IMBRUVICA®

1. Name of the Medicinal Product

1.1 Product Name

IMBRUVICA (ibrutinib)

1.2 Strength

140 mg capsules

1.3 Pharmaceutical Dosage Form

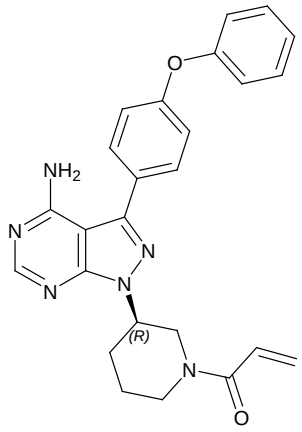
Immediate-release Capsules

2. Quality and Quantitative Composition

2.1 Qualitative Declaration

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula C25H24N6O2 and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water.

The chemical name for ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has the following structure:



2.2 Quantitative Declaration

IMBRUVICA (ibrutinib) capsules for oral administration contain 140 mg ibrutinib as the active ingredient.

3. Pharmaceutical Form

IMBRUVICA (ibrutinib) capsules for oral administration are supplied as white opaque capsules. Each white opaque capsule is marked with "ibr 140 mg" in black ink.

4. Clinical Particulars

4.1 Therapeutic indication

4.1.1 Mantle Cell Lymphoma

IMBRUVICA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial *[see Clinical Studies (5.1.1)]*.

4.1.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

4.1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

4.1.4 Waldenström's Macroglobulinemia

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

4.1.5 Marginal Zone Lymphoma

IMBRUVICA is indicated 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.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (5.1.4)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4.1.6 Chronic Graft versus Host Disease

IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

4.2 Posology and method of administration

4.2.1 Dosing Guidelines

Administer IMBRUVICA orally once daily at approximately the same time each day. The dose should be taken orally with a glass of water. Do not open, break, or chew the capsules.

4.2.2 Recommended Dosage

Mantle Cell Lymphoma and Marginal Zone Lymphoma

The recommended dose of IMBRUVICA for MCL and MZL is 560 mg orally once daily until disease progression or unacceptable toxicity.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Waldenström's Macroglobulinemia

The recommended dose of IMBRUVICA for CLL/SLL and WM as a single agent, in combination with rituximab for WM, or in combination with bendamustine and rituximab for CLL/SLL is 420 mg orally once daily until disease progression or unacceptable toxicity.

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

Chronic Graft versus Host Disease

The recommended dose of IMBRUVICA for cGVHD is 420 mg orally once daily 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.

4.2.3 Dose Modifications for Adverse Reactions

Interrupt IMBRUVICA therapy for any Grade 3 or greater non-hematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by 140 mg per day. A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue IMBRUVICA.

Recommended dose modifications are described below:

Toxicity Occurrence	**Dose Modification for MCL and MZL After Recovery Starting Dose = 560 mg**	**Dose Modification for CLL/SLL, WM, and cGVHD After Recovery Starting Dose = 420 mg**
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart at 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart at 140 mg daily
Fourth	Discontinue IMBRUVICA	Discontinue IMBRUVICA

4.2.4 Dose Modifications for Use with CYP3A Inhibitors

Recommended dose modifications are described below *[see Interaction with other medicinal products and other forms of interactions (4.5.1)]*:

Patient Population	**Coadministered Drug**	**Recommended IMBRUVICA Dose**
B-Cell Malignancies*	• Moderate CYP3A inhibitor	280 mg once daily

		Modify dose as recommended *[see Posology and method of administration (4.2.3)]*.
	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily Modify dose as recommended *[see Posology and method of administration (4.2.3)]*.
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole IV injection 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	70 mg once daily Interrupt dose as recommended *[see Posology and method of administration (4.2.3)]*.
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.
Chronic Graft versus Host Disease	• Moderate CYP3A inhibitor	420 mg once daily Modify dose as recommended *[see Posology and method of administration (4.2.3)]*.
	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	280 mg once daily Modify dose as recommended *[see Posology and method of administration (4.2.3)]*.
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole IV injection 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	140 mg once daily Interrupt dose as recommended *[see Posology and method of administration (4.2.3)]*.
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.

* IMBRUVICA 70 mg is not available in Thailand

After discontinuation of a CYP3A inhibitor, resume previous dose of IMBRUVICA [see *Posology and method of administration (4.2.2)* and *Interaction with other medicinal products and other forms of interactions (4.5)*].

4.2.5 Dose Modifications for Use in Hepatic Impairment*

The recommended dose is 140 mg daily for patients with mild hepatic impairment (Child-Pugh class A).

The recommended dose is 70 mg daily for patients with moderate hepatic impairment (Child-Pugh class B)*.

Avoid the use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C) *[see Use in Specific Populations (4.2.7.4)] and Pharmacological Properties (5)]*.

* IMBRUVICA 70 mg is not available in Thailand

4.2.6 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. Extra doses of IMBRUVICA should not be taken to make up for the missed dose.

4.2.7 USE IN SPECIFIC POPULATIONS

4.2.7.1 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

4.2.7.2 Pediatric Use

The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Pediatric studies have not been completed.

4.2.7.3 Geriatric Use

Of the 1011 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 22% were ≥75 years of age. No overall differences in effectiveness were observed between younger and

older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

4.2.7.4 Hepatic Impairment

Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely *[see Posology and method of administration (4.2.5) and Pharmacological Properties (5)].*4.2.7.5 Plasmapheresis

Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

4.3 Contraindication

None

4.4 Special warnings and precautions for use

4.4.1 Hemorrhage

Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,011 patients exposed to IMBRUVICA in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.
Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies]*

4.4.2 Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 24% of 1,011 patients exposed to IMBRUVICA in clinical trials. *[see Undesirable effects (4.8.1, 4.8.2)]*. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

4.4.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA. Monitor complete blood counts monthly.

4.4.4 Cardiac Arrhythmias

Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,011 patients exposed to IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. *[see Undesirable effects (4.8.1)]*.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Posology and method of administration (4.2.3)]*.

4.4.5 Hypertension

Hypertension has occurred in 12% of 1,011 patients treated with IMBRUVICA in clinical trials with a median time to onset of 5 months (range, 0.03 to 22 months). 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.

4.4.6 Second Primary Malignancies

Other malignancies (9%) including non-skin carcinomas (2%) have occurred in 1,011 patients treated with IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

4.4.7 Tumor Lysis Syndrome

Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

4.4.8 Embryo-Fetal Toxicity

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Pregnancy and lactation (4.6.1)]*.

4.5 Interaction with other medicinal products and other forms of interactions

4.5.1 Effect of CYP3A Inhibitors on Ibrutinib

The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations *[see Pharmacological Properties (5.2)]*. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors *[see Posology and method of administration (4.2.4)]*.*

Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) *[see Posology and method of administration (4.2.4)]*.* IMBRUVICA 70 mg is not available in Thailand

4.5.2 Effect of CYP3A Inducers on Ibrutinib

The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Pharmacological Properties (5)]*.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

Risk Summary

IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities *(see Data)*. 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 the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

4.6.2 Lactation

Risk Summary

There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

4.7 Effects on ability to drive and use machine

Not applicable

4.8 Undesirable effects

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Special warnings and precautions for use (4.4.1)]*
- Infections *[see Special warnings and precautions for use (4.4.2)]*
- Cytopenias *[see Special warnings and precautions for use (4.4.3)]*
- Cardiac Arrhythmias *[see Special warnings and precautions for use (4.4.4)]*
- Hypertension *[see Special warnings and precautions for use (4.4.5)]*
- Second Primary Malignancies *[see Special warnings and precautions for use (4.4.6)]*
- Tumor Lysis Syndrome *[see Special warnings and precautions for use (4.4.7)]*

4.8.1 Clinical Trials Experience

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Mantle Cell Lymphoma

The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	**Grade 3 or 4 (%)**
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and three randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS) in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil, and HELIOS included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1102, RESONATE, RESONATE-2, and HELIOS in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1102, RESONATE, RESONATE-2, and HELIOS discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1102

Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

*One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

RESONATE

Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
Body System Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
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	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

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

* Includes multiple ADR terms

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

RESONATE-2

Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	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
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular disorders				
Hypertension*	14	4	1	0
Nervous system disorders				
Headache	12	1	10	2

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

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

* Includes multiple ADR terms

HELIOS

Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash *	32	4	25	1
Bruising *	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular disorders				
Hemorrhage*	19	2	9	1
Hypertension *	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

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

* Includes multiple ADR terms

<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR.

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma

The data described below reflect exposure to IMBRUVICA in three single-arm open-label clinical trials (Study 1118, Study 1121, and INNOVATE monotherapy arm) and one randomized controlled trial (INNOVATE) in patients with WM or MZL, including a total n=307 patients overall and n=232 patients exposed to IMBRUVICA. Study 1118 included 63 patients with previously treated WM who received single agent IMBRUVICA. Study 1121 included 63 patients with previously treated MZL who received single agent IMBRUVICA. INNOVATE included 150 patients with treatment naïve or previously treated WM who received IMBRUVICA or placebo in combination with rituximab. The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received IMBRUVICA.

The most commonly occurring adverse reactions in Studies 1118, 1121, and INNOVATE (≥ 20%) were thrombocytopenia, diarrhea, bruising, neutropenia, musculoskeletal pain, hemorrhage, anemia, rash, fatigue, and nausea.

Seven percent of patients receiving IMBRUVICA across Studies 1118, 1121, and INNOVATE discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were atrial fibrillation, interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 13% of patients.

Study 1118 and INNOVATE Monotherapy Arm

Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118 and 33 months in the INNOVATE Monotherapy Arm.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	38	2
	Nausea	21	0
	Stomatitis*	15	0
	Constipation	12	1
	Gastroesophageal reflux disease	12	0
Skin and subcutaneous tissue disorders	Bruising*	28	1
	Rash*	21	1
Vascular disorders	Hemorrhage*	28	0
	Hypertension*	14	4
General disorders and administrative site conditions	Fatigue	18	2
	Pyrexia	12	2

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain* Muscle spasms	21 19	0 0
Infections and infestations	Upper respiratory tract infection Skin infection* Sinusitis* Pneumonia*	19 18 16 13	0 3 0 5
Nervous system disorders	Headache Dizziness	14 13	0 0
Respiratory, thoracic and mediastinal disorders	Cough	13	0

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 10: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

	Percent of Patients (N=94)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	38	11
Neutrophils Decreased	43	16
Hemoglobin Decreased	21	6

INNOVATE

Adverse reactions described below in Table 11 reflect exposure to IMBRUVICA + R with a median duration of 25.8 months and exposure to placebo + R with a median duration of 15.5 months in patients with treatment naïve or previously treated WM in INNOVATE.

Table 11: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Bruising*	37	1	5	0
Rash*	24	1	11	0

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	35	4	21	3
Arthralgia	24	3	11	1
Muscle spasms	17	0	12	1
Vascular disorders				
Hemorrhage*	32	3	17	3
Hypertension*	20	13	5	4
Gastrointestinal disorders				
Diarrhea	28	0	15	1
Nausea	21	0	12	0
Dyspepsia	16	0	1	0
Constipation	13	1	11	1
Infections and infestations				
Pneumonia*	19	13	5	3
Skin infection*	17	3	3	0
Urinary tract infection	13	0	0	0
Bronchitis	12	3	7	0
Influenza	12	0	7	1
Viral upper respiratory tract infection	11	0	7	0
General disorders and administration site conditions				
Peripheral edema	17	0	12	1
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	11	0
Blood and Lymphatic System Disorders				
Neutropenia*	16	12	11	4

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Cardiac Disorders				
Atrial fibrillation	15	12	3	1
Nervous system disorders				
Dizziness	11	0	7	0
Psychiatric disorders				
Insomnia	11	0	4	0
Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Grade 3 or 4 infusion related reactions were observed in 1% of patients treated with IMBRUVICA + R.

Study 1121

Adverse reactions and laboratory abnormalities described below in Tables 12 and 13 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 12: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 1121 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising *	41	0
	Rash*	29	5
	Pruritus	14	0

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
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
Vascular disorders	Hemorrhage*	30	0
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 13: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

Chronic Graft versus Host Disease

The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 14 and 15 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 14: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	10
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Metabolism and nutrition disorders	Hypokalemia	12	7

The system organ class and individual ADR preferred terms are sorted in descending frequency order.

* Includes multiple ADR terms.

Table 15: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	33	0
Neutrophils Decreased	10	10
Hemoglobin Decreased	24	2

Additional Important Adverse Reactions

Cardiac Arrhythmias

In randomized controlled trials (n=1377; median treatment duration of 14.0 months for patients treated with IMBRUVICA and 7.5 months for patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 8% versus 2% and for Grade 3 or greater was 4% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea

Diarrhea of any grade occurred at a rate of 40% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range: 0 to 475) versus 47 days (range: 0 to 492) for any grade diarrhea and 77 days (range: 3 to 310) versus 194 days (range: 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 84% versus 88% had complete resolution, and 16% versus 12% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 6 days (range: 1 to 655) versus 5 days (range: 1 to 367) for any grade diarrhea and 6 days (range: 1 to 78) versus 19 days (range: 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively. Less than 1% of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Visual Disturbance

Blurred vision and decreased visual acuity of any grade occurred in 12% of patients treated with IMBRUVICA (10% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and <1% Grade 2 and 3). The median time to first onset was 96 days (range, 0 to 617) versus 109 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 61% versus 71% had complete resolution and 39% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 31 days (range, 1 to 457) versus 29 days (range, 1 to 253) in IMBRUVICA-treated subjects compared to the control arm, respectively.

4.8.2 Postmarketing Experience

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

- Hepatobiliary disorders: hepatic failure including acute and/or fatal events, hepatic cirrhosis
- Respiratory disorders: interstitial lung disease

- Metabolic and nutrition disorders: tumor lysis syndrome *[*see *Special warnings and precautions for use (4.4.7)]*
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasis, panniculitis
- Infections: hepatitis B reactivation

4.9 Overdose

There is no specific experience in the management of ibrutinib overdose in patients. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Closely monitor patients who ingest more than the recommended dosage and provide appropriate supportive treatment.

5. Pharmacological Properties

Mechanism of Action

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

5.1 Pharmacodynamic Properties

In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).

In vitro Platelet Aggregation

Ibrutinib demonstrated inhibition of collagen-induced platelet aggregation, with IC_{50} values at 4.6 μM (2026 ng/mL), 0.8 μM (352 ng/mL), and 3 μM (1321 ng/mL) in blood samples from healthy donors, donors taking warfarin, and donors with severe renal dysfunction, respectively. Ibrutinib did not show meaningful inhibition of platelet aggregation for ADP, arachidonic acid, ristocetin, and TRAP-6.

Cardiac Electrophysiology

At a single dose 3 times the maximum recommended dose (1680 mg), IMBRUVICA did not prolong the QT interval to any clinically relevant extent.

CLINICAL STUDIES

5.1.1 Mantle Cell Lymphoma

The safety and efficacy of IMBRUVICA in patients with MCL who have received at least one prior therapy were evaluated in Study PCYC-1104-CA (referred to as Study 1104) (NCT01236391), an open-label, multi-center, single-arm trial of 111 previously treated patients. The median age was 68 years (range, 40 to 84 years), 77% were male, and 92% were Caucasian. At baseline, 89% of patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 11% with prior stem cell transplantation. At baseline, 39% of subjects had at least one tumor ≥ 5 cm, 49% had bone marrow involvement, and 54% had extranodal involvement at screening.

IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Responses to IMBRUVICA are shown in Table 16.

Table 16: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with MCL in Study 1104

	Total (N=111)
ORR (%)	65.8
95% CI (%)	(56.2, 74.5)
CR (%)	17.1
PR (%)	48.6
Median DOR months (95% CI)	17.5 (15.8, NE)

CI = confidence interval; CR = complete response; PR = partial response; NE = not evaluable

An Independent Review Committee (IRC) performed independent reading and interpretation of imaging scans. The IRC review demonstrated an ORR of 69%.

The median time to response was 1.9 months.

Lymphocytosis

Upon initiation of IMBRUVICA, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 33% of patients in the MCL study. The onset of isolated lymphocytosis occurs during the first few weeks of IMBRUVICA therapy and resolves by a median of 8 weeks.

5.1.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma

The safety and efficacy of IMBRUVICA in patients with CLL/SLL were demonstrated in one uncontrolled trial and three randomized, controlled trials.

Study 1102

Study PCYC-1102-CA (referred to as Study 1102) (NCT01105247), an open-label, multi-center trial, was conducted in 48 previously treated CLL patients. The median age was 67 years (range, 37 to 82 years), 71% were male, and 94% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 80 months and the median number of prior treatments was 4 (range, 1 to 12 treatments). At baseline, 46% of subjects had at least one tumor ≥ 5 cm.

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The ORR and DOR were assessed using a modified version of the International Workshop on CLL Criteria by an Independent Review Committee. The ORR was 58.3% (95% CI: 43.2%, 72.4%), all partial responses. None of the patients achieved a complete response. The DOR ranged from 5.6 to 24.2+ months. The median DOR was not reached.

RESONATE

The RESONATE study (A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) (NCT01578707) was conducted in patients with previously treated CLL or SLL. Patients (n=391) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression, or unacceptable toxicity or ofatumumab at an initial dose of 300 mg, followed one week later by a dose of 2000 mg weekly for 7 doses and then every 4 weeks for 4 additional doses. 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 trial enrolled 373 patients with CLL and 18 patients with SLL. 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 tumor ≥ 5 cm. Thirty-two percent of patients had 17p deletion.

Efficacy results for RESONATE are shown in Table 17 and the Kaplan-Meier curves for PFS, assessed by an IRC according to IWCLL criteria, and OS are shown in Figures 1 and 2, respectively.

Table 17: Efficacy Results in Patients with CLL/SLL in RESONATE

Endpoint	IMBRUVICA N=195	Ofatumumab N=196
Progression Free Survival[b]		
Number of events (%)	35 (17.9)	111 (56.6)
Disease progression	26	93
Death events	9	18
Median (95% CI), months	NE	8.1 (7.2, 8.3)
HR (95% CI)	0.22 (0.15, 0.32)	
Overall Survival[a]		
Number of deaths (%)	16 (8.2)	33 (16.8)
HR (95% CI)	0.43 (0.24, 0.79)	
Overall Response Rate[b]	42.6%	4.1%

[a] Median OS not evaluable for either arm

[b] IRC evaluated. All partial responses achieved; none of the patients achieved a complete response.

CI = confidence interval; HR = hazard ratio; NE = not evaluable

Figure 1: Kaplan-Meier Curve of Progression Free Survival (ITT Population) in Patients with CLL/SLL in RESONATE

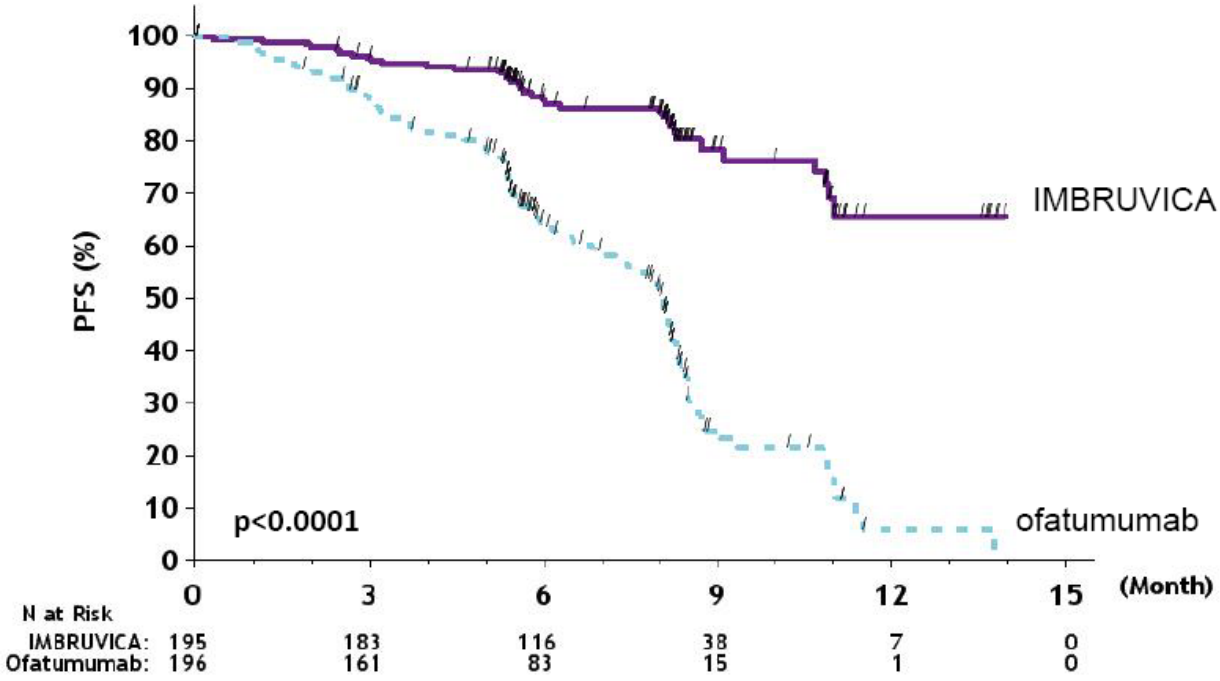
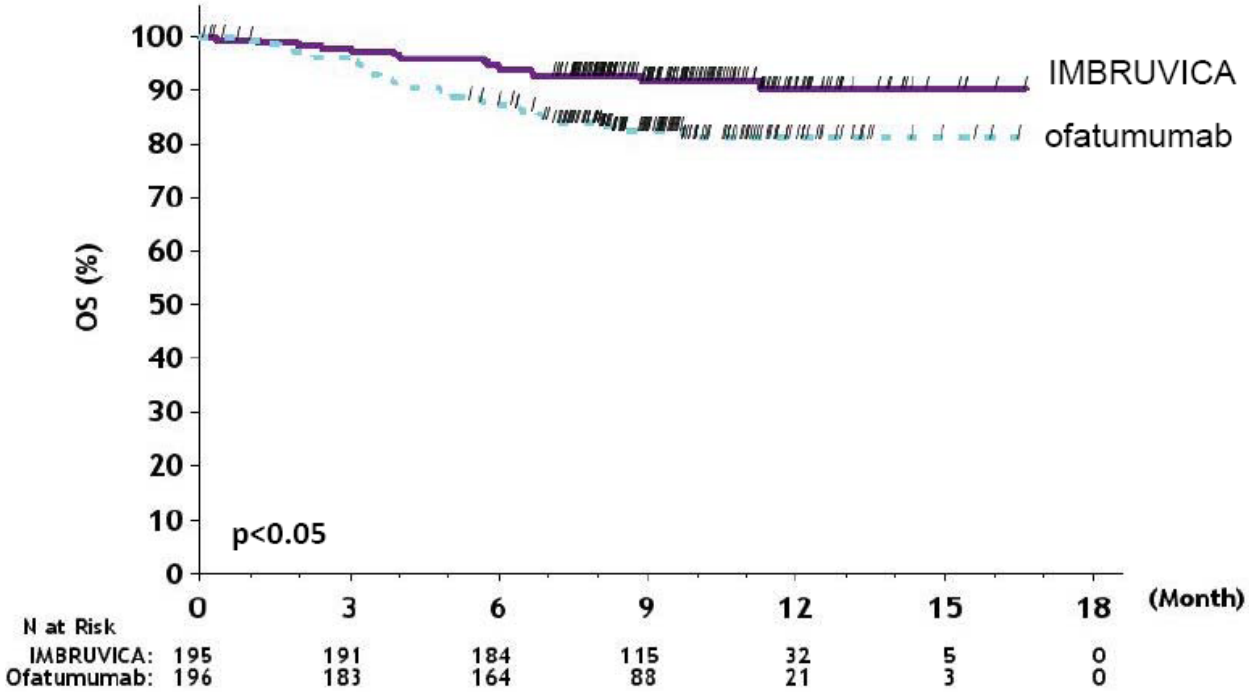


Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in Patients with CLL/SLL in RESONATE



CLL/SLL with 17p deletion (del 17p CLL/SLL) in RESONATE

RESONATE included 127 patients with del 17p CLL/SLL. 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 an IRC. Efficacy results for del 17p CLL/SLL are shown in Table 18.

Table 18: Efficacy Results in Patients with del 17p CLL/SLL in RESONATE

Endpoint	IMBRUVICA N=63	Ofatumumab N=64
Progression Free Survival[a]		
Number of events (%)	16 (25.4)	38 (59.4)
Disease progression	12	31
Death events	4	7
Median (95% CI), months	NE	5.8 (5.3, 7.9)
HR (95% CI)	0.25 (0.14, 0.45)	
Overall Response Rate[a]	47.6%	4.7%

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

CI = confidence interval; HR = hazard ratio; NE = not evaluable

RESONATE-2

The RESONATE-2 study (A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 versus Chlorambucil in Patients 65 Years or Older with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma) (NCT01722487) was conducted in patients with treatment naïve CLL or SLL who were 65 years of age or older. Patients (n = 269) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for a maximum of 12 cycles, with an allowance for intrapatient dose increases up to 0.8 mg/kg based on tolerability.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety one percent of patients had a baseline ECOG performance status of 0 or 1 and 9% had an ECOG performance status of 2. The trial enrolled 249 patients with CLL and 20 patients with SLL. At baseline, 20% of patients had 11q deletion. The most common reasons for initiating CLL therapy include: progressive marrow failure demonstrated by anemia and/or thrombocytopenia (38%), progressive or symptomatic lymphadenopathy (37%), progressive or symptomatic splenomegaly (30%), fatigue (27%) and night sweats (25%).

With a median follow-up of 28.1 months, there were 32 observed death events [11 (8.1%) and 21 (15.8%) in IMBRUVICA and chlorambucil treatment arms, respectively]. With 41% of patients switching from chlorambucil to IMBRUVICA, the overall survival analysis in the ITT patient population resulted in a statistically significant HR of 0.44 [95% CI (0.21, 0.92)] and 2-year survival

rate estimates of 94.7% [95% CI (89.1, 97.4)] and 84.3% [95% CI (76.7, 89.6)] in the IMBRUVICA and chlorambucil arms, respectively.

Efficacy results for RESONATE-2 are shown in Table 19 and the Kaplan-Meier curve for PFS, assessed by an IRC according to IWCLL criteria is shown in Figure 3.

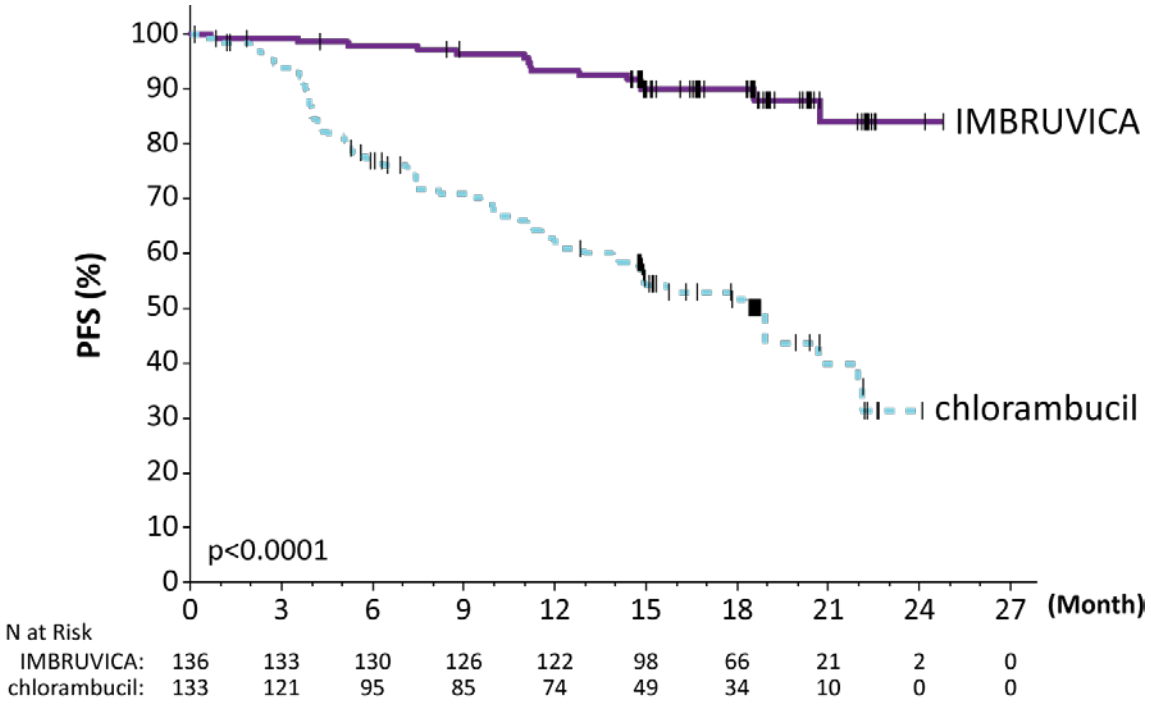
Table 19: Efficacy Results in Patients with CLL/SLL in RESONATE-2

Endpoint	IMBRUVICA N=136	Chlorambucil N=133
Progression Free Survival[a]		
Number of events (%)	15 (11.0)	64 (48.1)
Disease progression	12	57
Death events	3	7
Median (95% CI), months	NE	18.9 (14.1, 22.0)
HR[b] (95% CI)	0.16 (0.09, 0.28)	
Overall Response Rate[a] (CR + PR)	82.4%	35.3%
P-value	<0.0001	

[a] IRC evaluated; Five subjects (3.7%) in the IMBRUVICA arm and two subjects (1.5%) in the Chlorambucil arm achieved complete response

[b] HR = hazard ratio; NE = not evaluable

Figure 3: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL/SLL in RESONATE 2



HELIOS

The HELIOS study (Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination with Bendamustine and Rituximab (BR) in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma) (NCT01611090) was conducted in patients with previously treated CLL or 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. All patients received BR for a maximum of six 28-day cycles. Bendamustine was dosed at 70 mg/m^2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 in the first cycle, Day 1, and 500 mg/m^2 Cycles 2 through 6, Day 1.

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 tumor $\geq$ 5 cm and 26% presented with del11q.

Efficacy results for HELIOS are shown in Table 20 and the Kaplan-Meier curves for PFS are shown in Figure 4.

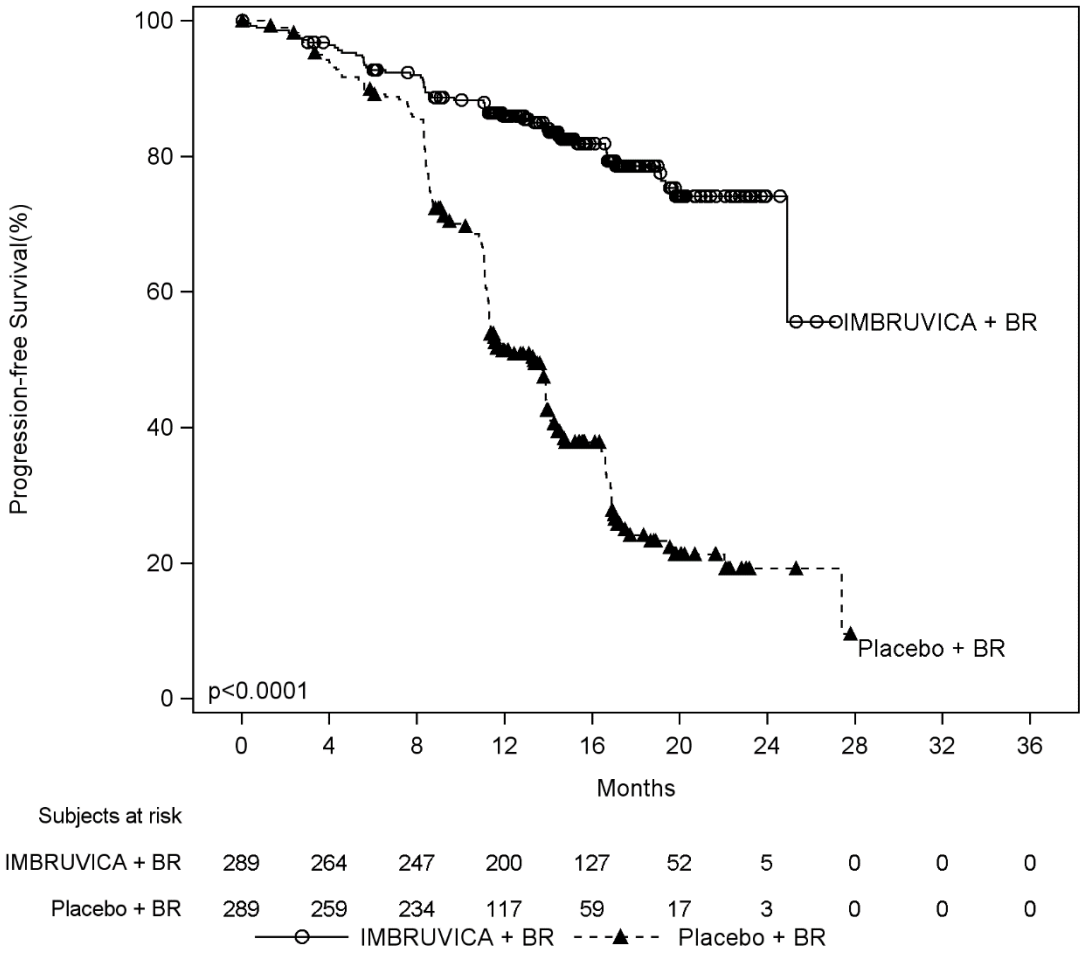
Table 20: Efficacy Results in Patients with CLL/SLL in HELIOS

Endpoint	IMBRUVICA + BR N=289	Placebo + BR N=289
Progression Free Survival[a]		
Number of events (%)	56 (19.4)	183 (63.3)
Median (95% CI), months	NE	13.3 (11.3, 13.9)
HR (95% CI)	0.20 (0.15, 0.28)	
Overall Response Rate[a]	82.7%	67.8%

[a] IRC evaluated, twenty-four subjects (8.3%) in the IMBRUVICA + BR arm and six subjects (2.1%) in the placebo + BR arm achieved complete response

BR = bendamustine and rituximab; CI = confidence interval; HR = hazard ratio; NE = not evaluable

Figure 4: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL/SLL in HELIOS



Lymphocytosis

Upon initiation of IMBRUVICA, an increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 66% of patients in the CLL studies. The onset of isolated lymphocytosis occurs during the first month of IMBRUVICA therapy and resolves by a median of 14 weeks (range, 0.1 to 104 weeks). When IMBRUVICA was administered with chemoimmunotherapy, lymphocytosis was 7% with IMBRUVICA + BR versus 6% with placebo + BR.

5.1.3 Waldenström's Macroglobulinemia

The safety and efficacy of IMBRUVICA in patients with WM were demonstrated in two single-arm trials and one randomized, controlled trial.

Study 1118 and INNOVATE Monotherapy Arm

The safety and efficacy of IMBRUVICA in WM were evaluated in Study PCYC-1118E (referred to as Study 1118) (NCT01614821), an open-label, multi-center, single-arm trial of 63 previously treated patients. The median age was 63 years (range, 44 to 86 years), 76% were male, and 95% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since

diagnosis was 74 months, and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL (range, 0.7 to 8.4 g/dL).

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The responses were assessed by investigators and an IRC using criteria adopted from the International Workshop of Waldenström's Macroglobulinemia. Responses, defined as partial response or better, per IRC are shown in Table 21.

Table 21: Response Rate and Duration of Response (DOR) Based on IRC Assessment in Patients with WM in Study 1118

	Total (N=63)
Response rate (CR+VGPR+PR), (%)	61.9
95% CI (%)	(48.8, 73.9)
Complete Response (CR)	0
Very Good Partial Response (VGPR), (%)	11.1
Partial Response (PR), (%)	50.8
Median duration of response, months (range)	NE (2.8+, 18.8+)

CI = confidence interval; NE = not evaluable

The median time to response was 1.2 months (range, 0.7-13.4 months).

The INNOVATE monotherapy arm 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 response rate observed in the INNOVATE monotherapy arm was 71% (0% CR, 29% VGPR, 42% PR). With a median follow-up time on study of 34 months (range, 8.6+ to 37.7 months), the median duration of response has not been reached.

INNOVATE

The INNOVATE study (A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenström's Macroglobulinemia) (NCT02165397) was conducted in treatment naïve or previously treated patients with WM. Patients (n = 150) were randomized 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with rituximab until disease progression or unacceptable toxicity. Rituximab was administered weekly at a dose of 375 mg/m^2 for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 consecutive weeks (weeks 17-20). The major efficacy outcome measure is progression-free survival (PFS) assessed by an IRC with additional efficacy measure of response rate.

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were Caucasian. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were

treatment naïve, and 55% of patients were previously treated. 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), and MYD88 L265P mutations were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status.

Efficacy results for INNOVATE as assessed by an IRC are shown in Table 22, and the Kaplan-Meier curves for PFS are shown in Figure 5.

Table 22: Efficacy Results in Patients with WM in INNOVATE

Endpoint	IMBRUVICA + R N=75	Placebo + R N=75
Progression Free Survival		
Number of events (%)	14 (19)	42 (56)
Median (95% CI), months	NE	20.3 (13.7, 27.6)
HR (95% CI)	0.20 (0.11, 0.38)	
P-value[a]	<0.0001	
Response Rate (CR+VGPR+PR)[b]	72%	32%
95% CI	(0.62, 0.82)	(0.21, 0.43)
Complete Response (CR)	3%	1%
Very Good Partial Response (VGPR)	23%	4%
Partial Response (PR)	47%	27%
Median duration of response, months (range)	NE (1.9+, 36.4+)	21.2 (4.6, 25.8)

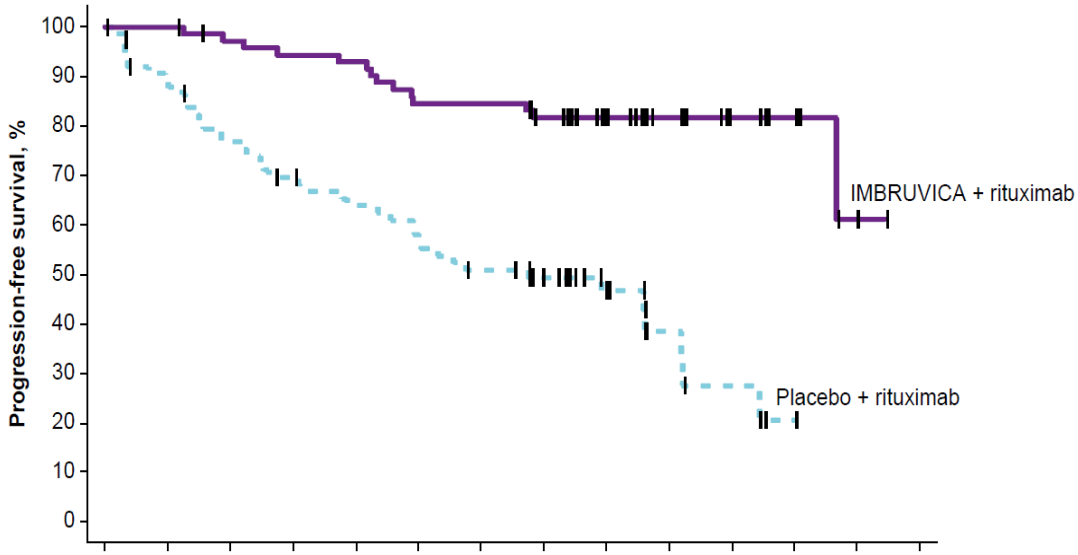
CI = confidence interval; HR = hazard ratio; NE = not evaluable; R = rituximab

[a] P-value is from log-rank test stratified by WM IPSS (low, med, high) and number of prior systemic treatment regimens (0, ≥1)

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

Median follow-up time on study = 26.5 months

Figure 5: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with WM in INNOVATE



Number at risk													
IMBRUVICA + rituximab	75	73	69	67	66	60	60	54	40	24	14	9	2	0
Placebo + rituximab	75	65	55	49	44	40	34	27	16	7	4	1	0	0

An exploratory analysis demonstrated a sustained hemoglobin improvement (defined as increase of ≥ 2 g/dL over baseline for at least 8 weeks without blood transfusions or growth factor support) in 65% of patients in the IMBRUVICA + R group and 39% of patients in the placebo + R group.

5.1.4 Marginal Zone Lymphoma

The safety and efficacy of IMBRUVICA in MZL were evaluated in Study PCYC-1121-CA (referred to as Study 1121) (NCT01980628), an open-label, multi-center, single-arm trial of patients who received at least one prior therapy. The efficacy analysis included 63 patients with 3 sub-types of MZL: mucosa-associated lymphoid tissue (MALT; N=32), nodal (N=17), and splenic (N=14). The median age was 66 years (range, 30 to 92 years), 59% were female, and 84% were Caucasian. Ninety two percent of patients had a baseline ECOG performance status of 0 or 1 and 8% had ECOG performance status 2. The median time since diagnosis was 3.8 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 responses were assessed by investigators and an IRC using criteria adopted from the International Working Group criteria for malignant lymphoma. Responses per IRC are shown in Table 23.

Table 23: Overall Response Rate (ORR) and Duration of Response (DOR) Based on IRC Assessment in Patients with MZL in Study 1121

	Total (N=63)
Response rate (CR + PR), (%)	46.0%
95% CI (%)	(33.4, 59.1)
Complete Response (CR), (%)	3.2
Partial Response (PR), (%)	42.9
Median duration of response, months (range)	NE (16.7, NE)

CI = confidence interval; NE = not evaluable

Median follow-up time on study = 19.4 months

The median time to response was 4.5 months (range, 2.3 to 16.4 months). Overall response rates were 46.9%, 41.2%, and 50.0% for the 3 MZL sub-types (MALT, nodal, splenic), respectively.

5.1.5 Chronic Graft versus Host Disease

The safety and efficacy of IMBRUVICA in cGVHD were evaluated in Study PCYC-1129-CA (referred to as Study 1129) (NCT02195869), an open-label, multi-center, single-arm trial of 42 patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy. The median age was 56 years (range, 19 to 74 years), 52% were male, and 93% were Caucasian. The most common underlying malignancies leading to transplantation were acute lymphocytic leukemia, acute myeloid leukemia, and CLL. The median time since cGVHD diagnosis was 14 months, the median number of prior cGVHD treatments was 2 (range, 1 to 3 treatments), and 60% of patients had a Karnofsky performance score of ≤ 80. 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 corticosteroid dose (prednisone or prednisone equivalent) at baseline was 0.3 mg/kg/day, and 52% of patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Prophylaxis for infections were managed per institutional guidelines with 79% of patients receiving combinations of sulfonamides and trimethoprim and 64% receiving triazole derivatives.

IMBRUVICA was administered orally at 420 mg once daily. The responses were assessed by investigators using the 2005 National Institute of Health (NIH) Consensus Panel Response Criteria with two modifications to align with the updated 2014 NIH Consensus Panel Response Criteria. Efficacy results are shown in Table 24.

Table 24: Best Overall Response Rate (ORR) and Sustained Response Rate Based on Investigator Assessment[a] in Patients with cGVHD in Study 1129

	Total (N=42)
ORR	28 (67%)
95% CI	(51%, 80%)
Complete Response (CR)	9 (21%)
Partial Response (PR)	19 (45%)
Sustained response rate[b]	20 (48%)

CI = confidence interval

[a] Investigator assessment based on the 2005 NIH Response Criteria with two modifications (added "not evaluable" for organs with non-cGVHD abnormalities, and organ score change from 0 to 1 was not considered disease progression)

[b] Sustained response rate is defined as the proportion of patients who achieved a CR or PR that was sustained for at least 20 weeks.

The median time to response coinciding with the first scheduled response assessment was 12.3 weeks (range, 4.1 to 42.1 weeks). Responses were seen across all organs involved for cGVHD (skin, mouth, gastrointestinal tract, and liver).

ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in Lee Symptom Scale overall summary score in 24% (10/42) of patients on at least 2 consecutive visits.

5.2 Pharmacokinetic properties

Ibrutinib exposure increases with doses up to 840 mg (1.5 times the maximum approved recommended dosage) in patients with B-cell malignancies. The mean steady-state AUC (% coefficient of variation) observed in patients at 560 mg with MCL is 865 (69%) ng·h/mL and with MZL is 978 (82%) ng·h/mL, and in patients at 420 mg with CLL/SLL is 708 (71%) ng·h/mL, with WM is 707 (72%) ng·h/mL, and with cGVHD is 1159 (50%) ng·h/mL. Steady-state concentrations of ibrutinib without CYP3A inhibitors were achieved with an accumulation ratio of 1 to 1.6 after 1 week of multiple daily doses of 420 mg or 560 mg.

Absorption

Absolute bioavailability of ibrutinib in fasted condition was 2.9% (90% CI: 2.1, 3.9) in healthy subjects. Ibrutinib is absorbed after oral administration with a median T_{max} of 1 hour to 2 hours.

Effect of Food

The administration of IMBRUVICA with a high-fat and high-calorie meal (800 calories to 1,000 calories with approximately 50% of total caloric content of the meal from fat) increased ibrutinib C_{max} by 2- to 4-fold and AUC by approximately 2-fold, compared with administration of ibrutinib after overnight fasting.

In vitro studies suggest that ibrutinib is not a substrate of p-glycoprotein (P-gp) or breast cancer resistance protein (BCRP).

Distribution

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

Elimination

Intravenous clearance was 62 L/h in fasted conditions and 76 L/h in fed conditions. In line with the high first-pass effect, the apparent oral clearance is 2000 L/h in fasted conditions and 1000 L/h in fed conditions. The half-life of ibrutinib is 4 hours to 6 hours.

Metabolism

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8.

Excretion

Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled ibrutinib, 90% of radioactivity was excreted within 168 hours, with 80% excreted in the feces and less than 10% eliminated in urine. Unchanged ibrutinib accounted for 1% of the radiolabeled excreted dose in feces and none in urine, with the remainder of the excreted dose being metabolites.

Specific Populations

Age and Sex

Age and sex have no clinically meaningful effect on ibrutinib pharmacokinetics.

Patients with Renal Impairment

Mild and moderate renal impairment (creatinine clearance [CLcr] > 25 mL/min as estimated by Cockcroft-Gault equation) had no influence on the exposure of ibrutinib. No data is available in patients with severe renal impairment (CLcr < 25 mL/min) or in patients on dialysis.

Patients with Hepatic Impairment

The AUC of ibrutinib increased 2.7-fold in subjects with mild hepatic impairment (Child-Pugh class A), 8.2-fold in subjects with moderate hepatic impairment (Child-Pugh class B) and 9.8-fold in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function. The C_{max} of ibrutinib increased 5.2-fold in mild hepatic impairment, 8.8-fold in moderate hepatic impairment and 7-fold in severe hepatic impairment relative to subjects with normal liver function *[see Use in specific populations (4.2.7.4)]*.

Drug Interaction Studies

Effect of CYP3A Inhibitors on Ibrutinib

The coadministration of multiple doses of ketoconazole (strong CYP3A inhibitor) increased the C_{max} of ibrutinib by 29-fold and AUC by 24-fold. The coadministration of multiple doses of voriconazole (strong CYP3A inhibitor) increased steady state C_{max} of ibrutinib by 6.7-fold and AUC by 5.7-fold. Simulations under fed conditions suggest that posaconazole (strong CYP3A inhibitor) may increase the AUC of ibrutinib 3-fold to 10-fold.

The coadministration of multiple doses of erythromycin (moderate CYP3A inhibitor) increased steady state C_{max} of ibrutinib by 3.4-fold and AUC by 3-fold.

Effect of CYP3A *Inducers on Ibrutinib*

The coadministration of rifampin (strong CYP3A inducer) decreased the C_{max} of ibrutinib by more than 13-fold and AUC by more than 10-fold. Simulations suggest that efavirenz (moderate CYP3A inducer) may decrease the AUC of ibrutinib by 3-fold.

Effect of Ibrutinib on CYP Substrates

In vitro studies suggest that ibrutinib and PCI-45227 are unlikely to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A at clinical doses. Both ibrutinib and PCI-45227 are unlikely to induce CYP1A2, CYP2B6 or CYP3A at clinical doses.

Effect of Ibrutinib on Substrates of Transporters

In vitro studies suggest that ibrutinib may inhibit BCRP and P-gp transport at clinical doses. The coadministration of oral P-gp or BCRP substrates with a narrow therapeutic index (e.g., digoxin, methotrexate) with IMBRUVICA may increase their concentrations.

5.3 Preclinical Safety data

5.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ibrutinib was not carcinogenic in a 6-month rasH2 mouse study 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 *[see Special warnings and precautions for use (4.4.6)]*.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Rats were administered oral daily doses of ibrutinib for 4 weeks prior to pairing and during pairing in males and 2 weeks prior to pairing and during pairing in females. Treatment of female rats continued following pregnancy up to gestation day (GD) 7, and treatment of male rats continued until end of study. No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (Human Equivalent Dose [HED] 16 mg/kg).

6. Pharmaceutical Particulars

6.1 List of excipient

Each capsule also contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black ink.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

See expiry date on the outer pack.

6.4 Special precautions for storage

Do not store bottles above 30°C.
Retain in original package until dispensing.
Keep IMBRUVICA and all medicines out of the reach of children.

6.5 Nature and contents of container

The 140 mg capsules are supplied as white opaque capsules, marked with “ibr 140 mg” in black ink, and are available in white HDPE bottles with a child-resistant closure:

- 90 capsules per bottle
- 120 capsules per bottle

Not all pack sizes may be marketed.

PATIENT COUNSELING INFORMATION

Advise the patient to read the approved patient labeling (Patient Information).

- *Hemorrhage:*
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Special warnings and precautions for use (4.4.1)]*.
- *Infections:*
  Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Special warnings and precautions for use (4.4.2)]*.
- *Cardiac Arrhythmias:*
  Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Special warnings and precautions for use (4.4.4)]*.
- *Hypertension:*
  Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see *Special warnings and precautions for use* (4.4.5)].
- *Second primary malignancies:*
  Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Special warnings and precautions for use (4.4.6)]*.
- *Tumor lysis syndrome:*
  Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Special warnings and precautions for use (4.4.7)]*.
- *Embryo-fetal toxicity:*
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant during

treatment and for 1 month after the last dose of IMBRUVICA *[see Special warnings and precautions for use (4.4.8)]*.

- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules approximately the same time each day *[see Posology and method of administration (4.2.1)]*.
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose *[see Posology and method of administration (4.2.6)]*.
- Advise patients of the common side effects associated with IMBRUVICA *[see Undesirable effects (4.8)]*. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Interaction with other medicinal products and other forms of interactions (4.5)]*.
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration *[see Undesirable effects (4.8.1)]*.

7. Marketing Authorization Holder
See the end of the leaflet.

8. Marketing Authorization Numbers and Date of Authorization

Manufactured by	**Market Authorization Number**	**Date of Authorization**
Catalent CTS, LLC. Kansas City, MO 64137, USA	1C 74/60 (NC)	02 November 2017
Cilag AG CH-8200 Schaffhausen, Switzerland	1C 73/60 (NC)	02 November 2017

9. Date of revision of the text
August 2018

WARNING ACCORDING TO THE ANNOUNCEMENT FROM MINISTRY OF PUBLIC HEALTH

This medicinal product may cause serious harm. It must be used only under physician's supervision.

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