give you another medicine. Talk to your doctor about what your test results mean.

Your doctor will check your blood pressure during treatment and may need to give you another medicine to control your blood pressure.

Children and adolescents
IMBRUVICA® is not recommended for use in patients under 18 years of age.

IMBRUVICA® with food
Do not take IMBRUVICA® with grapefruit or Seville oranges; this includes eating them, drinking the juice, or taking supplements that might contain them. These products may increase the amount of IMBRUVICA® in your blood.

Pregnancy, breast-feeding and fertility
IMBRUVICA® can harm your unborn baby.

Do not get pregnant while you are taking IMBRUVICA®. Women of childbearing age must use two forms of effective birth control methods together during treatment with IMBRUVICA® and for at least 3 months after the last dose of IMBRUVICA®.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your healthcare professional for advice before taking IMBRUVICA®.

Tell your healthcare professional immediately if you become pregnant.

Do not breast-feed while you are taking IMBRUVICA®.

Do not father a child while taking IMBRUVICA® and for 3 months after stopping treatment. Use condoms and do not donate sperm during treatment and for 3 months after your treatment has finished. If you plan to father a child, talk to your healthcare professional before taking IMBRUVICA®.

Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with IMBRUVICA®.

Driving and using machines
You may feel tired or dizzy after taking IMBRUVICA®, which may affect your ability to drive and use tools or machines. Ask your healthcare professional about your ability to drive and use tools or machines while taking IMBRUVICA®.

Tell your doctor or pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with IMBRUVICA®:
- medicines called antibiotics used to treat bacterial infections (clarithromycin, ciprofloxacin, erythromycin, rifampin).

- medicines for fungal infections (ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole).
- medicines for HIV infection (indinavir, nelfinavir, ritonavir, saquinavir, atazanavir, darunavir/ritonavir, cobicistat, fosamprenavir).
- medicine to prevent nausea and vomiting (aprepitant).
- medicines called kinase inhibitors for treatment of other cancers (crizotinib, imatinib).
- medicines called calcium channel blockers for high blood pressure, chest pain, irregular heartbeat and other heart problems (diltiazem, verapamil).
- medicines called statins to treat high cholesterol (rosuvastatin).
- heart medicines/anti-arrhythmics (amiodarone, dronedarone).
- medicines that may increase your risk of bleeding, including:
  - aspirin and anti-inflammatories such as ibuprofen or naproxen.
  - blood thinners such as warfarin, heparin or other medicines for blood clots such as dabigatran, rivaroxaban, apixaban.
  - supplements such as fish oil, vitamin E and flaxseed.
- medicines used to prevent seizures or to treat epilepsy or medicines used to treat a painful condition of the face called trigeminal neuralgia (carbamazepine and phenytoin).
- an herbal medicine used for depression (St. John's Wort).

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

How to take IMBRUVICA®:
Take IMBRUVICA® as prescribed by your doctor.

Swallow IMBRUVICA® whole, with a glass of water. Do not open, break or chew them. Do not take IMBRUVICA® with grapefruit juice.

Take IMBRUVICA® at about the same time each day.

Drink plenty of fluids to stay hydrated while taking IMBRUVICA®. This will help your kidneys continue to function properly.

Usual adult dose:
- **Chronic Lymphocytic Leukemia (CLL):** 420 mg once a day
- **Waldenström's Macroglobulinemia (WM):** 420 mg once a day
- **Chronic graft versus host disease (cGVHD):** 420 mg once a day
- **Mantle Cell Lymphoma (MCL):** 560 mg once a day
- **Marginal Zone Lymphoma (MZL):** 560 mg once a day

Your doctor may decide that you should take a lower dose if you get side effects.

For the treatment of CLL and WM, your doctor may prescribe IMBRUVICA® alone or in combination with other treatments.

IMBRUVICA® is given as a continuous daily therapy, which means you need to take it every day until your disease no longer responds to treatment or you experience unacceptable side effects. Do not change your dose or stop taking IMBRUVICA® unless your doctor tells you to.

Overdose:

If you think you have taken too much IMBRUVICA® contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you miss a dose of IMBRUVICA® take it as soon as you remember on the same day. Take your next dose of IMBRUVICA® at your regular time on the next day. Do not take extra doses of IMBRUVICA® to make up for a missed dose. Call your healthcare professional if you are not sure of what to do.

What are possible side effects from using IMBRUVICA®?

These are not all the possible side effects you may feel when taking IMBRUVICA®. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

- Lymphocytosis: An increase in the number of white blood cells, specifically lymphocytes may be reported in your blood test results (see **Other warnings you should know about)**. This increase in white blood cells is expected in the first few weeks of treatment and may last for 3 or more months. Uncommonly, this increase may be severe, causing cells to clump together (leukostasis). Your doctor will monitor your blood counts. Talk to your doctor about what your blood test results mean.
- Diarrhea: You may experience an increase in frequency of loose or watery stools. If you have diarrhea that lasts for more than a week, your doctor may need to give you treatment to manage your diarrhea such as a fluid and salt replacement or another medicine. Contact your doctor if your diarrhea persists.
- Viral, bacterial, or fungal infections: Infections can be serious and may lead to death. Contact your doctor if you have fever, chills, weakness, confusion, body aches, cold or flu symptoms, feel tired or feel short of breath, or have any other signs or symptoms of a possible infection.
- Fatigue, lack of energy, anxiety, difficulty falling or staying asleep
- Common cold
- Muscle aches, muscle spasm, joint aches
- Headache, dizziness, weakness
- Rash, skin infection
- Inflammation of the fatty tissue underneath the skin
- Nausea, sore mouth, constipation, vomiting, loss of appetite, stomach pain, indigestion
- Nail changes such as brittle fingernails and toenails
- Types of skin cancers that are not melanoma, most frequently squamous cell or basal cell skin cancers, have happened in people taking IMBRUVICA®. Other cancers that are not skin cancer have happened in people taking IMBRUVICA®. Talk to your doctor about monitoring for new skin cancer symptoms.

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	Only if severe	In all cases	
Very common			
Low red blood cells (anemia) (symptoms like fatigue, loss of energy, weakness, shortness of breath)		✓	
Low white blood cells (neutrophils) (symptoms like fever, chills or sweating or any signs of infection)		✓	
Low platelets (symptoms like bruising, bleeding, fatigue and weakness)		✓	
Edema (symptoms like swollen hands, ankles or feet)		✓	
Being short of breath		✓	
Fever		✓	
Pneumonia (symptoms like cough with or without mucus, fever, chills, shortness of breath)		✓	
Sinus infection (symptoms like thick, yellow, smelly discharge from the nose, pressure or pain in the face and eyes, congestion, headache)		✓	
Bruising, small red or purple spots caused by bleeding under the skin	✓		
High blood pressure		✓	
Common			
Urinary tract infection (symptoms like pain or burning when urinating, bloody or cloudy urine, foul smelling urine)		✓	
Hypokalemia (low potassium levels in the blood): muscle weakness, cramps, twitches, abnormal heart rhythms		✓	
Nose bleeds		✓	

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	Only if severe	In all cases	
Severe diarrhea (symptoms like increased number of bowel movements, watery or bloody stool, stomach pain and/or cramps)		✓	
Irregular heart rhythm (arrhythmic symptoms may include palpitations, lightheadedness, dizziness, shortness of breath, chest discomfort, fainting)		✓	
Blurred vision	✓		
Infection of the blood (symptoms like feeling dizzy or faint, confusion or disorientation, diarrhea, nausea, vomiting, slurred speech, severe muscle pain)			✓
Serious bleeding problems sometimes resulting in death (symptoms like blood in your stool or urine, bleeding that lasts for a long time or that you cannot control, coughing up blood or blood clots, increased bruising, feel dizzy or weak, confusion, change in your speech, or a headache that lasts a long time)			✓
Inflammation within the lungs (symptoms like difficulty breathing or persistent cough)		✓	
Tumour Lysis Syndrome (symptoms like nausea, vomiting, decreased urination, irregular heartbeat, confusion, delirium, seizures)			✓
Elevated levels of uric acid in the blood (symptoms like red, warm, and swollen joints, flank pain, blood in urine, or cream-colored skin nodules)		✓	

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	Only if severe	In all cases	
Peripheral Neuropathy (symptoms like weakness, numbness, tingling, pain, or hot or cold sensation in hands, feet or other parts of the body)	✓		
Uncommon			
Severe increase in white blood cells (symptoms like fever, fainting, bleeding, bruising, weight loss, general pain, lack of energy, severe headache, trouble walking)		✓	
Severe allergic reactions (symptoms like swelling of face, eyes, lips, mouth, or tongue, trouble swallowing or breathing, itchy skin rash, redness of the skin)			✓
Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)			✓
Kidney failure (symptoms like decreased or lack of urination, nausea, swelling of the ankles, legs or feet, fatigue, confusion, seizures or coma)			✓
Severe liver problems (symptoms like nausea, loss of appetite, fatigue, yellowing of your skin and eyes (jaundice), pain in your upper right abdomen, distension of your abdomen, swelling in the legs, dark urine, disorientation, or confusion)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect® (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect® (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store IMBRUVICA® at room temperature between 15ºC and 30ºC.

Keep out of the reach and sight of children.

If you want more information about IMBRUVICA®:

- Talk to your healthcare professional.
- For questions or concerns, contact the manufacturer, Janssen Inc. (www.janssen.com/canada).
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html), the manufacturer's website www.janssen.com/canada, or by contacting the manufacturer at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc., Toronto, Ontario, M3C 1L9.

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