PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrIMBRUVICA®

ibrutinib tablets

Tablets, 140 mg, 280 mg, 420 mg, 560 mg, Oral

ibrutinib capsules

Capsules, 140 mg, Oral

ibrutinib oral suspension

Suspension, 70 mg/mL, Oral

Protein Kinase Inhibitor

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9
www.janssen.com/canada

Date of Initial Authorization:
November 17, 2014

Date of Revision:
August 1, 2023

Submission Control Number: 266710

RECENT MAJOR LABEL CHANGES

1 Indications	08/2023
3 Serious Warnings and Precautions Box	08/2023
4 Dosage and Administration, 4.1 Dosing Considerations	08/2023
4 Dosage and Administration, 4.2 Recommended dose and dosage adjustment	08/2023
4 Dosage and Administration, 4.4 Administration	08/2023
7 Warnings and Precautions, Cardiovascular	06/2022
7 Warnings and Precautions, Gastrointestinal	08/2023
7 Warnings and Precautions, Hemorrhage	12/2021
7 Warnings and Precautions, Hepatic/Biliary/Pancreatic	08/2023
7 Warnings and Precautions, Immune	08/2023
7 Warnings and Precautions, Monitoring and Laboratory Tests	05/2021
7 Warnings and Precautions, 7.1.1 Pregnant Women	03/2021
7 Warnings and Precautions, 7.1.3 Pediatrics	08/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

IMBRUVICA® (ibrutinib) is indicated:

- for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL), including those with 17p deletion.

  Clinical effectiveness of IMBRUVICA® in previously untreated adult 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.

- in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL, including those with 17p deletion.

- in combination with rituximab for the treatment of adult patients with previously untreated CLL.

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

- in combination with venetoclax for the treatment of adult patients with previously untreated CLL, including those with 17p deletion.

- for the treatment of adult patients with CLL who have received at least one prior therapy, including those with 17p deletion.

- in combination with bendamustine and rituximab for the treatment of adult patients with CLL who have received at least one prior therapy.

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

- for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

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

- for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

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

- in combination with rituximab for the treatment of adult patients with WM.

- for the treatment of adult patients with steroid dependent or refractory chronic graft versus host disease (cGVHD).

- for the treatment of pediatric patients age 1 year and older with cGVHD after failure of one or more lines of systemic therapy.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed, Health Canada has authorized IMBRUVICA® for the treatment of pediatric patients age 1 year and older with cGVHD after failure of one or more lines of systemic therapy (see 1 INDICATIONS and 14.1 Clinical Trials by Indication, Chronic Graft Versus Host Disease (cGVHD) - Pediatrics).

1.2 Geriatrics

Geriatrics (>65 years of age): In studies of patients with B-cell malignancies treated with IMBRUVICA®, no overall differences in the efficacy of IMBRUVICA® treatment were observed between patients ≥65 years of age 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 7.1.4 Geriatrics).

A study of 42 patients with cGVHD treated with IMBRUVICA® did not include sufficient numbers of patients ≥65 years of age to determine differences in efficacy or safety between older (≥65 years of age) and younger adult patients.

2 CONTRAINDICATIONS

Ibrutinib is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Major bleeding events, some fatal, have been reported (see 7 WARNINGS AND PRECAUTIONS, Hemorrhage)
- Dose reductions or avoidance of IMBRUVICA® should be considered for patients with hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 4.2 Recommended Dose and Dose Adjustment, Special Populations and Conditions, Hepatic impairment)
- Fatal and serious cardiac arrhythmias or cardiac failure have been reported (see 7 WARNINGS AND PRECAUTIONS, Cardiac Arrhythmias and Cardiac Failure)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Consider dose reductions or avoidance in patients with hepatic impairment (see 4.2 Recommended Dose and Dose Adjustment, Special Populations and Conditions, 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- If a moderate or strong CYP3A inhibitor must be used, consider a dose modification (see 4.2 Recommended Dose and Dose Adjustment, Concomitant use of CYP3A Inhibitors).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Adults

The recommended dose of IMBRUVICA® for CLL or WM is 420 mg once daily. When given as a single agent, IMBRUVICA® is administered until disease progression or is no longer tolerated by the patient. When given in combination, IMBRUVICA® is administered as follows:

In patients with previously untreated CLL, IMBRUVICA® can be used in combination with obinutuzumab or rituximab, until disease progression or is no longer tolerated by the patient. For information on the dosing of obinutuzumab or rituximab, consult the corresponding Product Monographs.

In patients with previously untreated CLL, IMBRUVICA® can be used in combination with venetoclax for a fixed duration of treatment. IMBRUVICA® should be administered as a single agent for 3 cycles (1 cycle is 28 days), followed by 12 cycles of IMBRUVICA® plus venetoclax, starting at Cycle 4. Venetoclax should be given as per the venetoclax Product Monograph.

In patients with previously treated CLL, IMBRUVICA® can be used in combination with bendamustine and rituximab, until disease progression or is no longer tolerated by the patient. For information on dosing of bendamustine and rituximab, consult the corresponding Product Monographs.

In patients with WM, IMBRUVICA® can be used in combination with rituximab, until disease progression or is no longer tolerated by the patient. For information on dosing and administration of rituximab, consult the Product Monograph. For rituximab dosing used in the pivotal clinical study, see 14 CLINICAL TRIALS, Waldenström's Macroglobulinemia (WM), Combination Therapy.

When administering IMBRUVICA® in combination with rituximab or obinutuzumab, consider administering IMBRUVICA® prior to rituximab or obinutuzumab 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.

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 10 CLINICAL PHARMACOLOGY).

Pediatrics

The recommended doses of IMBRUVICA® for cGVHD are:

- 420 mg orally once daily for pediatric patients age 12 years and older, and
- 240 mg/m^2 orally once daily for pediatric patients 1 to < 12 years of age (Table 1).

IMBRUVICA® should be given until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity. When a patient no longer requires therapy for the treatment of cGVHD, IMBRUVICA® should be discontinued considering the medical assessment of the individual patient.

Recommended dosage for pediatric patients 1 to < 12 years of age based on body surface area (BSA) using either IMBRUVICA® capsules/tablets or oral suspension is presented in Table 1:

Table 1: Recommended Dosing for Pediatric Patients 1 to < 12 years of age for cGVHD

	240 mg/m^2	
BSA Range (m^2)	**Dose of IMBRUVICA® Capsules/Tablets to Administer (mg)**	**Volume of IMBRUVICA® 70 mg/mL Oral Suspension to Administer (mL)**
> 0.3 - 0.4	-	1.2
> 0.4 - 0.5	-	1.5
> 0.5 - 0.6	-	1.9
> 0.6 - 0.7	140	2.2
> 0.7 - 0.8	-	2.6
> 0.8 - 0.9	-	2.9
> 0.9 - 1.0	-	3.3
> 1.0 - 1.1	280	3.6
> 1.1 - 1.2	280	4
> 1.2 - 1.3	280	4.3
> 1.3 - 1.4	-	4.6
> 1.4 - 1.5	-	5
> 1.5 - 1.6	-	5.3
> 1.6	420	6

BSA=body surface area

See Instructions for Use leaflet provided in the carton for administration, handling and disposal details of IMBRUVICA® oral suspension.

Dosage Adjustment

IMBRUVICA® therapy should be withheld for any new onset or worsening Grade 2 cardiac failure, Grade 3 cardiac arrhythmias, 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), resume IMBRUVICA® therapy at the recommended dose as per the tables below.

Recommended dose modifications for non-cardiac events are provided in Table 2.

Table 2: Recommended dose modifications for non-cardiac events

Events	Toxicity occurrence	CLL/WM/adults and adolescent patients (≥ 12 years) with cGVHD dose modification after recovery	cGVHD dose modification for pediatric patients (1 to <12 years) after recovery	MCL/MZL dose modification after recovery
Grade 3 or 4 non-hematological toxicities Grade 3 or 4 neutropenia with infection or fever Grade 4 hematological toxicities	First*	restart at 420 mg daily	restart at 240 mg/m^2 daily	restart at 560 mg daily
	Second	restart at 280 mg daily	restart at 160 mg/m^2 daily	restart at 420 mg daily
	Third	restart at 140 mg daily	restart at 80 mg/m^2 daily	restart at 280 mg daily
	Fourth	discontinue IMBRUVICA®		
*When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the toxicity reoccurs, reduce daily dose.				

Recommended dose modifications for events of cardiac failure or cardiac arrythmias are described in Table 3.

Table 3: Recommended dose modifications for events of cardiac failure or cardiac arrhythmias

Events	Toxicity occurrence	CLL/WM/adults and adolescent patients (≥ 12 years) with cGVHD dose modification after recovery	cGVHD dose modification for pediatric patients (1 to <12 years) after recovery	MCL/MZL dose modification after recovery
Grade 2 cardiac failure	First	restart at 280 mg daily	restart at 160 mg/m^2 daily	restart at 420 mg daily
	Second	restart at 140 mg daily	restart at 80 mg/m^2 daily	restart at 280 mg daily
	Third	discontinue IMBRUVICA®		
Grade 3 cardiac arrhythmias	First	restart at 280 mg daily[†]	restart at 160 mg/m^2 daily[†]	restart at 420 mg daily[†]
	Second	discontinue IMBRUVICA®		
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	discontinue IMBRUVICA®		
[†] Evaluate the benefit-risk before resuming treatment.				

Recommended cGVHD dose modifications for pediatric patients 1 to < 12 years of age based on body surface area (BSA) using either IMBRUVICA® capsules/tablets or oral suspension are presented in Table 4.

Table 4: Recommended dose modification for pediatric patients 1 to < 12 years of age based on BSA

	160 mg/m^2		80 mg/m^2	
BSA (m^2) Range	**Dose of IMBRUVICA® Capsules/Tablets to Administer (mg)**	**Volume of IMBRUVICA® Oral Suspension to Administer (mL)**	**Dose of IMBRUVICA® Capsules/Tablets to Administer (mg)**	**Volume of IMBRUVICA® Oral Suspension to Administer (mL)**
> 0.3 - 0.4	-	0.8	-	0.4
> 0.4 - 0.5	-	1	-	0.5
> 0.5 - 0.6	-	1.3	-	0.6
> 0.6 - 0.7	-	1.5	-	0.7
> 0.7 - 0.8	140	1.7	-	0.9
> 0.8 - 0.9	140	1.9	-	1
> 0.9 - 1.0	140	2.2	-	1.1
> 1.0 - 1.1	140	2.4	-	1.2
> 1.1 - 1.2	-	2.6	-	1.3
> 1.2 - 1.3	-	2.9	-	1.4
> 1.3 - 1.4	-	3.1	-	1.5
> 1.4 - 1.5	-	3.3	140	1.7
> 1.5 - 1.6	280	3.5	140	1.8
> 1.6	280	4	140	2

BSA= body surface area

Concomitant use of CYP3A Inhibitors

Concomitant use of moderate and strong CYP3A inhibitors increases the exposure of ibrutinib (see 9 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 Table 5. 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.

Table 5: Use with CYP3A inhibitors

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.
	• Other strong CYP3A inhibitors	Concomitant use should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If these strong CYP3A inhibitors 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 (adults and pediatric patients ≥12 years of age)	• 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.
	• Posaconazole at doses higher than 200 mg BID (suspension) or 300 mg QD (delayed-release tablet)* • Other strong CYP3A inhibitors	Concomitant use should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If these strong CYP3A inhibitors must be used short term (7 days or less), withhold IMBRUVICA® treatment temporarily for the duration of the CYP3A inhibitor treatment.

Patient Population	Co-administered Drug	Recommended IMBRUVICA® Dose for the Duration of the Inhibitor Use [a]
Chronic Graft versus Host Disease (pediatric patients 1 to <12 years of age)	• Mild CYP3A inhibitors	240 mg/m^2 once daily. No dose adjustment required.
	• Moderate CYP3A inhibitors	240 mg/m^2 once daily. No dose adjustment required.
	• Voriconazole	160 mg/m^2 once daily
	• Posaconazole	80 mg/m^2 once daily
	• Other strong CYP3A inhibitors	Concomitant use should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If these strong CYP3A inhibitors 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.		

Special Populations and Conditions

Pediatrics (<18 years of age): Based on the data submitted and reviewed, Health Canada has authorized IMBRUVICA® for the treatment of pediatric patients 1 year and older with cGVHD after failure of one or more lines of systemic therapy (see 1 INDICATIONS). The recommended dose is 420 mg once daily for the patients 12 years of age or older, and 240 mg/m^2 once daily for the patients 1 to < 12 years of age. See 4.2 Recommended Dose and Dosage Adjustment for details.

Geriatrics (≥65 years of age): No dose adjustment is required based on age (see 7.1.4 Geriatrics).

Renal impairment: No specific clinical studies have been conducted in patients with impaired renal function (see 10.3 Pharmacokinetics). No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained (see 7 WARNINGS AND PRECAUTIONS, Renal).

Hepatic impairment:

Adult Patients with B-cell Malignancies: IMBRUVICA® should not be used in patients with moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C) (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic). 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.

Patients with cGVHD: Avoid the use of IMBRUVICA® in patients with total bilirubin level > 3 x upper limit of normal (ULN) (unless of non-hepatic origin or due to Gilbert's Syndrome). The recommended dosage is 140 mg daily for patients 12 years of age and older with total bilirubin level >1.5 to 3 x ULN (unless of non-hepatic origin or due to Gilbert's Syndrome). The recommended dosage is 80 mg/m^2 daily for patients 1 to < 12 years of age with total bilirubin level >1.5 to 3 x ULN (unless of non-hepatic origin or due to Gilbert's syndrome). Monitor patients for signs of toxicity.

4.4 Administration

IMBRUVICA® capsules and tablets 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.

Swallow IMBRUVICA® oral suspension and drink water after swallowing. An adult caregiver should administer the dose, and only use the dosing syringes included in the package for oral administration. Follow Instructions for Use leaflet provided in the carton for further administration details of IMBRUVICA® oral suspension.

IMBRUVICA® must not be taken with grapefruit juice.

4.5 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.

5 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 6: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule 140 mg	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.
Oral	Tablet 140 mg, 280 mg, 420 mg, 560 mg	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).
Oral	Suspension 70 mg/mL	Benzyl alcohol, citric acid monohydrate, disodium phosphate, hypromellose, microcrystalline cellulose and carmellose sodium, purified water, sucralose.

IMBRUVICA® (ibrutinib) 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).

- 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.

IMBRUVICA® (ibrutinib) capsules

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

- 140 mg capsules: White hard gelatin capsules marked with “ibr 140 mg” in black ink, containing 140 mg ibrutinib.

IMBRUVICA® (ibrutinib) oral suspension

IMBRUVICA® oral suspension is supplied in a 150 mL amber glass bottle with child-resistant closure, co-packaged with a bottle adapter (which must be inserted into the bottle at first use) and two 5 mL reusable oral dosing syringes with 0.1 mL graduations. The supplied oral dosing syringes should not be used for any other medications.

- 70 mg/mL oral suspension: White to almost white suspension.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

Second Primary Malignancies

In the pooled safety database, non-melanoma skin cancers occurred in 5% of adult patients treated with IMBRUVICA® (see 8.1 Adverse Reactions Overview, Non-melanoma skin cancer). Non-skin related malignancies occurred in 3% of patients in the pooled safety database.

Monitor patients for the appearance of non-melanoma skin cancers.

Cardiovascular

Cardiac Arrhythmias and Cardiac Failure

Fatal and serious cardiac arrhythmias or cardiac failure have occurred in patients treated with IMBRUVICA®. Patients with significant cardiac co-morbidities may be at greater risk of events, including sudden fatal cardiac events. Deaths due to cardiac causes or sudden deaths occurred in 1% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens.

Grade 3 or greater ventricular tachyarrhythmias were reported in 0.2%, Grade 3 or greater atrial fibrillation and atrial flutter were reported in 3.7%, and Grade 3 or greater cardiac failure was reported in 1.3% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens. These events have occurred particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia (see 8.2 Clinical Trial Adverse Reactions and 8.5 Post-Market Adverse Reactions).

Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating IMBRUVICA®. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns. Consider the benefits and risks of IMBRUVICA® treatment (including a potential increase in the risk of hemorrhage with concomitant use of anticoagulant or antiplatelet agents; see 7 WARNINGS AND PRECAUTIONS, Hemorrhage) and follow the dose modification guidelines (see 4 DOSAGE AND ADMINISTRATION).

PR Interval Prolongation

IMBRUVICA® causes a dose- and concentration-dependent prolongation of the PR interval of the electrocardiogram (see 9 DRUG INTERACTIONS and 10 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 18% of the adult patients treated with IMBRUVICA®. Grade 3 or 4 hypertension occurred in 8% of patients. Based on data available from 1,124 patients, the median time to onset was 5.9 months (range, 0.3 to 24 months).

An increase in the prevalence of hypertension has been observed over time on treatment with IMBRUVICA®; see 8.1 Adverse Reaction Overview, 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.

Cerebrovascular Accidents

Cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of IMBRUVICA®, with and without concomitant atrial fibrillation and/or hypertension, although causality with ibrutinib has not been established (see 8.5 Post-Market Adverse Reactions). Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended (see 7 WARNINGS AND PRECAUTIONS, Cardiac Arrhythmias and Hypertension).

Driving and Operating Machinery

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.

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 9 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 9 DRUG INTERACTIONS and 4 DOSAGE AND ADMINISTRATION).

Concomitant use of IMBRUVICA® and drugs that strongly induce CYP3A decreases ibrutinib exposure and should be avoided (see 9 DRUG INTERACTIONS).

Endocrine and Metabolism

Tumour Lysis Syndrome

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

Gastrointestinal

Diarrhea

In the pooled safety database, diarrhea occurred in approximately 48% of the adult patients with B-cell malignancies treated with IMBRUVICA®, with Grade 3 or 4 diarrhea in 4% of patients (see 8 ADVERSE REACTIONS). In a study of 42 adult patients with cGVHD treated with IMBRUVICA®, diarrhea occurred in 36% of patients, with Grade 3 or 4 diarrhea in 10% of patients.

In pediatric cGVHD patients treated with IMBRUVICA®, diarrhea occurred in approximately 26% of patients, with grade 3 or 4 diarrhea occurring in 1 (2%) patient.

To prevent dehydration, administer fluid and electrolyte replacement and antidiarrheal medications as needed. Follow IMBRUVICA® dose modification guidance as needed (see 4 DOSAGE AND ADMINISTRATION).

Hematologic

Cytopenias

In the pooled safety database of adult 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 8 ADVERSE REACTIONS). Patients should have their complete blood counts monitored monthly and their doses modified as necessary (see 4 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 previously untreated patients with CLL receiving IMBRUVICA® in combination with obinutuzumab, treatment-emergent lymphocytosis occurred in 7% of patients; median time to treatment-emergent lymphocytosis was approximately 1 week, and median time to resolution was approximately 3 weeks; all of these patients achieved resolution. In a study of previously treated 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 was observed in less than 1% of patients with WM treated with IMBRUVICA®.

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.

Leukostasis

Isolated cases of leukostasis have been reported in patients treated with IMBRUVICA®. Cases were typically reported within two to three weeks of IMBRUVICA® 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 withholding 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 adult patients. Some events were fatal.

Bleeding events of any grade, including contusion, epistaxis, and petechiae, occurred in 48% of patients treated with IMBRUVICA®, both with and without thrombocytopenia. In clinical trials, eye hemorrhage has been reported in 0.3%, retinal hemorrhage in 0.4%, and vitreous hemorrhage in 0.2% of patients. 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 an increased risk of major bleeding compared to those without these concomitant drugs. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Patients were excluded from participation in IMBRUVICA® studies if they had a recent history of stroke or intracranial hemorrhage. The majority of clinical trials for IMBRUVICA® excluded patients requiring warfarin or other vitamin K antagonists. Patients with congenital bleeding diathesis have not been studied.

IMBRUVICA® should be used with caution in patients requiring anticoagulants or medications that inhibit platelet function. Monitor for signs and symptoms of bleeding. 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.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

Ibrutinib is metabolized in the liver. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥3.0 x ULN were excluded from IMBRUVICA® clinical trials. In a study in patients with hepatic impairment, data showed a significant increase in ibrutinib exposure (see 10.3 Pharmacokinetics, 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.

Adult Patients with B-cell Malignancies: IMBRUVICA® should not be used in patients with moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C). 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 4 DOSAGE AND ADMINISTRATION).

Patients with cGVHD: Avoid the use of IMBRUVICA® in patients with total bilirubin level > 3 x ULN (unless of non-hepatic origin or due to Gilbert's Syndrome). The recommended dosage is 140 mg daily for patients 12 years of age and older with total bilirubin level >1.5 to 3 x ULN (unless of non-hepatic origin or due to Gilbert's Syndrome). The recommended dosage is 80 mg/m^2 daily for patients 1 to < 12 years of age with total bilirubin level >1.5 to 3 x ULN (unless of non-hepatic origin or due to Gilbert's syndrome). Monitor patients for signs of toxicity (see 4 DOSAGE AND ADMINISTRATION).

Immune

Infections

In the pooled safety database, infections (including sepsis, bacterial, viral, or fungal infections) occurred in approximately 70% of adult patients with B-cell malignancies treated with IMBRUVICA®, with Grade 3 or 4 infections in approximately 18% of patients, and fatal infections in 1% of patients. In a study of 42 adult 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. In pediatric cGVHD patients treated with IMBRUVICA®, infections occurred in approximately 66% of patients, with Grade 3 or 4 infections in 32% of patients, and fatal infections in 1 (2%) patient.

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 9 DRUG INTERACTIONS and 4 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.

Monitoring and Laboratory Tests

Patients should have their baseline renal function and hepatic status, and coagulation status measured prior to IMBRUVICA® initiation. Patients should also be assessed for cardiac arrhythmia and cardiac failure 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, cardiac failure, 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.

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 7 WARNINGS AND PRECAUTIONS, Hemorrhage).

Renal

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 10.3 Pharmacokinetics).

Reproductive Health: Female and Male Potential

- **Fertility**

  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 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

- **Teratogenic Risk:**

  Based on findings in animals, IMBRUVICA® may cause fetal harm when administered to pregnant women and should not be used during pregnancy (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). Women of child-bearing potential should be advised to avoid becoming pregnant and use highly effective contraceptive measures while receiving IMBRUVICA® and for 3 months after ending treatment (see 7.1.1 Pregnant Women).

  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.

Respiratory

Interstitial Lung Disease

Cases of interstitial lung disease (ILD), including cases confirmed by biopsy, have been reported in patients treated with IMBRUVICA® (see 8.1 Adverse Reaction Overview and 8.5 Post-Market Adverse 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 4 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.

7.1 Special Populations

7.1.1 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 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). Based on these findings, IMBRUVICA® may cause fetal harm when administered to pregnant women.

IMBRUVICA® should not be used during pregnancy. 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.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed, Health Canada has authorized IMBRUVICA® for the treatment of pediatrics age 1 year and older with cGVHD after failure of one or more lines of systemic therapy. See 8 ADVERSE REACTIONS for the safety findings. Patient numbers were too small to permit a meaningful exploration of potential differences in safety between age subgroups (i.e., ≥ 1 to < 6 vs. ≥ 6 to < 12 vs. ≥ 12 years of age).

Health Canada has not authorized IMBRUVICA® for other pediatric indications.

7.1.4 Geriatrics

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 10.3 Pharmacokinetics, Special Populations and Conditions).

In the pooled safety database, 50% of patients with B-cell malignancies were 65 years of age or older. Grade 3 or higher pneumonia occurred more frequently (≥5%) among elderly patients treated with IMBRUVICA® (9% of patients ≥65 years of age versus 3% of patients <65 years of age), in addition to grade 3 or higher thrombocytopenia (9% of patients ≥ 65 years of age versus 4% of patients <65 years of age). Grade ≥3 serious adverse events were also reported more frequently in elderly patients than in younger patients (43% versus 28%, respectively), as were adverse events leading to drug discontinuation (14% versus 9%, respectively) and fatal adverse events (6% versus 2%, respectively).

A study of 42 adult 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 six controlled, randomized clinical studies (RESONATE-2 [Study PCYC-1115-CA], iLLUMINATE [Study PCYC-1130-CA], Study ECOG-1912, RESONATE [Study PCYC-1112-CA], HELIOS [Study CLL3001], and GLOW [Study CLL3011]) and two single-arm, open-label clinical studies (Study PCYC-1102-CA and CAPTIVATE [Study PCYC-1142-CA]). The studies included

patients with CLL treated with 420 mg IMBRUVICA® daily, as a single agent, in combination with obinutuzumab, in combination with rituximab, in combination with bendamustine and rituximab, or in combination with venetoclax.

The most commonly occurring adverse reactions in the studies (≥20%) were diarrhea, neutropenia, fatigue, musculoskeletal pain, rash, nausea, thrombocytopenia, anemia, haemorrhage (including bruising), arthralgia, headache, cough, upper respiratory tract infection, pyrexia and hypertension. The most common Grade 3/4 adverse reactions (≥5%) were neutropenia, thrombocytopenia, hypertension, and pneumonia.

Approximately 7% of patients receiving IMBRUVICA® in the studies discontinued treatment due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation (≥0.5%) included pneumonia, hemorrhage, atrial fibrillation, neutropenia and rash. Adverse reactions leading to dose reduction occurred in approximately 9% 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 15). 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 (iNNOVATE [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 Study PCYC-1118E and iNNOVATE 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 – Adults

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

The most commonly occurring adverse reactions in Study PCYC-1129-CA (≥ 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.

Chronic Graft Versus Host Disease (cGVHD) studies - Pediatrics

The data described below reflect exposure to IMBRUVICA® in pediatric and young adult patients age 1 to 22 years of age (n=47) after failure of one or more lines of systemic therapy from the PCYC-1146-IM (iMAGINE) clinical trial.

The most commonly occurring adverse reactions (≥ 20%) were diarrhea, abdominal pain, stomatitis, pyrexia, pneumonia and bruising. The most common Grade 3/4 adverse reactions (≥5%) were stomatitis, pyrexia, pneumonia, sepsis and hypokalemia. Serious adverse reactions occurred in 64% of patients.

Eleven percent of patients receiving IMBRUVICA® in iMAGINE discontinued treatment due to adverse reactions. The most common adverse reaction leading to discontinuation was hemorrhage (4.3%). Adverse reactions leading to dose reduction occurred in 15% of patients.

Non-melanoma skin cancer

The incidence of non-melanoma skin cancer in IMBRUVICA®-treated patients was approximately 6% across pivotal phase 2 and 3 studies in adult patients with CLL, MCL, MZL, WM, and cGVHD.

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 adult 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® (8%; Grade 3+4, 3%) than in the comparator arms (1.5%; Grade 3+4, 0.4%).

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 (iNNOVATE), 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 iNNOVATE), 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 indicate that there is generally no cumulative or unique late-onset toxicity with continued IMBRUVICA® treatment. The long-term safety data is based on studies in patients with CLL/small lymphocytic lymphoma (SLL) (n=808; treatment-naïve n=162, relapsed/refractory n=646) treated with IMBRUVICA® as a single agent or in combination for a median of 51 months (range, 0.2 to 98 months) with 70% and 52% of patients receiving treatment for more than 2 years and 4 years, respectively, and studies in patients with MCL (n=370) treated with IMBRUVICA® for a median of 11 months (range, 0 to 87 months) with 31% and 17% of patients receiving treatment for more than 2 years and 4 years, respectively. The prevalence of hypertension increased: year 0-1, 10% (Grade≥3, 4%); year 1-2, 13% (Grade≥3, 6%); year 2-3, 19% (Grade≥3, 8%); year 3-4, 19% (Grade≥3, 9%); and year 4-5, 21% (Grade≥3, 9%); the incidence for the 5-year period was 20% (Grade≥3, 11%).

Long-term safety of IMBRUVICA®, including its effect on growth, development and immune reconstitution has not been evaluated in pediatric patients.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

Single-agent therapy

Adverse reactions described in Table 7 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 RESONATE-2 (Study PCYC-1115-CA). Hematologic laboratory abnormalities are described in Table 20.

Table 7: Adverse reactions† reported from RESONATE-2

System Organ Class Adverse reaction	IMBRUVICA® (N=135)		Chlorambucil (N=132)	
	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				

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

* 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.

Combination therapy with obinutuzumab

Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA® + obinutuzumab with a median duration of 29.3 months, which is approximately 5.8 times the median exposure to chlorambucil + obinutuzumab of 5.1 months in iLLUMINATE (Study PCYC-1130-CA). Hematologic laboratory abnormalities are described in Table 21.

Table 8: Adverse reactions reported in ≥10% (All Grades) of patients in the IMBRUVICA® + obinutuzumab arm from iLLUMINATE

System Organ Class Adverse Reaction	IMBRUVICA® + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	48	39	64	48

	IMBRUVICA® + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
System Organ Class Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Thrombocytopenia*	36	19	28	11
Anemia	17	4	25	8
Cardiac disorders				
Atrial fibrillation	12	5	0	0
Gastrointestinal disorders				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Nausea	12	0	30	0
General disorders and administration site conditions				
Pyrexia	19	2	26	1
Fatigue	18	0	17	2
Peripheral edema	12	0	7	0
Infections and infestations				
Pneumonia*	16	9	9	3
Upper respiratory tract infection	14	1	6	0
Skin infection*	13	1	3	0
Urinary tract infection	12	3	7	1
Nasopharyngitis	12	0	3	0
Conjunctivitis	11	0	2	0
Injury, Poisoning and Procedural Complications				
Infusion related reaction	25	2	58	8
Metabolism and nutrition disorders				
Hyperuricemia	13	1	0	0
Musculoskeletal and connective tissue disorders				

	IMBRUVICA® + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
System Organ Class Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Musculoskeletal pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
Psychiatric disorders				
Insomnia	12	0	4	0
Respiratory, thoracic and mediastinal disorders				
Cough	27	1	12	0
Skin and subcutaneous tissue disorders				
Rash*	36	3	11	0
Bruising*	32	3	3	0
Vascular disorders				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3

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

Combination therapy with rituximab

Adverse reactions described in Table 9 reflect exposure to IMBRUVICA® + rituximab with a median duration of 34.3 months, and exposure to fludarabine + cyclophosphamide + rituximab of 4.7 months in Study ECOG-1912. Hematology and chemistry laboratory abnormalities are described in Table 22.

Table 9: Adverse reactions reported in ≥10% (All Grades) of patients in the IMBRUVICA® + rituximab arm from Study ECOG-1912

	IMBRUVICA® + Rituximab (N=352)		Fludarabine + Cyclophosphamide + Rituximab (N=158)	
System Organ Class Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Blood and lymphatic system disorders				

System Organ Class Adverse Reaction	IMBRUVICA® + Rituximab (N=352)		Fludarabine + Cyclophosphamide + Rituximab (N=158)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Anemia	71	7	81	18
Thrombocytopenia*	61	5	77	18
Neutropenia*	54	33	68	49
Gastrointestinal disorders				
Diarrhea	53	4	27	1
Nausea	40	1	64	1
Stomatitis*	22	1	8	1
Abdominal pain*	18	2	9	1
Vomiting	18	2	28	0
Constipation	17	0	32	0
Dyspepsia	14	0	3	0
Gastroesophageal reflux disease	13	0	6	0
General disorders and administration site conditions				
Fatigue	80	2	78	3
Peripheral edema	28	1	17	0
Pyrexia	27	1	27	1
Pain	23	2	8	0
Chills	11	<1	17	1
Infections and infestations				
Upper respiratory tract infection	29	1	19	2
Skin infection*	16	1	3	1
Pneumonia*	11	3	6	3
Metabolism and nutrition disorders				
Hyperuricemia	18	1	4	0

System Organ Class Adverse Reaction	IMBRUVICA® + Rituximab (N=352)		Fludarabine + Cyclophosphamide + Rituximab (N=158)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Decreased appetite	15	0	20	1
Hypokalemia	13	1	11	1
Hypoalbuminemia	11	0	8	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	61	5	35	2
Arthralgia	41	5	9	1
Muscle spasms	12	0	1	0
Nervous system disorders				
Headache	40	1	27	1
Dizziness	21	1	13	1
Peripheral neuropathy*	19	1	13	1
Psychiatric disorders				
Insomnia	16	1	19	1
Anxiety	14	<1	10	0
Respiratory, thoracic and mediastinal disorders				
Cough	32	<1	25	0
Dyspnea	22	2	21	1
Oropharyngeal pain	13	<1	5	0
Nasal congestion	12	0	7	0
Skin and subcutaneous tissue disorders				
Rash*	49	4	29	5
Bruising*	36	1	4	1
Pruritus	13	<1	8	0
Dry skin	11	<1	6	0
Vascular disorders				

System Organ Class Adverse Reaction	IMBRUVICA® + Rituximab (N=352)		Fludarabine + Cyclophosphamide + Rituximab (N=158)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hypertension*	42	19	22	6
Hemorrhage*	31	2	8	1

* Includes multiple adverse drug reaction preferred terms.
Serious and Non-serious events for Study E1912 were not distinguished in the data collection.
Events are sorted by system organ class and by decreasing frequency of adverse reaction term in the IMBRUVICA® + rituximab arm.

An exposure to IMBRUVICA® + rituximab for an additional 4 months (median duration of 38 months) showed no new safety issues or changes to the safety profile of IMBRUVICA® + rituximab.

Fixed duration combination therapy with venetoclax

Adverse reactions described below in Table 10 reflect exposure to IMBRUVICA® + venetoclax with a median duration of 13.8 months and exposure to chlorambucil + obinutuzumab with a median duration of 5.1 months in the randomized, active-controlled phase 3 study, GLOW (Study CLL3011). Hematology and chemistry laboratory abnormalities are described in Table 23.

Table 10: Adverse reactions[a] reported in ≥10% (All Grades) of patients with CLL/SLL in the IMBRUVICA® + venetoclax arm from the fixed duration GLOW study

System Organ Class Preferred Term	IMBRUVICA® + Venetoclax (N=106) (%)		Chlorambucil + Obinutuzumab (N=105) (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Blood and Lymphatic System Disorders				
Neutropenia*	42	35	59	51
Anaemia*	18	3	18	2
Thrombocytopenia*	14	7	28	21
Cardiac Disorders				
Atrial Fibrillation	14	7	2	0
Gastrointestinal Disorders				
Diarrhea	51	10	12	1
Nausea	26	0	26	0
Stomatitis*	15	0	3	0
Vomiting	14	1	13	0
Constipation	10	0	7	0
General Disorders and Administration Site Conditions				

System Organ Class Preferred Term	IMBRUVICA® + Venetoclax (N=106) (%)		Chlorambucil + Obinutuzumab (N=105) (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Fatigue	15	1	10	0
Peripheral edema	15	0	3	0
Infections And Infestations				
Urinary Tract Infection	16	2	5	2
Pneumonia*	13	9[b]	10	6[b]
Upper Respiratory Tract Infection	12	0	13	0
Metabolism and Nutrition Disorders				
Decreased Appetite	13	1	6	1
Hyperphosphataemia	10	1	0	0
Musculoskeletal And Connective Tissue Disorders				
Musculoskeletal Pain*	25	3	19	0
Arthralgia	11	1	7	0
Skin and Subcutaneous Tissue Disorders				
Rash*	28	7	14	1
Bruising*	23	1	3	0
Vascular Disorders				
Hemorrhage*	23	4	5	1
Hypertension*	14	9	5	2

[a] Adverse reactions: Events occurring at ≥10% (all grades) incidence in the IMBRUVICA® + venetoclax arm.
[b] Includes Grade 5 events
* Includes multiple adverse reaction preferred terms

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

Adverse reactions described below in Table 11 reflect exposure to IMBRUVICA® in combination with venetoclax with a median duration of 14.1 months in the single-arm phase 2 study, CAPTIVATE (Study PCYC-1142-CA). Hematology and chemistry laboratory abnormalities are described in Table 24.

Table 11: Adverse reactions[a] reported in ≥10% (All Grades) of patients with CLL/SLL in the CAPTIVATE[b] study

System Organ Class Preferred Term	IMBRUVICA® + Venetoclax (N=323) (%)	
	All Grades	Grade ≥3
Blood and Lymphatic System Disorders		
Neutropenia*	48	38
Thrombocytopenia*	20	4
Cardiac Disorders		
Palpitations	11	0
Gastrointestinal Disorders		
Diarrhea	67	4
Nausea	44	1
Stomatitis*	30	1
Abdominal Pain*	24	1
Vomiting	22	1
Dyspepsia	18	0
Constipation	16	0
Gastroesophageal Reflux Disease	13	0
General Disorders and Administration Site Conditions		
Fatigue	26	2
Pyrexia	13	0
Infections and Infestations		
Upper Respiratory Tract Infection	26	0
Skin Infection*	20	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Pain*	41	1
Arthralgia	34	2
Muscle Spasms	25	0
Nervous System Disorders		
Headache	27	1
Dizziness	16	0
Respiratory, Thoracic And Mediastinal Disorders		
Cough	17	0

System Organ Class Preferred Term	IMBRUVICA® + Venetoclax (N=323) (%)	
	All Grades	Grade ≥3
Oropharyngeal Pain	14	0
Skin and Subcutaneous Tissue Disorders		
Bruising*	47	0
Rash*	38	3
Dry Skin	11	0
Vascular Disorders		
Hemorrhage*	33	1
Hypertension*	17	7

[a] Adverse reactions: Events occurring at ≥10% (all grades) incidence.
[b] Pooled safety data is from the Fixed Duration (FD) cohort and first 16 cycles of the Minimal Residual Disease (MRD) cohort. Events are sorted by System Organ Class and by decreasing frequency of individual ADR preferred term.
* Includes multiple adverse reaction preferred terms

In the fixed duration cohort, no TLS was reported in patients treated with IMBRUVICA® in combination with venetoclax. In the Minimal Residual Disease (MRD) cohort, Grade 3 laboratory TLS was reported in 1 patient (0.6%) treated with IMBRUVICA® in combination with venetoclax during the first 16 cycles.

Previously Treated Chronic Lymphocytic Leukemia

Single-agent therapy

Adverse reactions described in Table 12 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 RESONATE (Study PCYC-1112-CA). Hematologic laboratory abnormalities are described in Table 25.

Table 12: Adverse reactions[†] reported from RESONATE

	IMBRUVICA® (N=195)		Ofatumumab (N=191)	
System Organ Class Adverse reaction	**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
Leukocytosis	4	3	1	0

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

	IMBRUVICA® (N=195)		Ofatumumab (N=191)	
System Organ Class Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
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 7 WARNINGS AND PRECAUTIONS, Hematologic).

Combination therapy

Adverse reactions described in Table 13 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 HELIOS (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 26.

Table 13: Adverse reactions† reported from HELIOS

	IMBRUVICA® + BR (N=287)		Placebo + BR (N=287)	
System Organ Class **Adverse Reaction Term**	**All Grades %**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
Blood and lymphatic system disorders				
Thrombocytopenia	31	15	24	15

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 %
Cardiac disorders				
Atrial fibrillation	7	3	2	1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
Skin and subcutaneous tissue disorders				
Rash*	24	3	18	1
Bruising*	18	<1	6	0
Vascular disorders				
Hypertension*	10	5	5	2

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%

Mantle Cell Lymphoma

Adverse reactions described in Table 14 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 27.

Table 14: 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

		Frequency	
System Organ Class	**Adverse Reaction**	**All Grades (%)**	**Grades 3 or 4 (%)**
	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

		Frequency	
System Organ Class	**Adverse Reaction**	**All Grades (%)**	**Grades 3 or 4 (%)**
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 7 WARNINGS AND PRECAUTIONS, Hematologic).

Marginal Zone Lymphoma

Adverse reactions described in Table 15 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 28.

Table 15: Adverse reactions reported in ≥10% (All Grades) 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 (%)
Blood and lymphatic system disorders	Anemia	33	14
	Thrombocytopenia*	25	2
	Neutropenia*	8	8
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2

System Organ Class	Adverse Reaction	All Grades (%)	Grades 3-4 (%)
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
General disorders and administration site conditions	Fatigue	44	6
	Edema peripheral	24	2
	Pyrexia	17	2
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Skin and subcutaneous tissue disorders	Bruising*	41	0
	Rash*	29	5
	Pruritus	14	0
Vascular disorders	Hemorrhage*	30	0
	Hypertension*	14	5

* Includes multiple adverse reaction terms.

Waldenström's Macroglobulinemia

Single-agent therapy

Adverse reactions described in Table 16 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 29.

Table 16: 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.			

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 17 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 iNNOVATE (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 30.

Table 17: Adverse reactions reported from iNNOVATE[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

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 %
General disorders and administration site conditions				
Peripheral edema	17	0	12	1
Infections and infestations				
Pneumonia*	19	13	5	3
Skin infection*	17	3	3	0
Urinary tract infection	13	0	0	0
Bronchitis	12	3	7	0
Influenza	12	0	7	1
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

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 %
Vascular disorders				
Hemorrhage*	32	3	17	3
Hypertension*	20	13	5	4

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

Chronic Graft Versus Host Disease

Adverse reactions described below in Table 18 reflect exposure to IMBRUVICA® (420 mg daily) with a median duration of 4.4 months in study PCYC-1129-CA. Hematologic laboratory abnormalities are described in Table 31.

Table 18: Adverse reactions reported in ≥10% (All Grades) of adult patients with cGVHD treated with 420 mg IMBRUVICA® - Study PCYC-1129-CA (N=42)

System Organ Class	Adverse Reaction	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Infections and infestations	Pneumonia*	21	10
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Injury, poisoning and procedural complications	Fall	17	0

System Organ Class	Adverse Reaction	All Grades (%)	Grades 3 or 4 (%)
Metabolism and nutrition disorders	Hypokalemia	12	7
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Nervous system disorders	Headache	17	5
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Skin and subcutaneous tissue disorders	Bruising*	41	0
	Rash*	12	0
Vascular disorders	Hemorrhage*	26	0

* Includes multiple adverse reaction terms.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Chronic Graft Versus Host Disease

Adverse reactions described below in Table 19 reflect exposure to IMBRUVICA® with a median duration of 7.1 months (range, 0.2, 25.9 months) in pediatrics and young adults in Study PCYC-1146-IM (see 14.1 Clinical Trials by Indication, Chronic Graft Versus Host Disease [cGVHD] - Pediatrics). Hematologic laboratory abnormalities are described in Table 32.

Table 19: Adverse reactions reported in ≥10% of pediatric and young adult patients with relapsed or refractory cGVHD – Study PCYC-1146-IM (N=47)

System Organ Class	Adverse Reaction	All Grades (%)	Grade 3 or higher (%)
Blood and lymphatic systems disorders	Anemia	13	3
Cardiac Disorders	Sinus tachycardia	11	0
Gastrointestinal disorders	Diarrhea	28	2
	Abdominal pain*	23	4
	Stomatitis*	21	9
	Vomiting	19	2
	Nausea	19	4

System Organ Class	Adverse Reaction	All Grades (%)	Grade 3 or higher (%)
General disorders and administration site conditions	Pyrexia	30	11
Immune system disorders	Hypogammaglobulinemia*	11	0
Infections and infestations	Pneumonia*	21	11
	Skin infection*	17	4
	Sepsis*	11	9
Investigations	ALT increased	11	2
Metabolism and nutrition disorders	Hypokalemia*	15	6
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	15	2
	Arthralgia	13	2
Nervous system disorders	Headache	17	0
Respiratory, thoracic and mediastinal disorders	Cough	19	2
Skin and subcutaneous tissue disorders	Bruising*	21	0
	Rash*	19	2
	Pruritus	13	0
Vascular disorders	Hemorrhage*	17	0
	Hypertension*	11	4

* Includes multiple adverse reaction terms.

8.3 Less Common Clinical Trial Adverse Reactions

Previously Untreated Chronic Lymphocytic Leukemia

Single-agent therapy

Less common adverse events reported in patients treated with IMBRUVICA® included:
Eye disorders: eye pain (6%), vitreous floaters (6%), cataract (5%), blindness unilateral (1%), retinal hemorrhage (<1%)
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%)

Combination therapy with obinutuzumab

Less common adverse events reported in patients treated with IMBRUVICA® + obinutuzumab included:
Cardiac disorders: cardiac arrhythmias [19.5%: including palpitations (6.2%), bradycardia (4.4%), tachycardia (2.7%), syncope (1.8%)]
Eye disorders: cataract (8.8%)

Combination therapy with rituximab

Less common adverse events reported in patients treated with IMBRUVICA® + rituximab included:
Cardiac disorders: atrial fibrillation (8%)
Eye disorders: vision blurred (9%), retinal and vitreous hemorrhage (<1%)
Infections and infestations: sinusitis (9%), urinary tract infection (9%)
Neoplasms benign, malignant and unspecified: non-melanoma skin cancer (4%)

Fixed duration combination therapy with venetoclax

Less common adverse events reported in patients treated with IMBRUVICA® + venetoclax included:
Cardiac disorders: cardiac failure (1%)
General disorders and administration site conditions: asthenia (6%)
Metabolism and nutrition disorders: hyponatremia (4%)

Pediatric patients with cGVHD

Cardiac disorders: cardiac failure (1.6%), ventricular tachyarrhythmia (1.6%)
Eye disorders: vision blurred (1.6%)
Gastrointestinal disorders: constipation (9.7%), dyspepsia (4.8%)
General disorders and administration site: edema peripheral (6.5%), fatigue (6.5%), asthenia (1.6%)
Infections and infestations: upper respiratory tract infection (6.5%)
Investigations: AST increased (9.7%)
Metabolism and nutrition disorders: decreased appetite (6.5%)
Musculoskeletal and connective tissue: muscle spasm (6.5%)
Psychiatric disorders: insomnia (6.5%)
Respiratory, thoracic and mediastinal disorders: interstitial lung disease (8.1%), dyspnea (4.8%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Previously Untreated Chronic Lymphocytic Leukemia

Single-agent therapy

Table 20: Hematologic laboratory abnormalities (per IWCLL criteria) from RESONATE-2 (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.

Combination therapy with obinutuzumab

Table 21: Hematologic laboratory abnormalities (per IWCLL criteria) from iLLUMINATE (Study PCYC-1130-CA)

Laboratory Parameter	IMBRUVICA® + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hemoglobin decreased[a]	27	0	34	0
Neutrophils decreased[b]	60	40	74	39
Platelets decreased[c]	62	22	57	17

[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 with rituximab

Table 22: Hematology (per IWCLL criteria) and chemistry laboratory abnormalities (per CTCAE) from Study ECOG-1912

	IMBRUVICA® + Rituximab (N=352)		Fludarabine + Cyclophosphamide + Rituximab (N=158)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology abnormalities				
Hemoglobin decreased[a]	26	0	51	2
Neutrophils decreased[b]	53	30	70	44
Platelets decreased[c]	43	7	69	25
Chemistry abnormalities[d]				
AST increased	25	3	23	<1
Bilirubin increased	30	2	15	0
Creatinine increased	38	1	17	1

[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.

[d] Based on laboratory measurements per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03

Fixed duration combination therapy with venetoclax

Table 23: Hematology (per IWCLL criteria) and chemistry laboratory abnormalities (per CTCAE) from GLOW (Study CLL3011)

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

[a] Based on laboratory measurements per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03

[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.

[d] 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.

Table 24: Hematology (per IWCLL criteria) and chemistry laboratory abnormalities (per CTCAE) from CAPTIVATE (Study PCYC-1142-CA)[a]

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

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

[b] Based on laboratory measurements per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03

[c] 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.

[d] 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.

[e] 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.

<1 used for frequency above 0 and below 0.5%

Previously Treated Chronic Lymphocytic Leukemia

Single-agent therapy

Table 25: Hematologic laboratory abnormalities (per IWCLL criteria) from RESONATE (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

Table 26: Hematologic laboratory abnormalities (per IWCLL criteria) from HELIOS (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

Table 27: Hematologic laboratory abnormalities (per CTCAE criteria) from Study PCYC-1104-CA

	IMBRUVICA® (N=111)	
Laboratory Parameter	**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

Table 28: Hematologic laboratory abnormalities (per CTCAE criteria) from Study PCYC-1121-CA

	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

Table 29: 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.

Combination therapy

Table 30: Hematologic laboratory abnormalities (per CTCAE criteria) from iNNOVATE (Study PCYC-1127-CA)

	IMBRUVICA® + Rituximab (N=75) n (%)		Placebo + Rituximab (N=75) n (%)	
Laboratory Parameter	**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 – Adults

Table 31: Hematologic laboratory abnormalities (per CTCAE criteria) in adult patients from Study PCYC-1129-CA

	IMBRUVICA® (N=42)	
Laboratory Parameter	**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.

Chronic Graft Versus Host Disease – Pediatrics

Table 32: Hematologic and chemistry laboratory abnormalities (per CTCAE criteria) in pediatric and young adult patients with relapsed or refractory cGVHD (Study PCYC-1146-IM)

Laboratory Parameter	**Relapsed/Refractory (N=47)**	
	All Grades (%)	**Grade 3 or 4 (%)**
Chemistry abnormalities[a]		
ALT increased	21	6
Creatinine increased	43	2

Hypokalemia	23	4
Hyponatremia	23	0
Hematology abnormalities		
Hemoglobin decreased[b]	49	13
Platelets decreased[c]	21	4

[a] Based on laboratory measurements per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03

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

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.

Treatment-emergent Grade 4 neutropenia occurred in 4% of patients.

8.5 Post-Market Adverse 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.

Table 33: Post-market adverse reactions

System Organ Class	Adverse Reaction
Cardiac disorders	Ventricular tachyarrhythmias (see 7 WARNINGS AND PRECAUTIONS)
	Cardiac failure (see 7 WARNINGS AND PRECAUTIONS)
Eye disorders	Eye hemorrhage, in some cases associated with loss of vision
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 7 WARNINGS AND PRECAUTIONS)
Infections and infestations	Progressive multifocal leukoencephalopathy (PML) (see 7 WARNINGS AND PRECAUTIONS)
	Hepatitis B reactivation (see 7 WARNINGS AND PRECAUTIONS)
	Hepatitis E virus infection
Metabolism and nutrition disorders	Tumour lysis syndrome (see 7 WARNINGS AND PRECAUTIONS)
Nervous system disorders	Peripheral neuropathy
	Cerebrovascular accident (includes events with fatal outcome) (see 7 WARNINGS AND PRECAUTIONS)
	Transient ischemic attack (see 7 WARNINGS AND PRECAUTIONS)

	Ischemic stroke (includes events with fatal outcome) (see 7 WARNINGS AND PRECAUTIONS)
Skin and subcutaneous tissue disorders	Angioedema
	Erythema
	Onychoclasis (commonly reported in clinical trials)
	Panniculitis
	Stevens-Johnson Syndrome
	Urticaria
	Neutrophilic dermatoses (neutrophilic dermatosis, acute febrile neutrophilic dermatosis, pyoderma gangrenosum)
Vascular disorders	Hemorrhage (see 7 WARNINGS AND PRECAUTIONS)

9 DRUG INTERACTIONS

9.2 Drug Interactions 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. If a moderate or strong CYP3A inhibitor must be used, refer to the dosing recommendations (see 4.2 Recommended Dose and Dosage Adjustment and 9.4 Drug-Drug Interactions).

9.4 Drug-Drug Interactions

The drugs listed in Table 34, Table 35, and Table 36 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Patients should be monitored closely for toxicity. Follow dose modification guidelines as needed (see 4 DOSAGE AND ADMINISTRATION).

Table 34: Agents that may alter ibrutinib plasma concentrations

Class/Common name	Source of Evidence	Effect	Clinical Comment
Agents that may increase ibrutinib plasma concentrations			
In patients with B-cell malignancies			
Moderate CYP3A inhibitor (e.g., erythromycin, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone)	CT, T	Co-administration of erythromycin increased C_{max} by 3.4-fold and increased AUC by 3.0-fold. Simulations under fasted conditions suggest diltiazem may increase the AUC of ibrutinib by 5-fold.	Reduce IMBRUVICA® dose to 280 mg for the duration of the CYP3A inhibitor use.
Voriconazole	CT	In patients with B-cell malignancies, co-administration of voriconazole increased C_{max} by 6.7-fold and increased AUC by 5.7-fold.	Reduce IMBRUVICA® dose to 140 mg for the duration of the CYP3A inhibitor use.
Other strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, itraconazole, cobicistat, and posaconazole)	CT, T	In healthy subjects, ketoconazole increased exposure (C_{max} and AUC_{∞}) of ibrutinib by 29- and 26-fold, respectively. Simulations under fed conditions suggest posaconazole may increase the AUC of ibrutinib 7-fold to 10-fold.	Concomitant use of other strong inhibitors of CYP3A should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If these strong CYP3A inhibitors must be used short term (7 days or less), withhold IMBRUVICA® treatment temporarily for the duration of the CYP3A inhibitor treatment.

Class/Common name	Source of Evidence	Effect	Clinical Comment
In patients with cGVHD			
Moderate CYP3A inhibitor (e.g., erythromycin, ciprofloxacin, fluconazole, imatinib)	C	In patients with cGVHD (≥12 years of age), co-administration of a moderate CYP3A inhibitor resulted in an increased AUC by 2.2-fold relative to subjects who did not receive CYP3A inhibitors.	No dose adjustment is required.
Voriconazole Posaconazole at doses less than or equal to 200 mg BID (suspension)	C	In patients with cGVHD (≥12 years of age), co-administration of ibrutinib with voriconazole or posaconazole resulted in an increased AUC by 3.1-fold relative to subjects who did not receive CYP3A inhibitors.	**For patients ≥12 years of age:** Reduce the IMBRUVICA® dose to 280 mg for the duration of the CYP3A inhibitor use. **For patients <12 years of age:** Reduce the IMBRUVICA® dose to 160 mg/m^2 once daily
Posaconazole at 300 mg QD (delayed release tablet)	T	Simulations under fed conditions suggest higher systemic exposure with posaconazole at 300 mg QD (delayed-release tablet) than posaconazole 200 mg BID (suspension).	**For patients ≥12 years of age:** Reduce the IMBRUVICA® dose to 140 mg for the duration of the CYP3A inhibitor use **For patients <12 years of age:** Reduce the IMBRUVICA® dose to 80 mg/m^2 once daily

Class/Common name	Source of Evidence	Effect	Clinical Comment
Posaconazole at higher doses or other strong CYP3A inhibitors.	T	Simulations under fed conditions in healthy subjects suggest posaconazole may increase the AUC of ibrutinib 7-fold to 10-fold.	Concomitant use should be avoided. **For patients ≥12 years of age:** If used short term (7 days or less), withhold IMBRUVICA® treatment temporarily for the duration of the CYP3A inhibitor treatment. **For patients <12 years of age:** If used short term (7 days or less), withhold IMBRUVICA® treatment temporarily for the duration of the CYP3A inhibitor treatment.
Agents that may decrease ibrutinib plasma concentrations			
Strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort)	CT	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. Consider alternative agents with less CYP3A induction.
Moderate CYP3A inducers (e.g., efavirenz)	T	Simulations suggest efavirenz may decrease the AUC of ibrutinib by up to 3-fold.	Consider alternative agents with less CYP3A induction.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Table 35: Agents that may have their plasma concentrations altered by ibrutinib

Class/Common name	Source of Evidence	Effect	Clinical Comment
P-glycoprotein (P-gp) substrates (e.g., aliskiren, digoxin, fexofenadine)	T	Ibrutinib is an inhibitor of P-glycoprotein (P-gp) *in vitro.* There are no clinical data available. Ibrutinib may inhibit intestinal P-gp after a therapeutic dose and alter the absorption of co-dosed drugs that are P-gp substrates.	To avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates, such as digoxin, should be taken at least 6 hours before or after IMBRUVICA®.
Breast cancer resistance protein (BCRP) substrates (e.g., methotrexate, topotecan, imatinib)	T	*In vitro* studies have also demonstrated that ibrutinib inhibits the 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.	To avoid a potential interaction in the GI tract, narrow therapeutic range BCRP substrates, such as methotrexate, should be taken at least 6 hours before or after IMBRUVICA®.
Drugs that undergo BCRP-mediated hepatic efflux (e.g., rosuvastatin)	T	Ibrutinib may inhibit BCRP in the liver and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux.	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.

Legend: T = Theoretical

Table 36: Pharmacodynamic drug interactions

Class/Common name	Source of Evidence	Effect	Clinical Comment
Anticoagulant and antiplatelet agents			
Anticoagulants or medications that inhibit platelet function	C	Use of IMBRUVICA® may increase the risk of bleeding.	IMBRUVICA® should be used with caution (see 7 WARNINGS AND PRECAUTIONS, Hemorrhage).
Drugs that prolong the PR interval			
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.	CT	IMBRUVICA® causes an increase in the PR interval.	The concomitant use of IMBRUVICA® should be undertaken with caution (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 10 CLINICAL PHARMACOLOGY).

Legend: C = Case Study; CT = Clinical Trial

Drug-Drug Interaction Studies and Simulations

Drug-drug interaction studies of ibrutinib with mild inhibitors of CYP3A have not been conducted. Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that mild CYP3A inhibitors (fluvoxamine and azithromycin) may increase the AUC of ibrutinib less than 2-fold in fasted condition.

IMBRUVICA® can be administered concomitantly with mild CYP3A inducers. Drug-drug interaction studies of ibrutinib with moderate or mild inducers of CYP3A have not been conducted.

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*. In a drug interaction study in patients with B-cell malignancies, a single 560 mg dose of ibrutinib did not have a clinically meaningful effect on the exposure of the CYP3A4 substrate midazolam, and 2 weeks of treatment with ibrutinib at 560 mg daily had no clinically

meaningful effect on the pharmacokinetics of midazolam or the CYP2B6 substrate bupropion. The same study examined the effect of 2 weeks of treatment with ibrutinib on oral contraceptives (ethinyl estradiol and levonorgestrel). Ibrutinib increased exposure to ethinyl estradiol (C_{max} increased 1.3-fold and AUC_{last} increased 1.4-fold), which is not expected to decrease the effectiveness of oral contraceptives.

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.

9.5 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 exposure (dose normalized 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 4 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 7 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 10.3 Pharmacokinetics). IMBRUVICA® can be taken with or without food.

9.6 Drug-Herb Interactions

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

9.7 Drug-Laboratory Test Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 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.

The dual acting combination of ibrutinib and venetoclax works synergistically through distinct and complementary modes of action, preferentially targeting distinct cell compartments and CLL cell subpopulations to eliminate both dividing and resting CLL cells. Ibrutinib mobilizes CLL cells out of lymph nodes and other lymphoid niches into the peripheral blood, rendering the CLL cells more susceptible to venetoclax-induced apoptosis. Ibrutinib also accelerates the apoptosis of CLL cells by enhancing their dependence on BCL-2, thereby increasing their sensitivity to venetoclax. In preclinical tumour models, the combination of ibrutinib and venetoclax resulted in increased cellular apoptosis and anti-tumour activity compared to either agent alone.

Ibrutinib is also a covalently binding inhibitor of the T-cell activation enzyme interleukin-2 inducible T-cell kinase (ITK). Both BTK and ITK have been shown to be critical in the pathogenesis of cGVHD.

10.2 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 a study of patients receiving IMBRUVICA® in combination with obinutuzumab, 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.

10.3 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 37. High intersubject variability of exposures was observed in patients.

Table 37: 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 (Vd) was 683 L and the apparent volume of distribution at steady state (Vd,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 14C-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 [14C] 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.

Special Populations and Conditions:

Pediatrics:

Pediatric Patients with B-cell Malignancies:

The safety, efficacy, and pharmacokinetics of ibrutinib in combination with either the rituximab, ifosfamide, carboplatin, etoposide and dexamethasone (RICE) regimen, or the rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone (RVICI) regimen were explored in Study 54179060LYM3003 (SPARKLE), a two part study in pediatric and young adult patients (range 3-19 years) with relapsed/refractory mature B-cell non-Hodgkin lymphoma. Results from the randomized part (Part 2) of the study did not show an additional efficacy benefit when ibrutinib was added to RICE or RVICI.

The pharmacokinetics of ibrutinib were explored in the run-in part (Part 1) of this study with sparse PK samples collected on Cycle 1 Day 1, Cycle 1 Day 7 and Cycle 2 Day 1 in 21 pediatric patients aged 3 to 17 years. A population pharmacokinetic (PK) approach was used for pediatric $AUC_{0\text{-}24h}$ estimation. As an exposure-response relationship has not been established between ibrutinib PK and a clinical (or surrogate) efficacy endpoint, the effective exposure range in

adults is unknown. Systemic exposures in adults at the clinically recommended doses are presented in Table 37.

Based on the population PK analysis, high variability of $AUC_{0\text{-}24h}$ was observed. Due to this variability and the limited sample size, no dose-exposure relationship was apparent in any age group. In seven patients aged 12 to 17 years who were administered a 240 or 329 mg/m^2 daily dose, the estimated mean $AUC_{0\text{-}24h}$ values of ibrutinib by dose and by study day ranged from 162 to 745 ng•h/mL (n = 3-5 per dose and study day). In ten patients aged 6 to 11 years who were administered a 240, 329 or 440 mg/m^2 daily dose, the estimated mean $AUC_{0\text{-}24h}$ values ranged from 70 to 399 ng•h/mL (n = 1-5 per dose and study day). In four patients aged 3 to 5 years who were administered a 240, 329 or 440 mg/m^2 daily dose, the estimated mean $AUC_{0\text{-}24h}$ values ranged from 129 to 775 ng•h/mL (n = 1-2 per dose and study day). There were significant reductions (48-74%) of $AUC_{0\text{-}24h}$ on Cycle 1 Day 7 when compared to Cycle 1 Day 1 in patients aged 6 to 17 years, for which a cause has not been established.

Pediatric Patients with cGVHD:

Based on the population PK analysis in patients with cGVHD (n = 57) who were administered ibrutinib 240 mg/m^2 daily (patients ≥1 to <12 years of age) or 420 mg daily (patients ≥12 to <22 years of age), apparent clearance and apparent volume of distribution at steady state were generally similar across the age and BSA range.

The recommended pediatric dosing regimen of 420 mg once daily in patients ≥12 to <22 years of age, resulted in median exposures generally within the exposure range observed in adult patients with cGVHD (geometric mean [95% prediction interval]: 975 [252 to 3767] ng•h/mL). Median (range) steady state $AUC_{0\text{-}24h}$ was 1640 ng•h/mL (150-4760 ng•h/mL) in patients aged 12 to 21 years (n=33).

The recommended pediatric dosing regimen of 240 mg/m^2 once daily in patients ≥1 to <12 years of age resulted in lower exposure with age and the median exposure was generally lower than the mean exposure in adult patients with cGVHD. Median (range) steady state $AUC_{0\text{-}24h}$ was 709 ng•h/mL (182-1620 ng•h/mL) in patients aged 6 to 12 years (n=16) and 416 ng•h/mL (94.6-1630 ng•h/mL) in patients aged 2 to 5 years (n=7). In one patient between 1 to <2 years old, the PK data was very limited. The expected mean $AUC_{0\text{-}24h}$ based on the population PK model for a 1 year old patient is 328 ng•h/mL, about 3-fold lower compared to the geometric mean $AUC_{0\text{-}24h}$ in adults.

- **Geriatrics:** Pharmacokinetic data in patients administered 420 mg daily dose showed higher systemic exposures of ibrutinib (25% higher AUC and 50% higher Cmax) and the dihydrodiol metabolite (48% higher AUC and 56% higher Cmax) at steady state in patients ≥65 years of age when compared with those <65 years.
- **Sex:** 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 Insufficiency:** Ibrutinib is metabolized in the liver. In a hepatic impairment trial in non-cancer patients administered a single dose of 140 mg of IMBRUVICA®, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (n=6; Child Pugh class A), moderate (n=10; Child Pugh class B), and severe (n=8; Child Pugh class C) hepatic impairment,

respectively. The free fraction of ibrutinib also increased with degree of impairment, with 3.0%, 3.8%, and 4.8% in subjects with mild, moderate, and severe liver impairment, respectively, compared to 3.3% in plasma from matched healthy controls within this study. The corresponding increase in unbound ibrutinib exposure ($AUC_{unbound,last}$) is estimated to be 4.1-, 9.8-, and 13-fold in subjects with mild, moderate, and severe hepatic impairment, respectively.

- **Renal Insufficiency:** 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.

11 STORAGE, STABILITY AND DISPOSAL

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

Oral suspension: Store at room temperature between 15°C-30°C. Do not freeze. Keep out of reach and sight of children. Store syringes and bottle upright in the original carton. Discard medication 3 months after opening the bottle for the first time.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

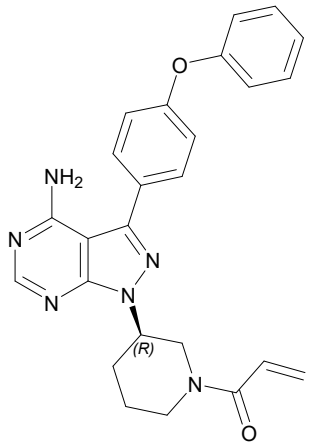
Drug Substance

Proper/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: Ibrutinib is a crystalline white to off-white solid. Ibrutinib is practically insoluble in water over a wide pH range (pH 3 to 8). The drug substance has one ionizable group, the protonated pyrimidine moiety, with a pKa of 3.74.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Table 38: Summary of patient demographics for clinical trials in previously untreated CLL

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Single-agent therapy					
RESONATE-2 (PCYC-1115-CA)	Randomized (1:1), open label, active controlled Phase 3 study in patients with previously untreated CLL	IMBRUVICA® 420 mg orally once daily Chlorambucil[a]	136 133 Total: 269	73 (65-90)	M: 63% F: 37%

Combination therapy					
iLLUMINATE (PCYC-1130-CA)	Randomized (1:1), open label, active controlled Phase 3 study in patients with previously untreated CLL	IMBRUVICA® 420 mg orally once daily + obinutuzumab[b] Chlorambucil[c] + obinutuzumab[b]	113 116 Total: 229	71 (40-87)	M: 64% F: 36%
ECOG-1912	Randomized (2:1), open label, active controlled Phase 3 study in patients with previously untreated CLL	IMBRUVICA® 420 mg orally once daily + rituximab[d] Fludarabine, cyclophosphamide, and rituximab (FCR)[e]	354 175 Total: 529	58 (28-70)	M: 67% F: 33%
Fixed duration combination therapy					
GLOW (CLL3011)	Randomized (1:1), open label, active controlled Phase 3 study in patients with previously untreated CLL	IMBRUVICA® 420 mg orally once daily + venetoclax[f] (Total of 15 cycles) Chlorambucil[c]+ obinutuzumab[b] (Total of 6 cycles)	106 105 Total: 211	71 (47-93)	M: 58% F: 42%
CAPTIVATE (PCYC-1142-CA)	Phase 2, 2-cohort study in patients with previously untreated CLL	Fixed duration cohort: IMBRUVICA® 420 mg orally once daily + venetoclax[f] (Total of 15 cycles) Minimum residual disease cohort: IMBRUVICA® 420 mg orally once daily + venetoclax[f,g] (Total of 15 cycles)	159 164 Total: 323	60 (33-71) 58 (28-69)	M: 67% F: 33% M: 63% F: 37%

[a]Chlorambucil orally 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
[b]Obinutuzumab 1000 mg intravenous on Days 1 (or 100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each)
[c]Chlorambucil 0.5 mg/kg orally on Days 1 and 15 of each 28-day cycle for 6 cycles
[d]Rituximab was initiated in Cycle 2 for the IR arm
[e]Fludarabine was administered at a dose of 25 mg/m^2, and cyclophosphamide was administered at a dose of 250 mg/m^2, both on Days 1, 2, and 3 of Cycles 1-6. Rituximab was initiated in Cycle 1 for the FCR arm and was administered at 50 mg/m^2 on Day 1 of the first cycle, 325 mg/m^2 on Day 2 of the first cycle, and 500 mg/m^2 on Day 1 of 5 subsequent cycles, for a total of 6 cycles.
[f] Single agent IMBRUVICA® was administered for 3 cycles followed by IMBRUVICA® in combination with venetoclax for 12 cycles (including 5-week dose ramp-up). Each cycle was 28 days. IMBRUVICA® was administered at a dose of 420 mg daily. Venetoclax was administered daily, starting with 20 mg for 1 week, followed by 1 week at each dose level of 50 mg, 100 mg, and 200 mg, then the recommended daily dose of 400 mg.
[g]Minimum residual disease (MRD) cohort continued with 1 additional cycle (cycle 16) during which MRD was assessed.

Single-agent therapy

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 small lymphocytic lymphoma (SLL) (RESONATE-2 [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 were either symptomatic or asymptomatic and had "active" disease meeting at least 1 of the International Workshop on CLL (IWCLL) 2008 criteria for requiring treatment. 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, 20% had 11q deletion, and of those with known immunoglobulin heavy chain variable region (IGHV) mutational status (n=200), 59% were unmutated.

At a median follow-up of 18.4 months, PFS as assessed by IRC according to IWCLL criteria indicated an 84% statistically significant reduction in the risk of death or progression in the IMBRUVICA® arm. 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 39 and the Kaplan-Meier curves for PFS and OS are shown in Figure 1 and Figure 2, respectively.

Table 39: Results of RESONATE-2 in patients with previously untreated CLL

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 RESONATE-2

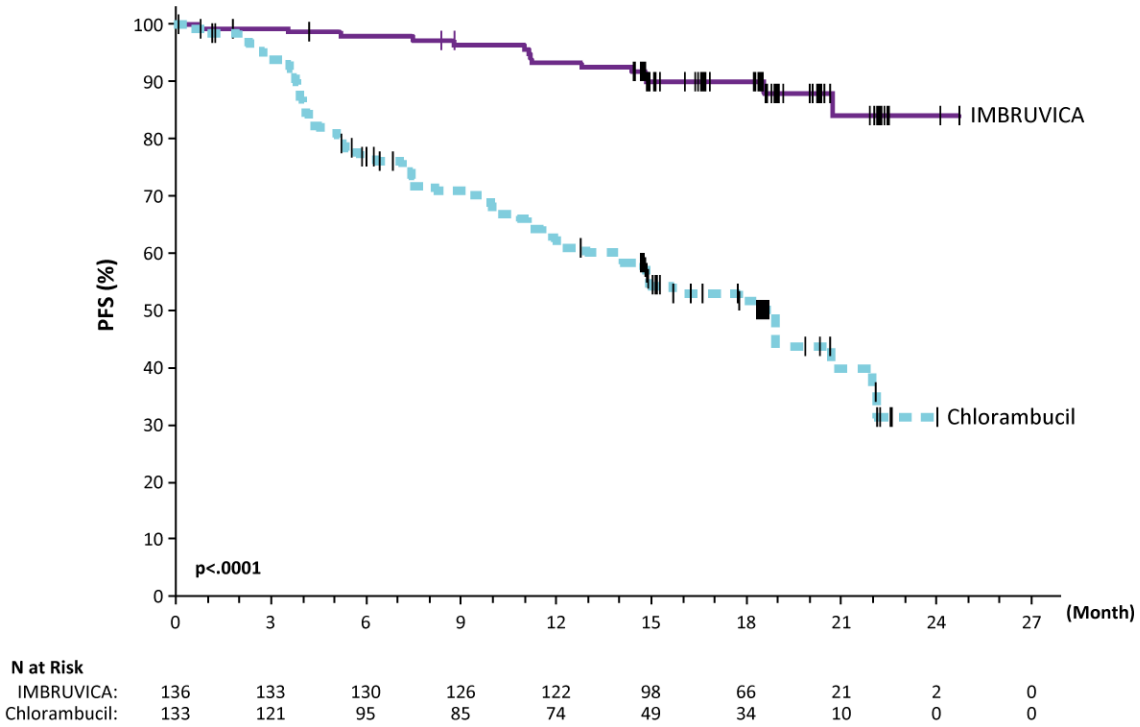
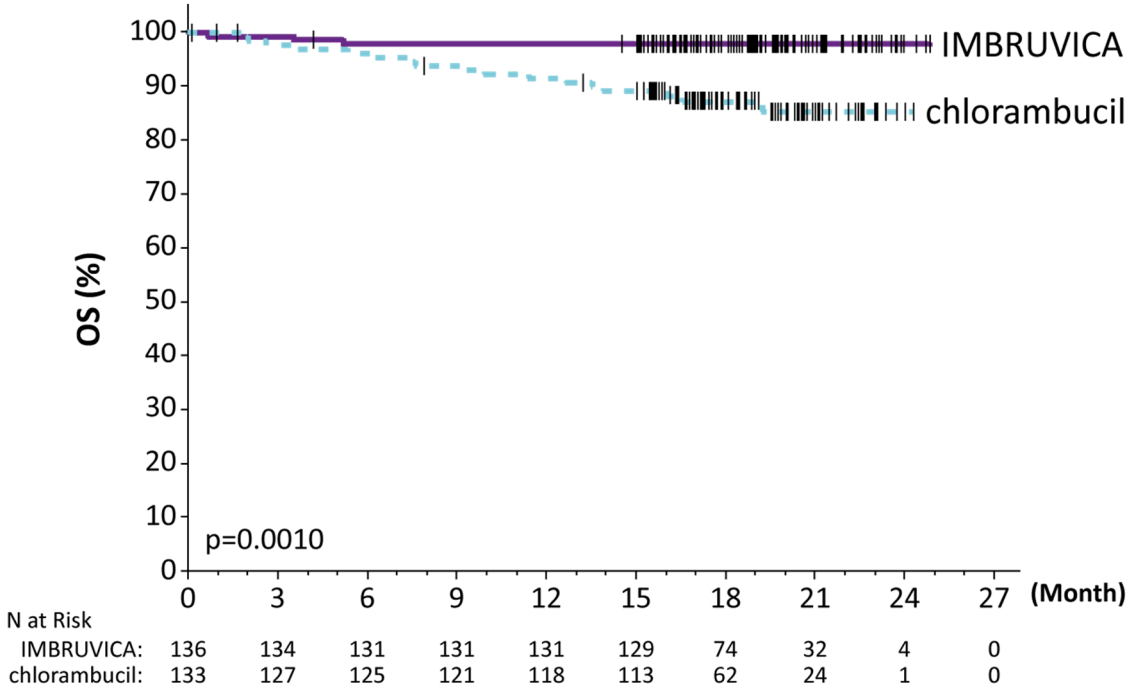


Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in RESONATE-2



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, patients with unmutated and mutated IGHV, 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).

With a median follow-up of 48 months (overall follow-up of 55 months) in RESONATE-2 and its extension study, the median investigator-assessed PFS was not reached in the IMBRUVICA® arm and was 15 months [95% CI (10.22, 19.35)] in the chlorambucil arm; (HR = 0.14 [95% CI (0.090, 0.21)]). The 4-year PFS estimate was 73.9% in the IMBRUVICA® arm and 15.5% in the chlorambucil arm, respectively. The Kaplan-Meier landmark estimate for OS at 48-months was 85.5% in the IMBRUVICA® arm and 75.6% in the chlorambucil arm, irrespective of 54.9% of patients who crossed over from the chlorambucil arm to receive ibrutinib treatment.

Combination therapy with obinutuzumab

The efficacy and safety of IMBRUVICA® in combination with obinutuzumab in patients with previously untreated CLL were demonstrated in a randomized controlled trial (iLLUMINATE [PCYC-1130-CA]).

iLLUMINATE was a randomized, multi-center, open-label, controlled phase 3 study of IMBRUVICA® in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab conducted in patients with previously untreated CLL, including 15 with clinical presentation of SLL. Patients were either symptomatic or asymptomatic and had "active" disease meeting at least 1 of the IWCLL 2008 diagnostic criteria for requiring treatment. The study enrolled patients who were ≥ 65 years of age or who were < 65 years of age with coexisting medical conditions, reduced renal function as measured by creatinine clearance <70 mL/min, or 17p deletion/tumour protein 53 (TP53) mutation. Patients (n=229) were randomized 1:1 to receive either IMBRUVICA® 420 mg daily until disease progression or unacceptable toxicity or chlorambucil at a dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for 6 cycles. In both arms, patients received 1000 mg of obinutuzumab on Days 1, 8 and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of obinutuzumab was divided between day 1 (100 mg) and day 2 (900 mg). The primary endpoint was progression-free survival (PFS) as assessed by an independent review committee (IRC) according to the International Workshop on CLL (IWCLL) criteria. After IRC-confirmed disease progression, patients in the chlorambucil + obinutuzumab arm may cross-over to receive next-line ibrutinib monotherapy.

The median age was 71 years (range, 40 to 87 years), 64% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (48%) or 1-2 (52%). At baseline, 52% had advanced clinical stage (Rai Stage III or IV), 32% of patients had bulky disease (≥ 5 cm), 44% with baseline anemia, 22% with baseline thrombocytopenia, 28% had a CrCL < 60 mL/min, and the median Cumulative Illness Rating Score for Geriatrics (CIRS-G) was 4 (range, 0 to 12). At baseline, 18% of patients had 17p deletion/TP53 mutation, 15% had 11q deletion, and of those with known IGHV mutational status (n=214), 57% were unmutated.

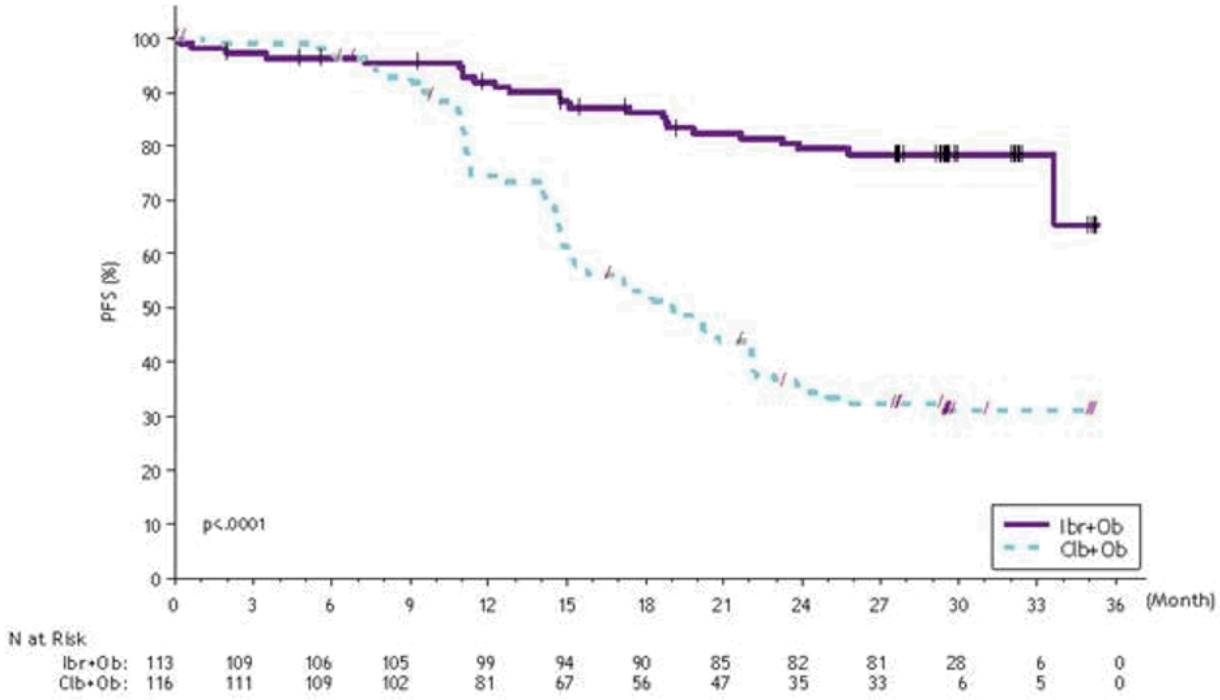
Progression-free survival (PFS) as assessed by IRC indicated a statistically significant reduction of 77% in the risk of death or progression in the IMBRUVICA® arm. With a median follow-up time on study of 31 months, the median PFS was not reached in the IMBRUVICA® + obinutuzumab arm and was 19 months in the chlorambucil + obinutuzumab arm. Efficacy results for Study PCYC-1130-CA are shown in Table 40 and the Kaplan-Meier curve for PFS is shown in Figure 3.

Table 40: Results of iLLUMINATE in patients with previously untreated CLL

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

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

Figure 3: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in iLLUMINATE



In the high-risk population (patients with any of 17p deletion/TP53 mutation, 11q deletion or unmutated IGHV) the PFS HR was 0.15 [95%CI (0.09, 0.27)]), which is consistent with other subgroups examined. In this population, the median PFS was not reached in the IMBRUVICA® + obinutuzumab and was 14.7 months for the chlorambucil + obinutuzumab arm.

PFS was similar across all subgroups examined, including patients <65 and ≥ 65 years of age, patients with and without 17p deletion/TP53 mutation, patients with and without 11q deletion, patients with mutated and unmutated IGHV, patients with and without advanced disease (Rai stage 0-II and stage III-IV), patients with and without bulky lymphadenopathy (<5cm and ≥5cm), and patients with and without functional impairment (ECOG performance status 0 and 1-2).

Combination therapy with rituximab

The efficacy and safety of IMBRUVICA® in combination with rituximab in patients with previously untreated CLL were demonstrated in a randomized controlled trial (ECOG-1912).

ECOG-1912 was a randomized, multi-center, open-label, controlled phase 3 study of IMBRUVICA® in combination with rituximab [IR] versus fludarabine, cyclophosphamide, and rituximab [FCR] chemoimmunotherapy conducted in patients with previously untreated active CLL (symptomatic/objective signs of disease requiring therapy), who were 70 years or younger, including 63 with clinical presentation of SLL. Patients with 17p deletion were excluded. All patients had a CrCL>40

mL/min at baseline. Patients were randomized 2:1 to receive either IR or FCR. IMBRUVICA® was administered at 420 mg daily until disease progression or unacceptable toxicity. Fludarabine was administered at a dose of 25 mg/m^2, and cyclophosphamide was administered at a dose of 250 mg/m^2, both on Days 1, 2, and 3 of Cycles 1-6. Rituximab was initiated in Cycle 2 for the IR arm and in Cycle 1 for the FCR arm and was administered at 50 mg/m^2 on Day 1 of the first cycle, 325 mg/m^2 on Day 2 of the first cycle, and 500 mg/m^2 on Day 1 of 5 subsequent cycles, for a total of 6 cycles. Each cycle was 28 days. The primary endpoint was PFS as assessed by an IRC according to the IWCLL criteria.

The median age was 58 years (range, 28 to 70 years), 67% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0-1 (98%) or 2 (2%). At baseline, 43% of patients presented with Rai stage III or IV, 37% had ≥ 5 cm bulky disease, and 59% of patients presented with high risk factors (mutated TP53, del11q, or unmutated IGHV). At baseline, 6% of patients had mutated TP53 (76% not mutated, 18% unknown), 22% had del11q, and 53% had unmutated IGHV (21% mutated, 26% unknown).

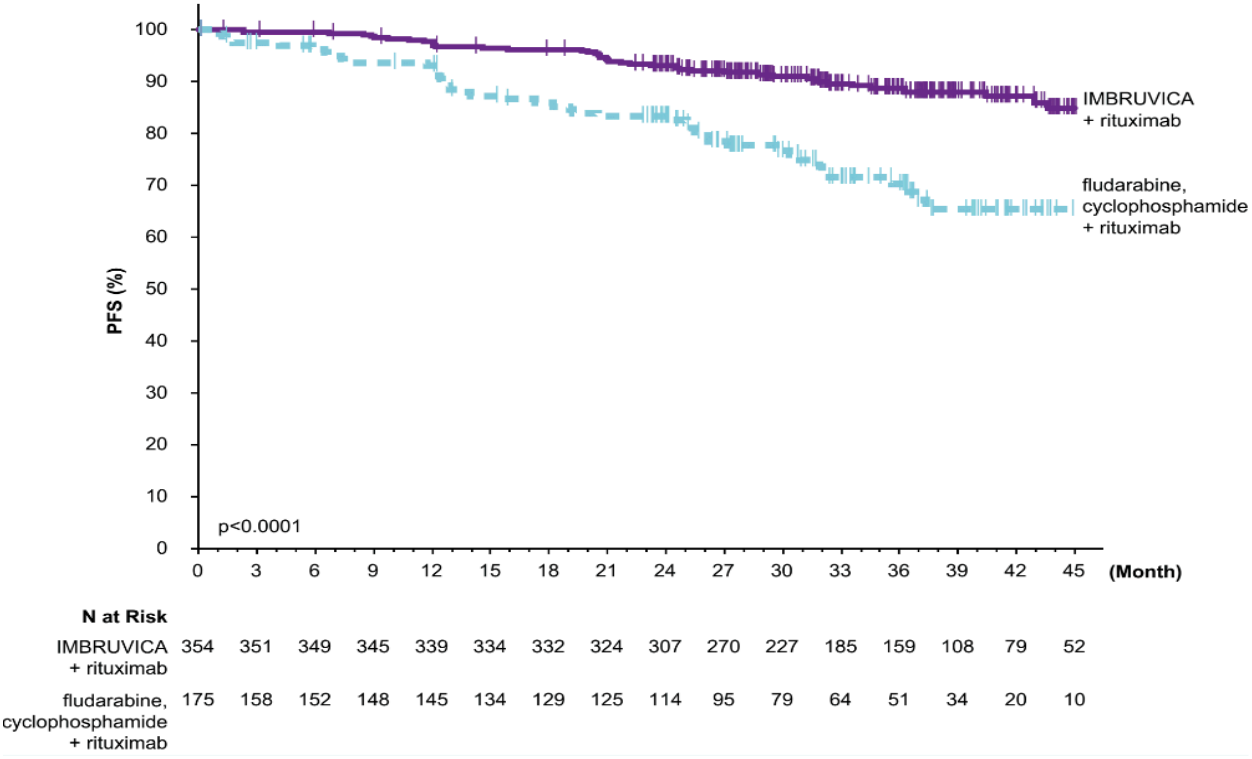
With a median follow-up time on study of 37 months, PFS as assessed by IRC indicated a statistically significant reduction of 66% in the risk of death or progression in the IMBRUVICA® arm vs. FCR. Efficacy results for Study ECOG-1912 are shown in Table 41 and the Kaplan-Meier curve for PFS is shown in Figure 4.

Table 41: Results of Study ECOG-1912 in patients with previously untreated CLL

Endpoint	Ibrutinib + Rituximab (IR) N=354	Fludarabine, Cyclophosphamide, and Rituximab (FCR) N=175
Progression Free Survival		
Number of events (%)	41 (12)	44 (25)
Median (95% CI), months	NE (49.4, NE)	NE (47.1, NE)
HR (95% CI)	0.34 (0.22, 0.52)	
P-value[a]	<0.0001	

[a] P-value is from unstratified log-rank test.
HR = hazard ratio; NE = not evaluable, CI = confidence interval

Figure 4: Kaplan-Meier Curve of Progression Free Survival (ITT Population) in Study ECOG-1912



Results for PFS were consistent across all predefined subgroups.

Prespecified Key Secondary Endpoints:

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

The high-risk population (TP53 mutation, del11q, or unmutated IGHV) showed a statistically significant reduction in disease progression with a PFS HR of 0.23 [95% CI (0.13, 0.40)], p<0.0001.

Fixed duration combination therapy with venetoclax

The efficacy and safety of fixed duration treatment with IMBRUVICA® in combination with venetoclax in patients with previously untreated CLL was demonstrated in two clinical studies: one Phase 3, randomized controlled trial (GLOW [CLL3011]), and one Phase 2, multi-centre, 2-cohort study (CAPTIVATE [PCYC-1142-CA]).

GLOW (CLL3011)

GLOW was a randomized, open-label, Phase 3 study of IMBRUVICA® in combination with venetoclax versus chlorambucil in combination with obinutuzumab, conducted in patients with previously untreated active CLL who were 65 years or older, and adult patients <65 years of age with a CIRS score >6 or CrCL ≥30 to <70 mL/min, including 14 patients with clinical presentation of SLL. Patients with del 17p or known TP53 mutations were excluded. Patients (n = 211) were randomized 1:1 to receive either

IMBRUVICA® in combination with venetoclax or chlorambucil in combination with obinutuzumab. Patients in the IMBRUVICA® plus venetoclax arm received single agent IMBRUVICA® for 3 cycles followed by IMBRUVICA® in combination with venetoclax for 12 cycles (including 5-week dose ramp-up). Each cycle was 28 days. IMBRUVICA® was administered at a dose of 420 mg daily. Venetoclax was administered daily, starting with 20 mg for 1 week, followed by 1 week at each dose level of 50 mg, 100 mg, and 200 mg, then the recommended daily dose of 400 mg. Patients randomized to the chlorambucil plus obinutuzumab arm received treatment for 6 cycles. Obinutuzumab was administered at a dose of 1000 mg on Days 1 (or 100 mg on Day 1 and 900 mg on Day 2), 8 and 15 in Cycle 1. In Cycles 2 to 6, 1000 mg obinutuzumab was given on Day 1. Chlorambucil was administered at a dose of 0.5 mg/kg body weight on Days 1 and 15 of Cycles 1 to 6. Patients with confirmed progression by IWCLL criteria after completion of either fixed duration regimen could be treated with single-agent IMBRUVICA®.

The median age was 71 years (range, 47 to 93 years), 58% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (35%), 1 (53%), or 2 (12%). At baseline, 18% of patients presented with del 11q and 52% with unmutated IGHV. The most common reasons for initiating CLL therapy included: constitutional symptoms (59%), progressive marrow failure (48%), lymphadenopathy (36%), splenomegaly (28%) and progressive lymphocytosis (19%). At baseline assessment for risk of tumour lysis syndrome, 25% of patients had high tumour burden. After 3 cycles of single-agent IMBRUVICA® lead-in therapy, 2% of patients had high tumour burden. High tumour burden was defined as any lymph node ≥10 cm; or any lymph node ≥5 cm and absolute lymphocyte count $\geq 25 \times 10^9$/L.

The primary endpoint in GLOW was PFS as assessed by an IRC according to the IWCLL criteria. A clinically meaningful and statistically significant improvement in PFS was observed for the IMBRUVICA® plus venetoclax fixed duration treatment arm compared with the chlorambucil plus obinutuzumab arm (HR=0.22; 95% CI: 0.13, 0.36; p<0.0001), representing a 78% reduction in the risk of disease progression or death with IMBRUVICA® plus venetoclax.

Improvements in key secondary endpoints of minimal residual disease (MRD) negativity rate in the bone marrow and complete response (CR) rate were also demonstrated. The MRD negativity rate in bone marrow as assessed by Next-Generation Sequencing (NGS) was significantly higher in the IMBRUVICA® plus venetoclax arm compared with the chlorambucil plus obinutuzumab arm (55.7% vs. 21.0%; respectively; p<0.0001). Fixed duration treatment of IMBRUVICA® plus venetoclax resulted in a significantly higher CR rate (i.e., proportion of subjects with CR or CRi) per IRC assessment compared with chlorambucil with obinutuzumab (38.7% vs. 11.4%, respectively; p<0.0001).

Efficacy results for Study CLL3011 (GLOW) with a median follow-up time of 28 months are shown in Table 42, the Kaplan-Meier curve for PFS is shown in Figure 5, and rates of MRD negativity are shown in Table 43.

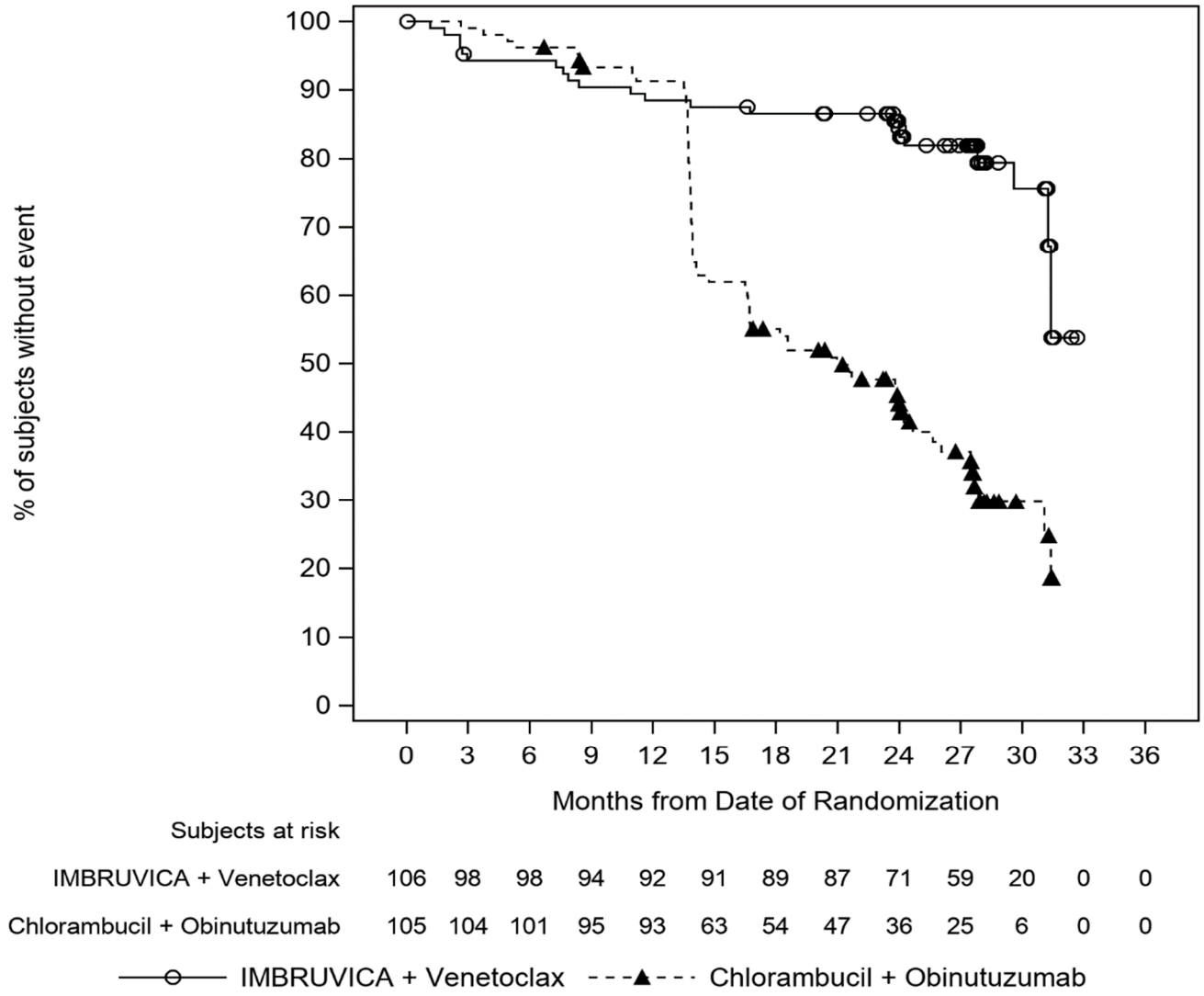
Table 42: Efficacy Results of Study CLL3011 (GLOW) in patients with previously untreated CLL

Endpoint[a]	**IMBRUVICA® + Venetoclax N=106**	**Chlorambucil + Obinutuzumab N=105**
Progression-Free Survival		
Number of events (%)	22 (20.8)	67 (63.8)
Median (95% CI), months	NE (31.2, NE)	21.0 (16.6, 24.7)
HR (95% CI)	0.22 (0.13, 0.36)	
P-value[b]	<0.0001	
Complete Response Rate (%)[c]	38.7	11.4
95% CI	(29.4, 48.0)	(5.3, 17.5)
P-value[d]	<0.0001	
Overall Response Rate (%)[e]	86.8	84.8
95% CI	(80.3, 93.2)	(77.9, 91.6)
p-value	0.6991	

[a] Based on IRC assessment
[b] P-value is from stratified log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no)
[c] Includes 3 patients in the IMBRUVICA® + venetoclax arm with a complete response with incomplete marrow recovery (CRi)
[d] P-value is from Cochran-Mantel-Haenszel chi-square test
[e] Overall response = CR+CRi+nPR+PR

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

Figure 5: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with Previously Untreated CLL in Study CLL3011 (GLOW)



The PFS treatment effect of IMBRUVICA® plus venetoclax versus chlorambucil plus obinutuzumab was consistent across predefined subgroups, including the high-risk population (TP53 mutation, del 11q, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.41)].

With a median follow-up of 28 months, overall survival data were not mature with a total of 23 deaths: 11 (10.4%) in the IMBRUVICA® plus venetoclax arm and 12 (11.4%) in the chlorambucil plus obinutuzumab arm.

Table 43: Minimal Residual Disease Negativity Rates in Patients with Previously Untreated CLL in Study CLL3011 (GLOW)

	NGS Assay[a]		Flow Cytometry[b]	
	IMBRUVICA® + Venetoclax N=106	Chlorambucil + Obinutuzumab N=105	IMBRUVICA® + Venetoclax N=106	Chlorambucil + Obinutuzumab N=105
MRD Negativity Rate				
Bone marrow, n (%)	59 (55.7)	22 (21.0)	72 (67.9)	24 (22.9)
95% CI	(46.2, 65.1)	(13.2, 28.7)	(59.0, 76.8)	(14.8, 30.9)
P-value	<0.0001		<0.0001	
Peripheral Blood, n (%)	63 (59.4)	42 (40.0)	85 (80.2)	49 (46.7)
95% CI	(50.1, 68.8)	(30.6, 49.4)	(72.6, 87.8)	(37.1, 56.2)
P-value	0.0055		<0.0001	

P-values are from Cochran-Mantel-Haenszel chi-square test. Except the p-value for MRD negativity rate in bone marrow by NGS, which is the primary MRD analysis and the first key secondary endpoint of GLOW, all other p-values are nominal.
All MRD results were derived from samples obtained from ≥80% of participants.

[a] Based on threshold of 10^{-4} using a next-generation sequencing assay (clonoSEQ)

[b] MRD was evaluated by flow cytometry of peripheral blood or bone marrow per central laboratory. The definition of negative status was <1 CLL cell per 10,000 leukocytes ($<1 \times 10^4$).

CI = confidence interval; NGS = next-generation sequencing

Three months after the completion of treatment, MRD negativity rates in peripheral blood were 54.7% (58/106) by NGS assay and 61.3% (65/106) by flow cytometry in patients treated with IMBRUVICA® plus venetoclax and, at the corresponding time point, were 39.0% (41/105) by NGS assay and 41.0% (43/105) by flow cytometry in patients treated with chlorambucil plus obinutuzumab. At three months after completion of treatment, 56 patients in the IMBRUVICA® plus venetoclax arm who were MRD negative in peripheral blood by NGS assay had matched bone marrow specimens; of these, 52 patients (92.9%) were MRD negative in both peripheral blood and bone marrow.

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

CAPTIVATE (PCYC-1142-CA)

CAPTIVATE was a Phase 2, multi-centre, 2-cohort study assessing both minimal residual disease (MRD)-guided discontinuation and fixed duration therapy with IMBRUVICA® in combination with venetoclax, conducted in adult patients who were 70 years or younger with previously untreated active CLL. The study enrolled 323 patients; of these, 159 patients were enrolled to fixed duration therapy consisting of 3 cycles of single agent IMBRUVICA® followed by IMBRUVICA® in combination with venetoclax for 12 cycles (including 5-week dose ramp-up). Each cycle was 28 days. IMBRUVICA® was administered at a

dose of 420 mg daily. Venetoclax was administered daily, starting with 20 mg for 1 week, followed by 1 week at each dose level of 50 mg, 100 mg, and 200 mg, then the recommended daily dose of 400 mg. Patients with confirmed progression by IWCLL criteria after completion of the fixed duration regimen could be retreated with single-agent IMBRUVICA®.

In the fixed duration cohort the median age was 60 years (range, 33 to 71 years), 67% were male, and 92% were Caucasian. All patients had a baseline ECOG performance status of 0 (69%) or 1 (31%). The trial enrolled 146 patients with CLL and 13 patients with SLL. At baseline, 13% of patients presented with del 17p, 18% with del 11q, 17% with del 17p or TP53 mutation, 56% with unmutated IGHV and 19% with complex karyotype. The most common reasons for initiating CLL therapy included: lymphadenopathy (65%), progressive lymphocytosis (51%), splenomegaly (30%), fatigue (24%), progressive marrow failure demonstrated by anemia and/or thrombocytopenia (23%), and night sweats (21%). At baseline assessment for risk of tumour lysis syndrome, 21% of patients had high tumour burden. After 3 cycles of single-agent IMBRUVICA® lead-in therapy, 1% of patients had high tumour burden. High tumour burden was defined as any lymph node ≥10 cm, or any lymph node ≥5 cm and absolute lymphocyte count $\geq 25 \times 10^9$/L.

The primary endpoint in the fixed duration cohort, the complete response rate as assessed by the investigator, was 55.3% (95% CI: 47.6, 63.1) for all participants. The CR rate per IRC assessment for all participants in the FD cohort was 59.7% (95% CI: 52.1, 67.4) and 61.0% (95% CI: 52.8, 69.2) for participants without del 17p. Per investigator assessment, the secondary efficacy endpoint of overall response rate was 96.2% for all participants.

Efficacy results for Study PCYC-1142-CA with a median follow-up time of 28 months are shown in Table 44, and rates of minimal residual disease (MRD) negativity are shown in Table 45.

Table 44: Efficacy Results of Study PCYC-1142-CA (CAPTIVATE; Fixed Duration Cohort)[a] in Patients with Previously Untreated CLL

Endpoint[a]	IMBRUVICA® + Venetoclax	
	Without Del 17p (N=136)	**All (N=159)**
Complete Response Rate, n (%)	76 (55.9)	88[b] (55.3)
95% CI (%)	(47.5, 64.2)	(47.6, 63.1)
Median duration of CR, months (range)[c]	NE (0.03+, 24.9+)	NE (0.03+, 24.9+)
Overall Response Rate, n (%)[d]	130 (95.6)	153 (96.2)
95% CI (%)	(92.1, 99.0)	(93.3, 99.2)
Best Overall Response		
CR	74 (54.4)	83 (52.2)
CRi	2 (1.5)	5 (3.1)
nPR	1 (0.7)	1 (0.6)
PR	53 (39.0)	64 (40.3)

[a] Based on investigator assessment

Endpoint[a]	IMBRUVICA® + Venetoclax	
	Without Del 17p (N=136)	All (N=159)
[b] Includes 5 patients with a complete response with incomplete marrow recovery (CRi) [c] A '+' sign indicates a censored observation [d] Overall response = CR + CRi + nPR + PR CR = complete response; CRi = complete response with incomplete marrow recovery; nPR = nodular partial response; PR = partial response; NE = not evaluable; NA = Not available		

Table 45: Minimal Residual Disease Negativity Rates in Patients with Previously Untreated CLL in Study PCYC-1142-CA (CAPTIVATE; Fixed Duration Cohort)

Endpoint	IMBRUVICA® + Venetoclax	
	Without Del 17p (N=136)	All (N=159)
MRD Negativity Rate		
Bone marrow, n (%)	84 (61.8)	95 (59.7)
95% CI	(53.6, 69.9)	(52.1, 67.4)
Peripheral Blood, n (%)	104 (76.5)	122 (76.7)
95% CI	(69.3, 83.6)	(70.2, 83.3)
MRD was evaluated by flow cytometry of peripheral blood or bone marrow per central laboratory. The definition of negative status was <1 CLL cell per 10,000 leukocytes ($<1\times10^4$). All MRD results were derived from samples obtained from ≥80% of participants. CI = confidence interval		

Three months after the completion of treatment with IMBRUVICA® plus venetoclax, the MRD negativity rate for all subjects was 56.6% (90/159) in the peripheral blood and 52.2% (83/159) in the bone marrow, and for subjects without Del 17p, 57.4% (78/136) in the peripheral blood and 54.4% (74/136) in the bone marrow. At this assessment, 84 patients who were MRD negative in peripheral blood had matched bone marrow specimens; of these, 76 patients (90%) were MRD negative in both peripheral blood and bone marrow.

CLL with del 17p/TP53 in CAPTIVATE (PCYC-1142-CA)

In patients in the fixed duration cohort with del 17p and/or TP53 mutation (n = 27: of which, n = 20 for del 17p), the overall response rate based on IRC assessment was 96.3%; the complete response rate was 55.6% and the median duration of complete response was not reached (range 4.3 to 22.6 months). The MRD negativity rate in patients with del 17p and/or TP53 mutation 3 months after completion of treatment in bone marrow and peripheral blood was 40.7% and 59.3%, respectively.

Previously Treated Chronic Lymphocytic Leukemia (CLL)

Table 46: Summary of patient demographics for clinical trials in previously treated CLL

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Single-agent therapy					
RESONATE (PCYC-1112-CA)	Randomized (1:1), open label, active controlled Phase 3 Study in patients with previously treated CLL	IMBRUVICA® 420 mg orally once daily Ofatumumab[a]	195 196 Total: 391	67 (30-88)	M: 68% F: 32%
PCYC-1102-CA	Open label, Phase 1b/2 Study in patients with previously treated CLL	IMBRUVICA® 420 mg orally once daily	51	68 (37-82)	M: 73% F: 27%
Combination therapy					
HELIOS (CLL3001)	Randomized (1:1), double blind, placebo- controlled Phase 3 Study in patients with previously treated CLL	IMBRUVICA® 420 mg orally once daily + bendamustine and rituximab (BR)[b] Placebo + BR[b]	289 289 Total: 578	64 (31-86)	M: 66% F: 34%

[a]ofatumumab for up to 12 doses (300/2000 mg)
[b]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).

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 (RESONATE [PCYC-1112-CA]), and one uncontrolled trial (PCYC-1102-CA).

RESONATE 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, 50% had 17p deletion/TP53 mutation, 31% had 11q deletion, and of those with known IGHV mutational status (n= 266), 68% were unmutated.

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 47 and the Kaplan-Meier curves for PFS and OS are shown in Figure 7 and Figure 8, respectively.

Table 47: Results of RESONATE in patients with previously treated CLL

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 with unmutated and mutated IGHV (not pre-specified subgroups), 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 6).

Figure 6: Subgroup Analysis of Progression-Free Survival by IRC (RESONATE; 420 mg)

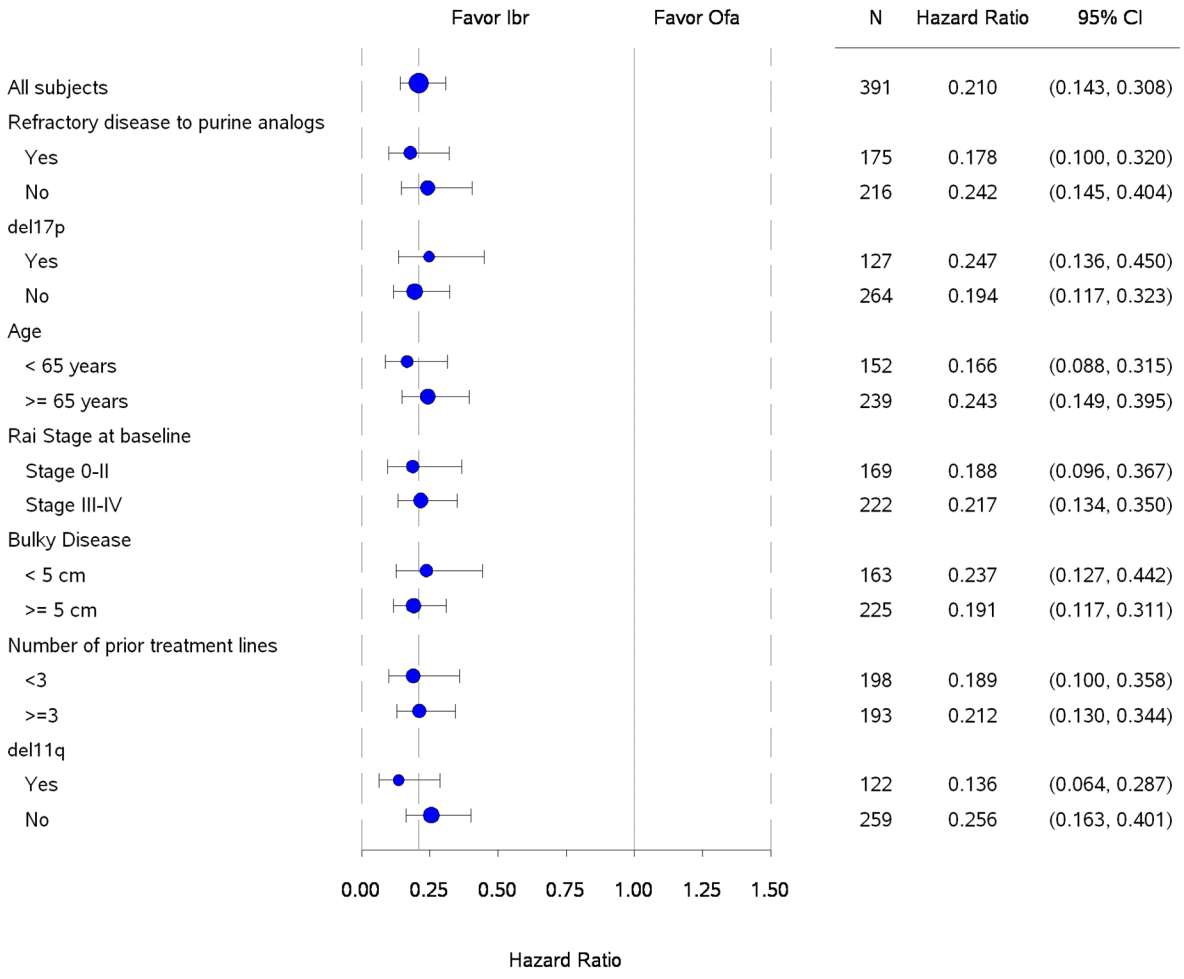


Figure 7: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in RESONATE

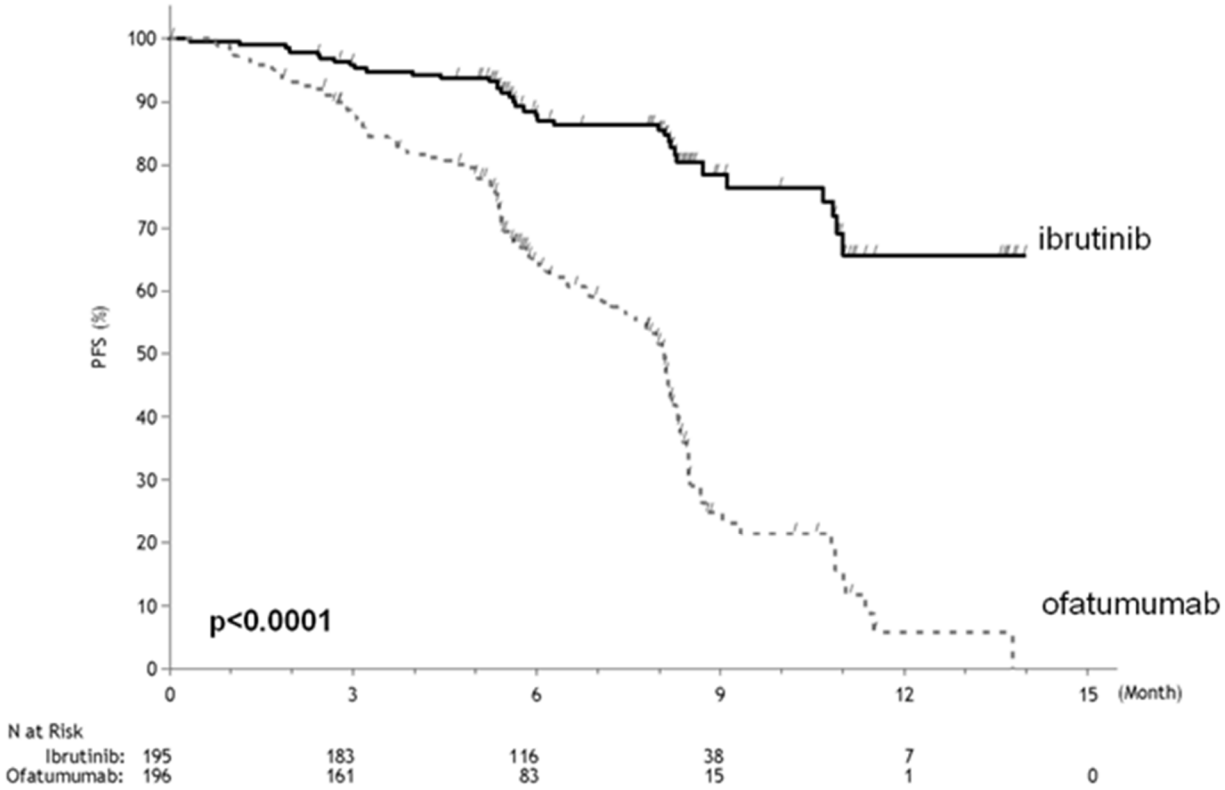
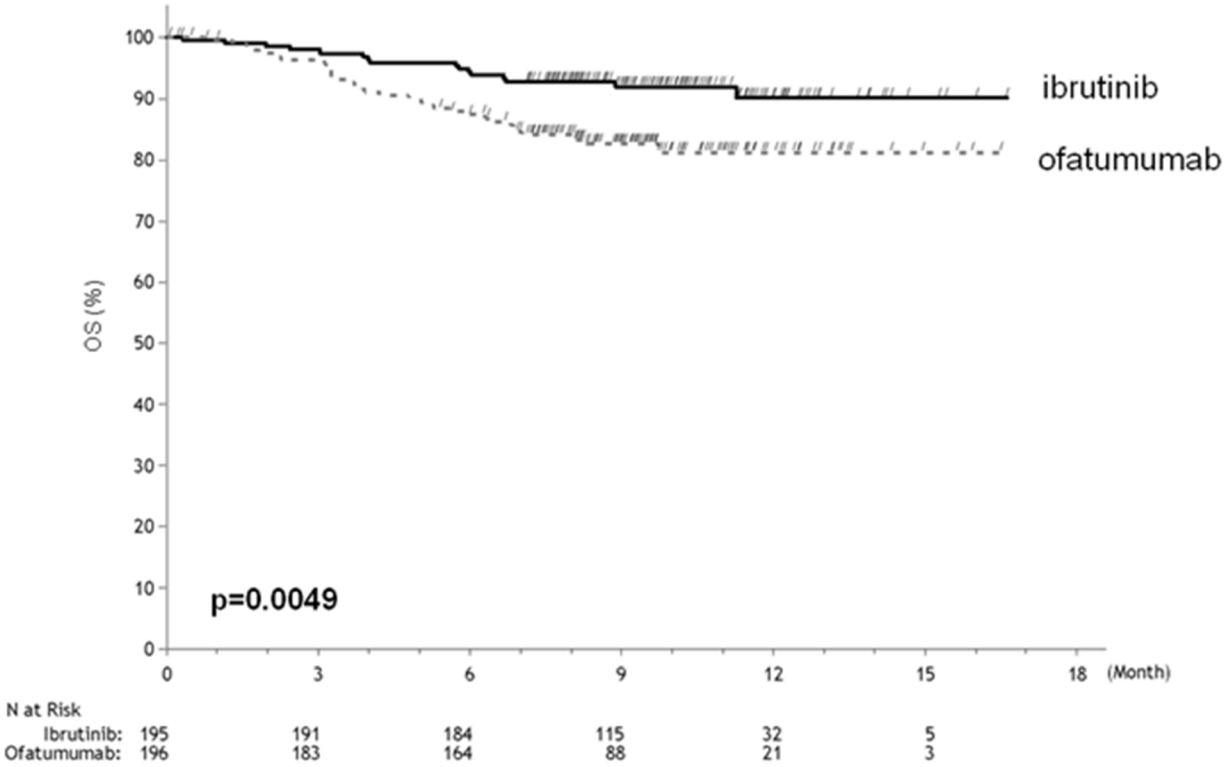


Figure 8: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study RESONATE



At a median follow-up of 65 months, the median investigator-assessed PFS according to IWCLL criteria was 44.1 months [95% CI (38.47, 56.18)] in the IMBRUVICA® arm and 8.1 months [95% CI (7.79, 8.25)] in the ofatumumab arm (HR=0.15; 95% CI: 0.11, 0.20). The median OS was 67.7 months [95% CI (61.0, not estimable)] in the IMBRUVICA® arm and 65.1 months [95% CI (50.6, not estimable)] in the ofatumumab arm (HR=0.81; 95% CI: 0.60, 1.10). The median OS for the ofatumumab arm includes data from 133 patients (67.9%) who crossed over to receive ibrutinib treatment. The ORR (per investigator) was 87.7% in the IMBRUVICA® arm versus 22.4% in the ofatumumab arm.

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 RESONATE. 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).

RESONATE 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 48.

Table 48: Results of RESONATE in patients with previously treated CLL with 17p deletion

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.		

With a median follow-up of 65.8 months in RESONATE (overall follow-up of 73.9 months), the median investigator-assessed PFS in patients with 17p deletion according to IWCLL criteria was 40.6 months [95% CI (25.36, 44.55)] in the IMBRUVICA® arm and 6.2 months [95% CI (4.63, 8.11)] in the ofatumumab arm, respectively; HR = 0.12, ([95% CI (0.073, 0.21)]. The investigator-assessed ORR in patients with 17p deletion in the IMBRUVICA® arm was 88.9% versus 18.8% in the ofatumumab arm.

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 (HELIOS [CLL3001]).

HELIOS 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 $\geq$5 cm, 26% had 11q deletion, and of those with known IGHV mutational status (n=519), 81% were unmutated.

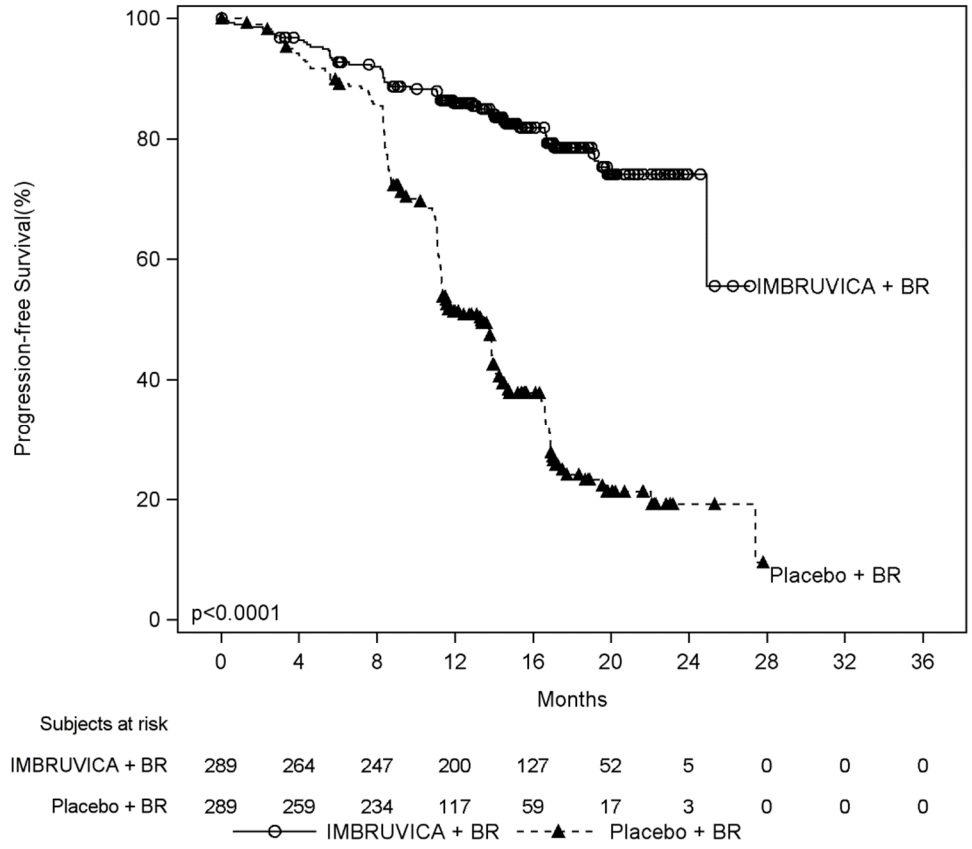
At a median duration of treatment of 14.7 months in the IMBRUVICA® in combination with BR arm, and 12.8 months in the placebo in combination with BR arm, PFS as assessed by IRC according to IWCLL criteria indicated a statistically significant, 80% reduction in the risk of death or progression. Efficacy results for HELIOS are shown in Table 49 and the Kaplan-Meier curve for PFS is shown in Figure 9.

Table 49: Results of HELIOS in patients with previously treated CLL

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 with unmutated and mutated IGHV, 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 9: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in HELIOS



Mantle Cell Lymphoma (MCL)

Table 50: Summary of patient demographics for clinical trials in MCL

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PCYC-1104-CA	Open label, Phase 2 Study in patients with relapsed or refractory MCL	IMBRUVICA® 560 mg orally once daily	111	68 (40-84)	M: 77% F: 23%

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 51.

Table 51: Results of Study PCYC-1104-CA in patients with MCL

ORR (CR+PR) (95% CI)	66.7% (57.1%, 75.3%)
CR	22.5%
PR	44.1%
n=111 CI = confidence interval; CR = complete response; ORR = overall response rate; PR = partial response	

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)

Table 52: Summary of patient demographics for clinical trials in MZL

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PCYC-1121-CA	Open label, Phase 2 Study in patients with MZL who received at least one prior line of systemic therapy	IMBRUVICA® 560 mg orally once daily	60	66 (30-92)	M: 43% F: 57%

The safety and efficacy of IMBRUVICA® were evaluated in a multicenter, single arm phase 2 study (PCYC-1121-CA) 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® and duration of response (DOR) based on IRC assessment are shown in Table 53.

Table 53: Results of Study PCYC-1121-CA in patients with MZL

	Total (N=60)*
Overall Response Rate (ORR) (CR + PR) (%)	48.3
95% CI (%)	(35.3, 61.7)
Complete Response (CR) (%)	3.3
Partial Response (PR) (%)	45.0
Median Duration of Response (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)

Table 54: Summary of patient demographics for clinical trials in WM

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Single-Agent Therapy					
PCYC-1118E	Open label, Phase 2 study in patients with previously treated WM	IMBRUVICA® 420 mg orally once daily	63	63 (44-86)	M: 76% F: 24%
iNNOVATE (PCYC-1127-CA)	Non-randomized single-agent therapy substudy arm in patients with previously treated WM	IMBRUVICA® 420 mg orally once daily	31	67 (47-90)	M: 64% F: 36%
Combination Therapy					
iNNOVATE (PCYC-1127-CA)	Randomized (1:1), double blind, placebo-controlled Phase 3 study in patients with WM	IMBRUVICA® 420 mg orally once daily + rituximab[a] Placebo + rituximab[a]	75 75 Total: 150	69 (36-89)	M: 66% F: 34%

[a]Intravenous rituximab 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).

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 (iNNOVATE [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 55). Efficacy results were also assessed by an IRC demonstrating an ORR of 82.5% (Table 55).

Table 55: Results of Study PCYC-1118E in patients with WM

Endpoint	Investigator Assessment	IRC Assessment
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)

n=63
[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 iNNOVATE 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 (iNNOVATE [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 of the overall population for iNNOVATE based on IRC assessment at a median time on study of 26.5 months are shown in Table 56 and the Kaplan-Meier curve for PFS is shown in Figure 10.

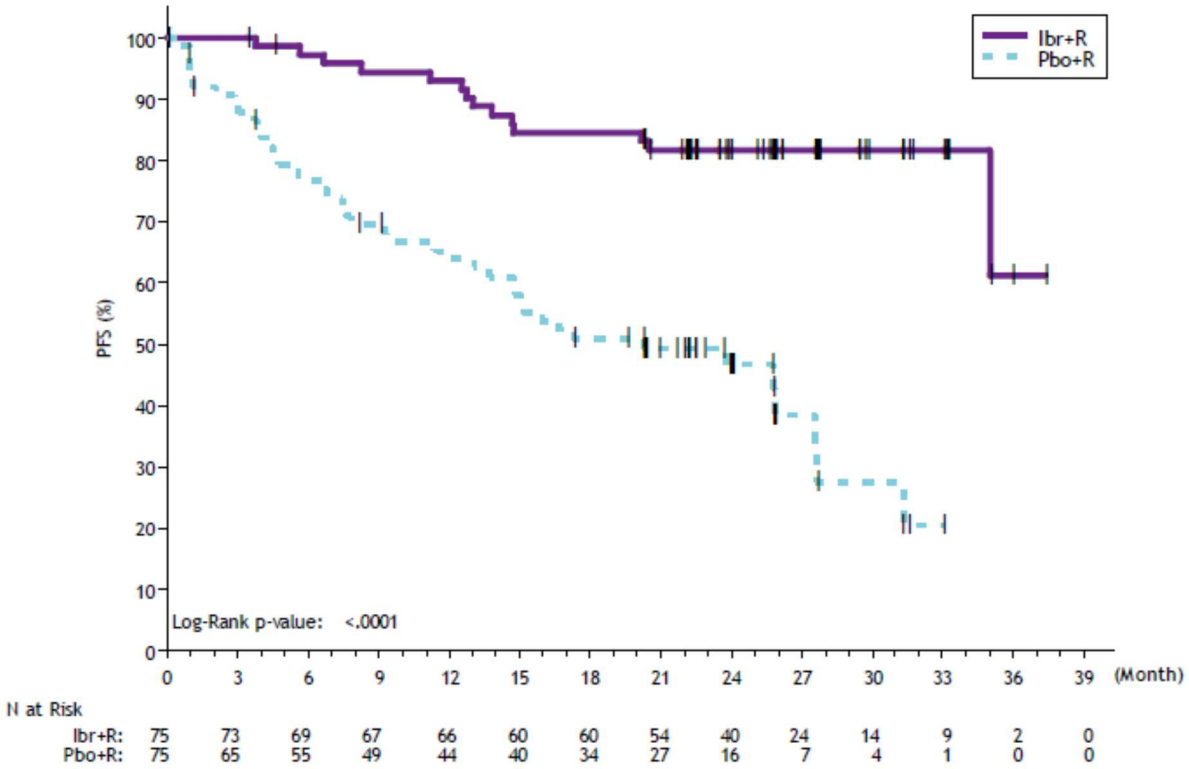
Table 56: Results of iNNOVATE in patients with WM

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 10: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in iNNOVATE



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) - Adults

Table 57: Summary of patient demographics for adult clinical trials in cGVHD

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PCYC-1129-CA	Open label, Phase 1b/2 Study in patients with cGVHD	IMBRUVICA® 420 mg orally once daily	42	56 (19-74)	M: 52% F: 48%

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 based on investigator assessment are shown in Table 58.

Table 58: Results of Study PCYC-1129-CA in patients with cGVHD

	Total (N=42)
Overall response rate (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.

Chronic Graft Versus Host Disease (cGVHD) - Pediatrics

Table 59: Summary of patient demographics for clinical trial in pediatric and young adult cGVHD

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
iMAGINE (PCYC-1146-IM)	Open-label, multicenter, Phase 1/2 dose-finding study in patients withmoderate or severe cGVHD after failure of one or more lines of systemic therapy.	Patients ≥ 12 years: IMBRUVICA® 420 mg orally once daily Pediatric patients < 12 years: IMBRUVICA® 240 mg/m^2 orally once daily	47	13.0 (1-19)	M: 70.2% F: 29.8%

The safety and efficacy of IMBRUVICA® were evaluated in an open-label, multi-centre, single-arm Phase 1/2 trial iMAGINE (PCYC-1146-IM) for the treatment of pediatric and young adult patients 1 year to less than 22 years of age with moderate or severe cGVHD as defined by the 2014 NIH Consensus Criteria for Clinical Trials in cGVHD. The study included 47 patients after failure of one or more prior lines of systemic therapy (Table 59).

All patients had platelets ≥ 30 x 10^9/L, absolute neutrophil count ≥ 1.0 x 10^9/L, AST or ALT ≤ 3 x ULN, total bilirubin ≤ 1.5 x ULN, and estimated creatinine clearance ≥ 30 mL/min. Patients were excluded if single organ genitourinary involvement was the only manifestation of cGVHD. IMBRUVICA® was administered at 420 mg orally once daily in patients ≥ 12 years of age and at 240 mg/m^2 orally once daily in pediatric patients < 12 years of age, until cGVHD progression, recurrence of underlying malignancy, or unacceptable toxicity. IMBRUVICA® could be discontinued after response in cGVHD disease symptoms and withdrawal of other systemic immunosuppressants. The study permitted continuation of other systemic immunosuppressants from baseline, as well as ancillary therapy and

supportive care for cGVHD. Temporary dose increase in the concomitant immunosuppressants was also permitted for the management of flares in cGVHD.

Of the 47 patients with relapsed or refractory cGVHD, the median age was 13 years (range, 1 to 19 years), 36% were White, 9% were Black, and 55% were other or unreported. The median time from initial cGVHD diagnosis was 16.1 months, and the median number of prior cGVHD regimens was 2 (range, 1 to 12). The majority of patients (75%) had severe disease at baseline. Twenty-nine (62%) patients received one or more concomitant systemic immunosuppressant medications.

The median follow-up time on study was 20 months. The efficacy of IMBRUVICA® was established based on overall response rate through Week 25. The overall response included complete response and partial response assessed according to the 2014 National Institutes of Health (NIH) Consensus Development Project Response Criteria. Efficacy results are shown in Table 60.

Table 60: Efficacy results in pediatric and young adult patients with relapsed or refractory cGVHD[a] in Study PCYC-1146-IM

	Total (N=47)
ORR through Week 25 (%)	28 (60%)
95% CI (%)	(44, 74)
Complete response (CR) (%)	2 (4%)
Partial response (PR) (%)	26 (55%)

CI = confidence interval; ORR = overall response rate

[a] Assessed based on 2014 NIH Consensus Development Project Response Criteria. Eight additional patients achieved a response (all PR) after Week 25.

In patients with relapsed/refractory cGVHD who had an overall response through Week 25, the median time to first response was 0.9 months (range, 0.9 to 6.1 months). The median duration of response (DOR) was 5.3 months (95% CI: 2.8, 8.8), when the DOR was calculated from first response to progression from nadir in any organ, death, or new systemic therapies for cGVHD. When the DOR was calculated from first response to progression from baseline, death, or new systemic therapies for cGVHD, the median was 14.8 months (95% CI: 4.6, NE). When the DOR was calculated from first response to death or new systemic therapies, the median was 14.8 months (95% CI: 4.6, NE).

Response results are supported by exploratory analyses of patient-reported symptom bother which showed, at least a 7-point decrease in Lee Symptom Scale overall summary score through Week 25 in 50% (13/26) of patients age 12 years and older.

14.2 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.

The relative bioavailability of was evaluated following single oral dose administration of suspension compared with capsules. The ibrutinib suspension showed comparable bioavailability based on AUC_{last} relative to the ibrutinib 140 mg capsule under fasting conditions. Following a single 560 mg dose under fasting conditions, 90% CIs were within the 80.00 to 125.00 bioequivalence limits, while C_{max} was 35.6% lower for the suspension. The difference in C_{max} is considered not to be clinically meaningful. The effect of food on suspension formulation was approximately 2-fold when administered 2 hours after completing a high-fat breakfast.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: 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.

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

Genotoxicity: 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.

Reproductive and Developmental Toxicology: 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).

Cardiovascular Function: The acute effects of ibrutinib treatment on cardiovascular function were 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}).

CNS and Respiratory Function: 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}).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]IMBRUVICA®

ibrutinib tablets

ibrutinib capsules

ibrutinib oral suspension

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

- Major bleeding events, some fatal, have been reported
- Your healthcare professional might change your dose or avoid IMBRUVICA® if you have liver problems
- Severe heart problems like arrhythmia (irregular heart rhythm) or heart failure have been reported. In some instances, these can cause death

What is IMBRUVICA® used for?

IMBRUVICA® is used to treat adults with:

- **Chronic Lymphocytic Leukemia (CLL):**
  - who have not had prior therapy, including those with a specific chromosome deletion, called the 17p deletion. For these patients, IMBRUVICA® can be used alone or in combination with obinutuzumab, rituximab, or oral venetoclax.
  - who have received at least one prior therapy, including those patients with the 17p deletion. For these patients, IMBRUVICA® can be used alone or in combination with bendamustine and rituximab.
- **Mantle Cell Lymphoma (MCL):** that was previously treated but has come back or did not respond to treatment.
- **Marginal Zone Lymphoma (MZL):** who have received at least one previous therapy including an antibody that acts against their cancer. This antibody is called anti-CD20. For these patients, IMBRUVICA® is used when patients need medicine and not radiation or surgery.
- **Waldenström's Macroglobulinemia (WM):** for these patients, IMBRUVICA® can be used alone or in combination with rituximab.
- **Chronic Graft Versus Host Disease (cGVHD):** when first line corticosteroid therapy did not work, and additional therapy is needed.

IMBRUVICA® is also used to treat children 1 year of age and older with:

- **Chronic Graft Versus Host Disease** (**cGVHD):** who have received at least one line of therapy that did not work.

It is not known if IMBRUVICA® is safe and effective in children under the age of 18 years for other diseases.

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.

When IMBRUVICA® and venetoclax are used together to treat adults with CLL, they are thought to have a dual effect of moving the cancer cells out of the areas where they grow and hide and push them into the blood. This allows for targeted killing of those cells.

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.
Oral suspension:	Benzyl alcohol, citric acid monohydrate, disodium phosphate, hypromellose, microcrystalline cellulose and carmellose sodium, purified water, sucralose.

IMBRUVICA® comes in the following dosage forms:

Tablets: 140 mg, 280 mg, 420 mg, 560 mg
Capsules: 140 mg
Oral suspension: 70 mg/mL

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.
- have or have had heart rhythm problems or severe heart failure, or if you have any of the following: fast and irregular heartbeat, light-headedness, dizziness, shortness of breath, chest discomfort, swollen legs, or if you faint.
- have or are at increased risk of heart disease (e.g. have diabetes).
- 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 healthcare professional may ask you to stop taking IMBRUVICA® for a short time.

Other warnings you should know about:

Heart problems: IMBRUVICA® may cause heart problems like **arrhythmia** (irregular heart rhythm) or **heart failure**. The heart problems may be severe and can cause death. The risks are higher if you already have heart problems (rhythm problems or heart failure), high blood pressure or diabetes. See the "Serious side effects and what to do about them" table, below, for more information on these and other serious side effects.

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 healthcare professional will check your blood counts before and during the treatment. In rare cases they may need to give you another medicine. Talk to your healthcare professional about what your test results mean.

Your healthcare professional will check your heart before you start IMBRUVICA® and during your treatment. They will also check your blood pressure during treatment and may need to give you another medicine to control your blood pressure.

IMBRUVICA® can affect some blood tests. Tell your healthcare professional you are taking IMBRUVICA® each time you get blood work done.

IMBRUVICA® with food: During the treatment period with IMBRUVICA®, 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:

- **Female patients:**
  - IMBRUVICA® can harm your unborn baby.
  - Do not get pregnant while you are taking IMBRUVICA®. Women of childbearing age must use highly effective birth control methods during treatment with IMBRUVICA® and for 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®.
- **Male patients:**
  - 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 healthcare professional 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, efavirenz).
- 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).
- a medicine to treat high blood pressure (aliskiren).
- a medicine to treat allergy symptoms (fexofenadine).
- a medicine to treat cancer (topotecan).
- 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® exactly as directed by your healthcare professional.
- 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.
- Do not take IMBRUVICA® with grapefruit juice.
- **Capsules or tablets:** Swallow IMBRUVICA® capsules or tablets whole, with a glass of water. Do not open, break or chew capsules or tablets.
- **Oral suspension:**
  - See Instructions for Use leaflet for full instructions.
  - Swallow IMBRUVICA® oral suspension and drink water after swallowing the medicine.
  - An adult should give the dose to the child. Use only the reusable oral dosing syringes provided to measure the right dose.

Usual dose:

Adults:

- **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

Children (1 year old and older):

- **Chronic Graft Versus Host Disease (cGVHD):**
  - age 12 years and older: 420 mg once a day
  - age 1 to < 12 years: As directed by your healthcare professional.

Your healthcare professional may decide that you should take a lower dose if you have liver problems or are taking certain medications. They may also lower your dose if you get side effects.

For the treatment of CLL and WM, your healthcare professional 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 healthcare professional tells you to.

If your healthcare professional has told you to take IMBRUVICA® for use in combination with oral venetoclax: IMBRUVICA® will be given for a fixed duration of up to 15 months.

Overdose:

If you think you, or a person you are caring for, have taken too much IMBRUVICA®, contact a 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 healthcare professional will monitor your blood counts. Talk to your healthcare professional 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 healthcare professional may need to give you treatment to manage your diarrhea such as a fluid and salt replacement or another medicine. Contact your healthcare professional if your diarrhea persists.
- Viral, bacterial, or fungal infections: Infections can be serious and may lead to death. Contact your healthcare professional 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, cough, stuffy or infected nose, sinuses or throat
- Chills
- Muscle aches/pain/spasm, joint aches/pain
- Headache, dizziness, weakness, anxiety
- Rash, itching, dry skin, skin infection
- Inflammation of the fatty tissue underneath the skin
- Nausea, sore mouth or throat, constipation, vomiting, loss of appetite, stomach pain, indigestion, mouth sores

- Nail changes such as brittle fingernails and toenails

IMBRUVICA® can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (low red blood cells): fatigue, loss of energy, weakness, shortness of breath		✓	
Neutropenia (low neutrophils, a type of white blood cell): fever, chills or sweating or any signs of infection		✓	
Thrombocytopenia (low platelets – the cells in your body that help blood to clot): bruising, bleeding, fatigue and weakness		✓	
Edema (abnormal accumulation of fluid): swollen hands, ankles or feet		✓	
Being short of breath		✓	
Fever		✓	
Pneumonia (infection of the lungs): cough with or without mucus, fever, chills, shortness of breath		✓	
Sinusitis (sinus infection): 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: 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			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Severe diarrhea: increased number of bowel movements, watery or bloody stool, stomach pain and/or cramps		✓	
Arrhythmia (irregular heart rhythm): palpitations, light-headedness, dizziness, shortness of breath, chest discomfort, fainting		✓	
Blurred vision	✓		
Infection of the blood: feeling dizzy or faint, confusion or disorientation, diarrhea, nausea, vomiting, slurred speech, severe muscle pain			✓
Serious bleeding problems sometimes resulting in death: 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			✓
Interstitial lung disease (inflammation within the lungs): difficulty breathing or persistent cough		✓	
Tumour Lysis Syndrome (sudden, rapid death of cancer cells due to the treatment): nausea, vomiting, decreased urination, irregular heartbeat, confusion, delirium, seizures			✓
Hyperuricemia (elevated levels of uric acid in the blood): red, warm, and swollen joints, flank pain, blood in urine, or cream-colored skin nodules		✓	
Peripheral neuropathy: weakness, numbness, tingling, pain, or hot or cold sensation in hands, feet or other parts of the body	✓		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Kidney failure: decreased or lack of urination, nausea, swelling of the ankles, legs or feet, fatigue, confusion, seizures or coma			✓
Heart failure (heart does not pump blood as well as it should)**:** breathlessness, difficulty breathing when lying down, swelling of the feet, ankles or legs, weakness/tiredness		✓	
UNCOMMON			
Leukostasis (severe increase in white blood cells): fever, fainting, bleeding, bruising, weight loss, general pain, lack of energy, severe headache, trouble walking		✓	
Severe allergic reactions: swelling of face, eyes, lips, mouth, or tongue, trouble swallowing or breathing, itchy skin rash, redness of the skin			✓
Stevens-Johnson Syndrome: severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes, and genitals			✓
Severe liver problems: nausea, loss of appetite, fatigue, jaundice (yellowing of your skin and eyes), pain in your upper right abdomen, dark urine, disorientation, confusion, pale stool		✓	
Inflammation of the eye (pink eye)	✓		
Mini-stroke (temporary low blood flow to the brain) **or stroke** (bleeding or blood clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, difficulty speaking or understanding speech, blurred vision, dizziness, difficulty walking and loss of balance, sudden headache, difficulty swallowing			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Squamous or basal cell cancer (types of skin cancer): unexplained skin discoloration, red, crusty, wart-like skin sores, shiny skin nodules		✓	
Neutrophilic dermatoses: one or more tender or painful bumps or ulcers on the skin, sometimes with a fever		✓	
Eye Hemorrhage (bleeding in the eye): red patch, line or dots on the white part of eye, seeing haze or shadows, floaters and cloudy vision, blurring or loss of vision		✓	
RARE			
Progressive multifocal leukoencephalopathy (a rare brain infection): progressive weakness on one side of the body, clumsiness of limbs, disturbance of vision, changes in thinking, memory and orientation, confusion, personality changes			✓

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 report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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:

- Keep out of the reach and sight of children.
- Capsules and tablets: Store at room temperature between 15°C and 30°C.
- Oral suspension: Store at room temperature between 15°C and 30°C. Do not freeze. Store reusable oral dosing syringes and bottle upright in the original carton. Discard unused medication 3 months after opening the bottle for the first time.

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/services/drugs-health-products/drug-products/drug-product-database.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.

Co-developed with Pharmacyclics.

Last revised: August 2023

Instructions for Use

PrIMBRUVICA®
(ibrutinib oral suspension)
Protein Kinase Inhibitor

This Instructions for Use contains information on how to give a dose of IMBRUVICA® oral suspension.

Important information you need to know before using IMBRUVICA®

Read this Instructions for Use before you give IMBRUVICA® and each time you get a refill.

There may be new information. This leaflet does not take the place of talking with your healthcare professional about medical conditions or treatment. IMBRUVICA® is intended for oral use only.

An adult caregiver should administer the dose prescribed by the healthcare professional.

Each mL contains 70 mg of ibrutinib.

Only use the oral dosing syringes provided with IMBRUVICA®. If both syringes are lost or damaged, contact your healthcare professional.

Discard medication 3 months after opening the bottle for the first time.

Storage information

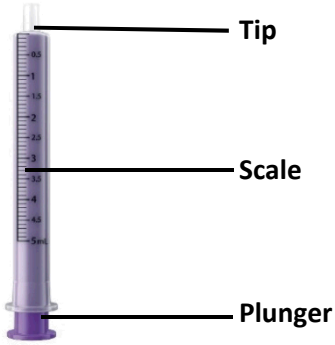
Store between 15°C to 30°C. Do not freeze IMBRUVICA®.
Store the bottle upright with the oral dosing syringes in the original carton.
Keep IMBRUVICA® and all medicines out of sight and reach of children.

Need help?

Call your healthcare professional to talk about any questions you may have. For additional assistance, call the manufacturer, Janssen Inc., at 1-800-567-3331 or 1-800-387-8781.

IMBRUVICA® at-a-glance

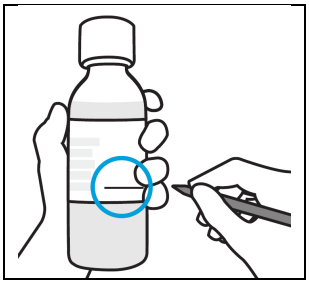
Plastic syringe



Bottle

Plastic Bottle Adapter

Before first use

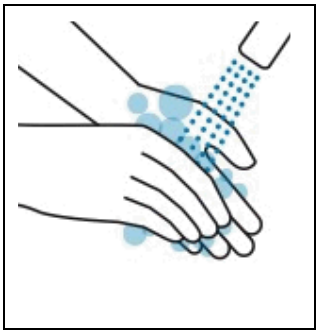


Record "discard after" date on the bottle label

Record the "discard after" date that is **3 months from the day you first opened the bottle**.
After 3 months of first opening the bottle, dispose of the closed bottle in accordance with local requirements.

Step 1 **Get ready**

Check "discard after" date on the IMBRUVICA® bottle
Check expiration date (EXP) on the carton or bottle
Do not use if the tamper seal on the bottle is broken.
Do not use if the expiry date or the "discard after" date has passed.



Wash hands

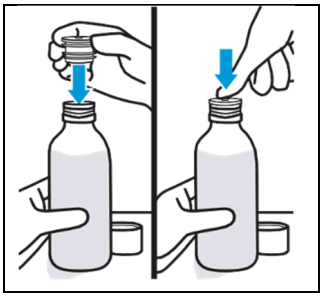
Wash your hands well with soap and warm water.

Step 2 Prepare IMBRUVICA®

Shake oral suspension

Slowly shake oral suspension before each use.

Do not shake rapidly to avoid foaming. Foaming may lead to incorrect dosing.



Insert plastic bottle adapter

Remove plastic bottle adapter from the carton. Twist off bottle cap.

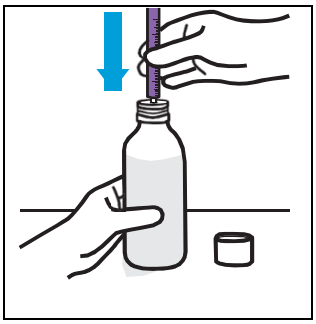
Place the bottle on a flat surface.
Push the plastic bottle adapter with your thumb into the bottle until it is fully inserted and even with the top of the bottle.

Do not remove the plastic bottle adapter from the bottle.

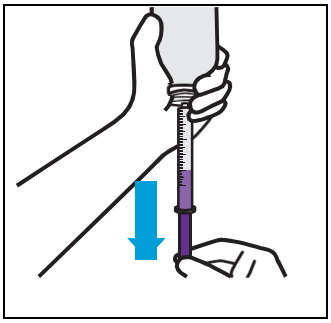
Step 3 Set prescribed dose

Push plunger all the way in to remove air

Only use the oral dosing syringe provided with IMBRUVICA®.



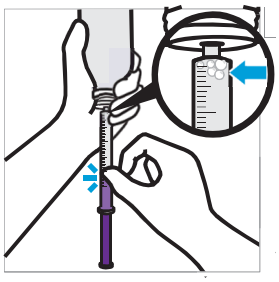
Insert syringe tip into plastic bottle adapter



Fill syringe

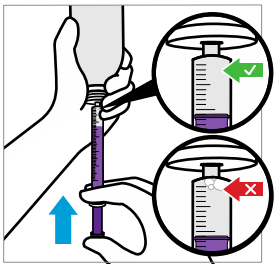
Turn the bottle upside down, as shown.
Pull the plunger to fill the syringe **slightly past the prescribed dose line** to help remove any air bubbles.

Dispose of bottle if there is not enough medicine for a full dose. Use a new bottle.



Tap syringe to move air bubbles to the top

Doing this helps set the correct dose.



Remove air bubbles and adjust dose

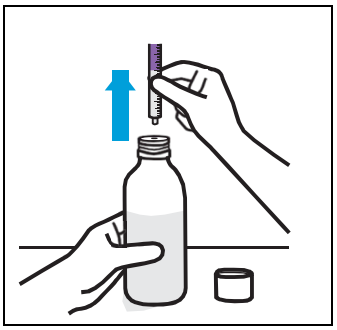
Press the purple plunger to align the top with the prescribed dose.

⚠ Air bubbles must be removed to ensure the correct dose. **Proceed to the next step only if you do not see any air bubbles.**

If you see air bubbles:

Fill the syringe again, tap to move air bubbles to the top and adjust dose.

If your dose is more than 5 mL, you will need to use the same syringe twice. Repeat steps 3 and 4 to complete your dose.



Remove syringe

Place the bottle on a flat surface.
Remove the syringe from the bottle.

Step 4 Deliver IMBRUVICA®

Deliver medication

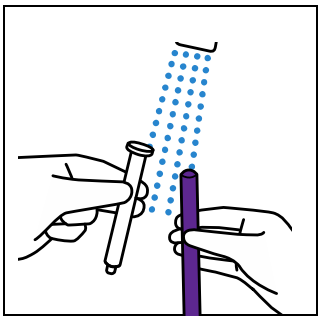
Place the syringe gently into mouth with **the tip pointing toward the cheek**. This allows the child to swallow naturally.

Slowly press the plunger until it stops to administer the full dose. **If your dose is more than 5 mL, you will need to use the same syringe twice.**

Repeat steps 3 and 4 to complete your dose. Make sure the child drinks water after swallowing the dose of medicine.

If the child spits out the medicine or if an incorrect dose is given, contact your healthcare professional.

Step 5 **Rinse/store**



Close bottle and rinse syringe

Twist cap on the bottle.
Do not remove the plastic adapter from the bottle.
Rinse the syringe with cold tap water and let it air dry.

Do not clean the syringe with soap or place the syringe in the dishwasher.

IMPORTANT NOTES ABOUT DISPOSING IMBRUVICA® (ibrutinib oral suspension)

- Dispose of the closed bottle in accordance with local requirements.
- **Do not** pour IMBRUVICA® down the drain (for example: sink, toilet, shower or tub).
- **Do not** recycle the bottle.

Questions/Concerns/Product Monograph: www.janssen.com/canada
Janssen Inc., Toronto,
Ontario M3C 1L9

Co-developed with Pharmacyclics

Last revised: August 2023