IBRUTINIB

Imbruvica®
Antineoplastic Agent

FORMULATION
Ibrutinib (Imbruvica®) film-coated tablets are available in the following strengths:

- 140 mg film-coated tablet
  Each film-coated tablet contains 140 mg ibrutinib. It is a yellow-green to green round film-coated tablet debossed with "ibr" on one side and "140" on the other.
- 420 mg film-coated tablet
  Each film-coated tablet contains 420 mg ibrutinib. It is a yellow-green to green oblong film-coated tablet debossed with "ibr" on one side and "420" on the other.

The excipients are colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, ferrosoferric oxide, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide.

PHARMACOLOGICAL PROPERTIES
Mechanism of action
Ibrutinib is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including MCL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and B-cell CLL. BTK's pivotal role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis and adhesion. Preclinical studies have shown that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

Lymphocytosis
Upon initiation of single agent treatment with Ibrutinib (Imbruvica®), a reversible increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and an absolute count >5,000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (66%) with CLL/SLL. This effect has also been observed in some patients (35%) with MCL treated with Ibrutinib (Imbruvica®). This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of Ibrutinib (Imbruvica®) therapy and typically resolves within a median of 8 weeks in patients with MCL and 14 weeks in patients with CLL/SLL (range, 0.1 to 104 weeks).

When Ibrutinib (Imbruvica®) was administered in combination with BR or with obinutuzumab in subjects with CLL/SLL, lymphocytosis was infrequent (7% with Ibrutinib (Imbruvica®) + BR versus 6% with placebo + BR and 7% with Ibrutinib (Imbruvica®) + obinutuzumab versus 1% with chlorambucil + obinutuzumab).

Lymphocytosis was not observed in patients with WM treated with Ibrutinib (Imbruvica®).

In vitro platelet aggregation
In an *in vitro* study, ibrutinib demonstrated inhibition of collagen-induced platelet aggregation in samples from the cohorts of subjects with either renal dysfunction, those on warfarin, or healthy subjects. The magnitude of inhibition of collagen-induced platelet aggregation in the cohort of subjects on aspirin was less pronounced since collagen-induced platelet aggregation was already reduced without ibrutinib.

Ibrutinib did not show meaningful inhibition of platelet aggregation for the 4 agonists adenosine diphosphate (ADP), arachidonic acid, ristocetin, and thrombin receptor-activating peptide 6 (TRAP-6) across any of these cohorts of subjects or healthy subjects.

Effect on QT/QTc interval and cardiac electrophysiology

The effect of ibrutinib on the QTc interval was evaluated in 20 healthy male and female subjects in a randomized, double-blind thorough QT study with placebo and positive controls. At a supratherapeutic dose of 1680 mg, ibrutinib did not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the baseline adjusted mean differences between ibrutinib and placebo was below 10 ms. In this same study, a concentration dependent shortening in the QTc interval was observed (-5.3 ms [90% CI: -9.4, -1.1] at a C_{max} of 719 ng/mL following the supratherapeutic dose of 1680 mg) that was considered not clinically relevant.

Clinical studies

Mantle cell lymphoma

The safety and efficacy of Ibrutinib (Imbruvica®) in MCL patients who received at least one prior therapy were evaluated in a single open-label, multi-center phase 2 study (PCYC-1104-CA) of 111 patients. The median age was 68 years (range, 40 to 84 years), 77% were male and 92% were Caucasian. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 35% with prior high-dose chemotherapy, 43% with prior bortezomib, 24% with prior lenalidomide, and 11% with prior autologous or allogeneic stem cell transplant. At baseline, 39% of patients had bulky disease (≥ 5 cm), 49% had high-risk score by Simplified MCL International Prognostic Index (MIPI), and 72% had advanced disease (extranodal and/or bone marrow involvement) at screening.

Ibrutinib (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 Ibrutinib (Imbruvica®) are shown in Table 1.

Table 1: Overall response rate (ORR) and duration of response (DOR) based on investigator assessment in patients with mantle cell lymphoma

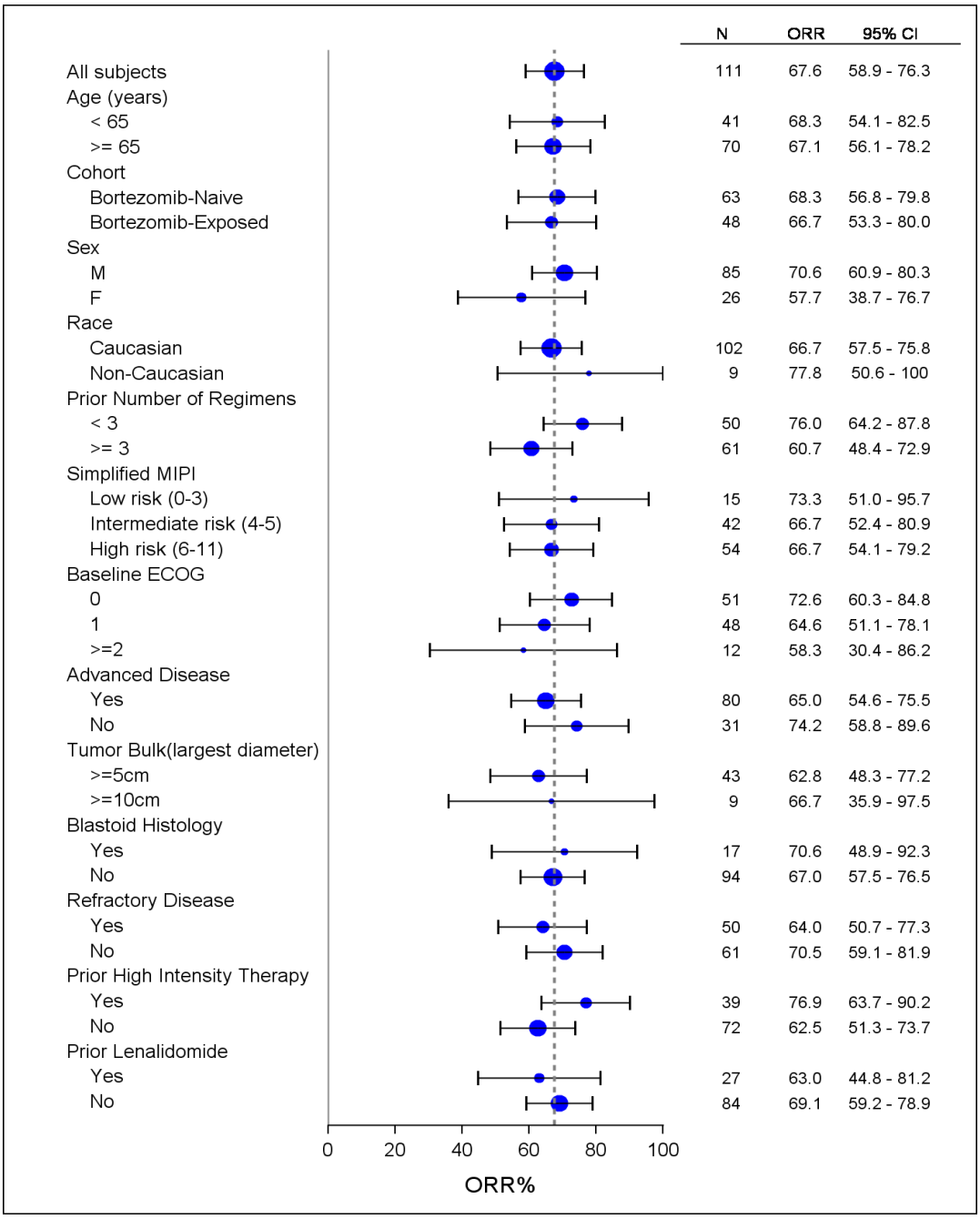
	Total N = 111
ORR (%)	67.6
95% CI (%)	(58.0; 76.1)
CR (%)	20.7
PR (%)	46.8
Median DOR (CR+PR) (months)	17.5 (15.8, NR)
Median time to initial response, months (range)	1.9 (1.4-13.7)
Median time to CR, months (range)	5.5 (1.7-11.5)

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

The efficacy data was further evaluated by an Independent Review Committee (IRC) demonstrating an ORR of 69%, with a 21% CR rate and a 48% PR rate. The IRC estimated median DOR was 19.6 months.

The overall response to Ibrutinib (Imbruvica®) was independent of prior treatment including bortezomib and lenalidomide or underlying risk/prognosis, bulky disease, gender or age (Figure 1).

Figure 1: Subgroup Analysis of Overall Response Rate by Investigator Assessment (Study PCYC-1104-CA; 560 mg)



The safety and efficacy of Ibrutinib (Imbruvica®) were demonstrated in a randomized phase 3, open-label, multicenter study including 280 patients with MCL who received at least one prior therapy (Study MCL3001). Patients were randomized 1:1 to receive either Ibrutinib (Imbruvica®) orally at 560 mg once daily on a 21-day cycle or temsirolimus intravenously at 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle. Treatment on both arms continued until disease progression or unacceptable toxicity. The median age was 68 years (range, 34 to 88 years), 74%

were male and 87% were Caucasian. The median time since diagnosis was 43 months, and median number of prior treatments was 2 (range: 1 to 9 treatments), including 51% with prior high-dose chemotherapy, 18% with prior bortezomib, 5% with prior lenalidomide, and 24% with prior stem cell transplant. At baseline, 53% of patients had bulky disease (≥ 5 cm), 21% had high-risk score by Simplified MIPI, 60% had extranodal disease and 54% had bone marrow involvement at screening.

Progression-free survival (PFS) was assessed by IRC according to the revised IWG for non-Hodgkin's lymphoma (NHL) criteria showed a 57% statistically significant reduction in the risk of death or progression for patients in the Ibrutinib (Imbruvica®) arm. Efficacy results for Study MCL3001 are shown in Table 2 and the Kaplan-Meier curve for PFS in Figure 2.

Table 2: Efficacy results in Study MCL3001

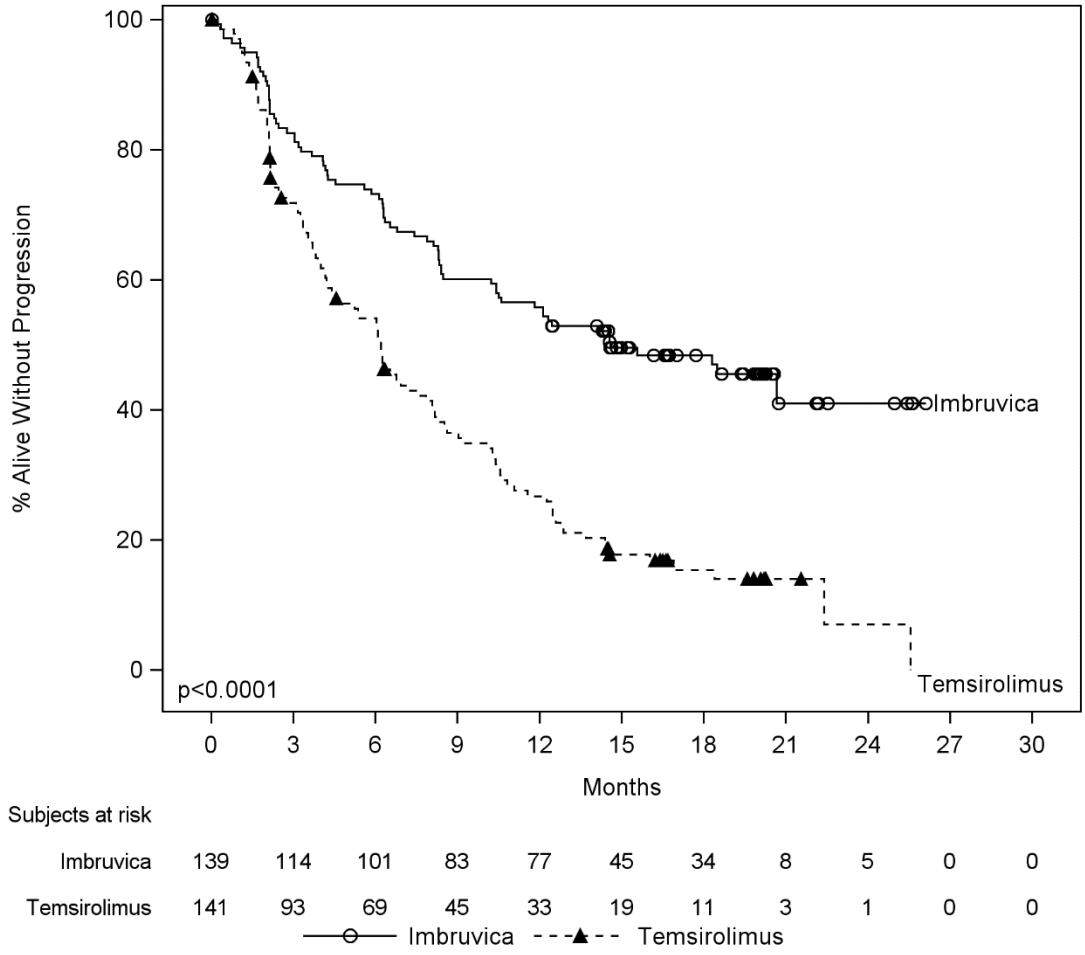
Endpoint	**Ibrutinib (Imbruvica®) N = 139**	**Temsirolimus N = 141**
Progression-Free Survival[a]		
Number of events (%)	73 (52.5)	111 (78.7)
Median Progression-Free Survival (95% CI), (months)	14.6 (10.4, NE)	6.2 (4.2, 7.9)
HR (95% CI)	0.43 [0.32, 0.58]	
Overall Response Rate (CR+PR)	71.9%	40.4%
p-value	p < 0.0001	

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

[a] IRC evaluated.

A smaller proportion of patients treated with Ibrutinib (Imbruvica®) experienced a clinically meaningful worsening of lymphoma symptoms versus temsirolimus (27% versus 52%) and time to worsening of symptoms occurred more slowly with Ibrutinib (Imbruvica®) versus temsirolimus (HR 0.27, p < 0.0001).

Figure 2: Kaplan-Meier curve of progression-free survival (ITT Population) in Study MCL3001



Chronic lymphocytic leukemia/Small lymphocytic lymphoma

The safety and efficacy of Ibrutinib (Imbruvica®) in patients with CLL/SLL were demonstrated in one uncontrolled study and four randomized, controlled studies.

Patients with treatment-naïve CLL/SLL

Single agent

Study PCYC-1115-CA

A randomized, multicenter, open-label phase 3 study of Ibrutinib (Imbruvica®) versus chlorambucil was conducted in patients with treatment-naïve CLL/SLL who were 65 years of age or older. Patients (n = 269) were randomized 1:1 to receive either Ibrutinib (Imbruvica®) 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for a maximum of 12 cycles, with an allowance for intrapatient dose increases up to 0.8 mg/kg based on tolerability. After confirmed disease progression, patients on chlorambucil were able to crossover to ibrutinib.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety-one percent of patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and 9% had an ECOG performance status of 2. The study enrolled 269 patients with CLL or SLL. At baseline, 45% had advanced clinical stage (Rai Stage III or IV), 35% of patients had at least one tumor

≥ 5 cm, 39% with baseline anemia, 23% with baseline thrombocytopenia, 65% had elevated β2 microglobulin > 3500 mcg/L, 47% had a CrCL < 60 mL/min, and 20% of patients presented with del 11q, 6% of patients presented with del 17p/tumor protein 53 (TP53) mutation, and 44% of patients presented with unmutated immunoglobulin heavy chain variable region (IGHV).

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

There was a statistically significant sustained platelet or hemoglobin improvement in the ITT population in favor of ibrutinib versus chlorambucil. In patients with baseline cytopenias, sustained hematologic improvement was: platelets 77% versus 43%; hemoglobin 84% versus 45% for ibrutinib and chlorambucil respectively.

Table 3: Efficacy results in Study PCYC-1115-CA

Endpoint	**Ibrutinib (Imbruvica®) N = 136**	**Chlorambucil N = 133**
Progression-Free Survival[a]		
Number of events (%)	15 (11.0)	64 (48.1)
Median (95% CI), months	Not reached	18.9 (14.1, 22.0)
HR (95% CI)	0.161 (0.091, 0.283)	
Overall response rate[a] (CR +PR)	82.4%	35.3%
p-value	<0.0001	
Overall survival[b]		
Number of deaths (%)	3 (2.2)	17 (12.8)
HR (95% CI)	0.163 (0.048, 0.558)	

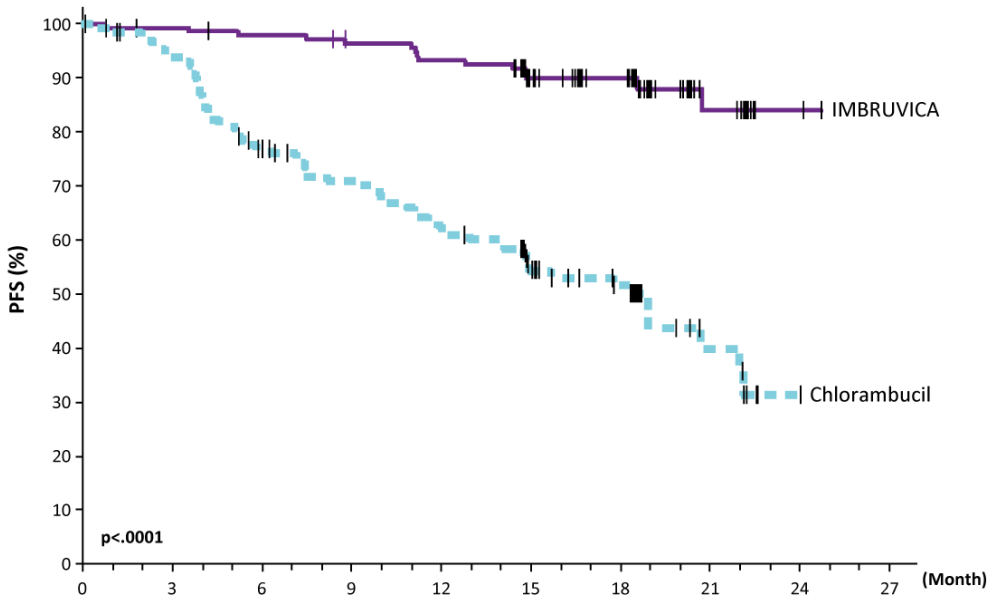
CI = confidence interval; HR = hazard ratio; CR = complete response; PR = partial response

[a] IRC evaluated.

[b] Median OS not reached for both arms.

$p < 0.005$ for OS.

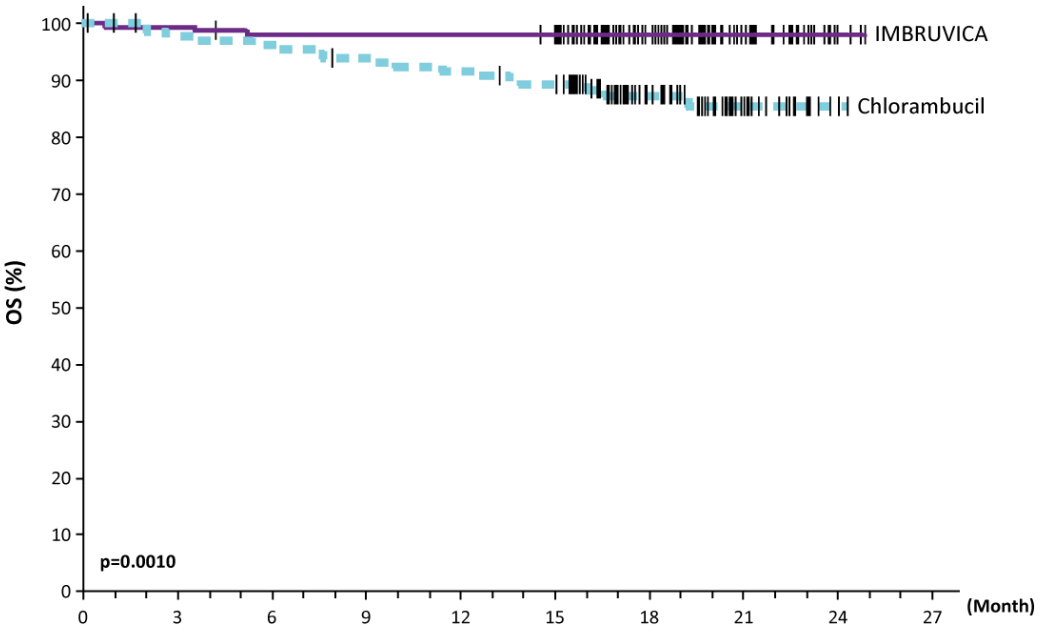
Figure 3: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1115-CA



N at Risk

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

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



N at Risk

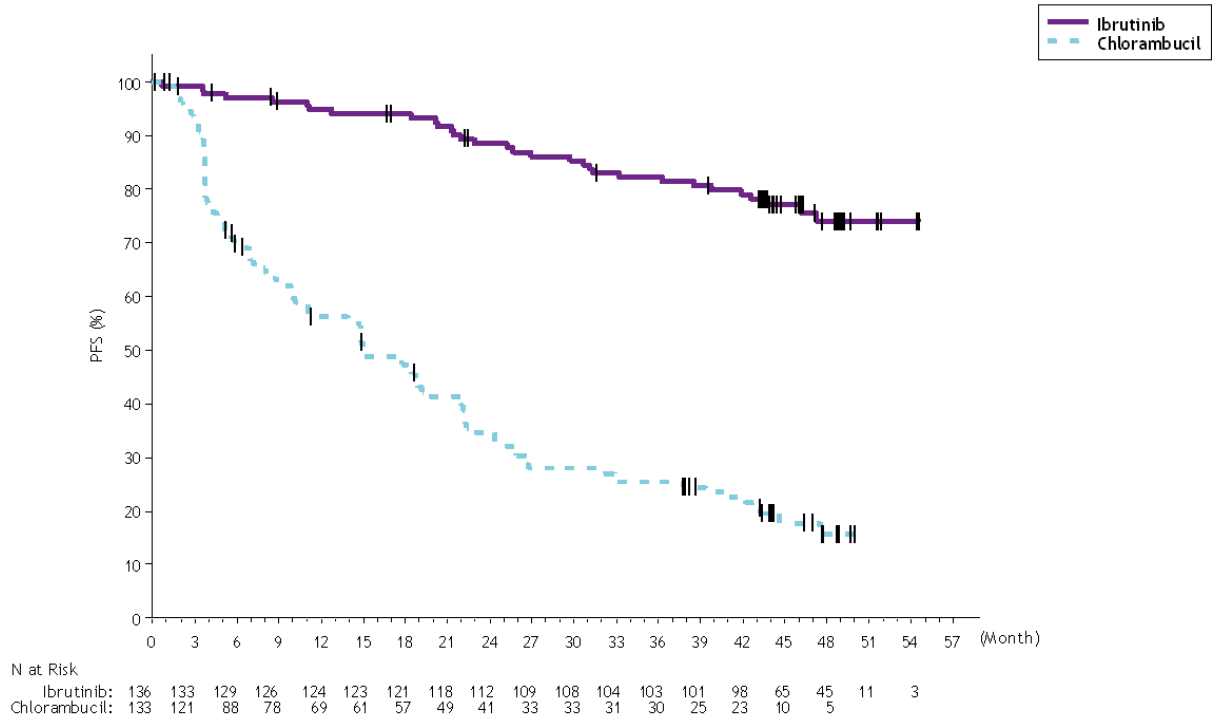
IMBRUVICA:	136	134	131	131	131	128	74	32	4	0
Chlorambucil:	133	127	125	121	118	113	62	24	1	0

Overall follow-up of 55 months (medial of 48 months)

With an overall follow-up of 55 months (median of 48 months) in Study PCYC-1115-CA and its extension study, an 86% reduction in the risk of death or progression by investigator assessment was observed for patients in the Ibrutinib (Imbruvica®) arm. The median investigator-assessed PFS was not reached in the Ibrutinib (Imbruvica®) arm and was 15 months [95% CI (10.22, 19.35)] in the chlorambucil arm; (HR = 0.14 [95% CI (0.09, 0.21)]). The 4-year PFS estimate was 73.9% in the Ibrutinib (Imbruvica®) arm and 15.5% in the chlorambucil arm, respectively. The updated Kaplan-Meier curve for PFS is shown in Figure 5. The investigator-assessed ORR was 91.2% in the Ibrutinib (Imbruvica®) arm versus 36.8% in the chlorambucil arm. The CR rate according to IWCLL criteria was 16.2% in the Ibrutinib (Imbruvica®) arm versus 3.0% in the chlorambucil arm. At the time of long-term follow-up, a total of 73 subjects (54.9%) originally randomized to the chlorambucil arm subsequently received ibrutinib as cross-over treatment. The Kaplan-Meier landmark estimate for OS at 48-months was 85.5% in the Ibrutinib (Imbruvica®) arm.

The treatment effect of ibrutinib in Study PCYC-1115-CA was consistent across high-risk patients with del 17p/TP53 mutation, del 11q, and/or unmutated IGHV.

Figure 5: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) by Investigator in Study PCYC-1115-CA with 55 Months Follow-up



Combination therapy

Study PCYC-1130-CA

A randomized, multi-center, open-label, Phase 3 study of Ibrutinib (Imbruvica®) in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab was conducted in patients with treatment naïve CLL/SLL. The study enrolled patients who were 65 years of age or older or < 65 years of

age with coexisting medical conditions, reduced renal function as measured by creatinine clearance <70 mL/min, or presence of del 17p/TP53 mutation. Patients (n=229) were randomized 1:1 to receive either Ibrutinib (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 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, 65% of patients presented with CLL/SLL with high risk factors (del 17p/TP53 mutation [18%], del 11q [15%], or unmutated IGHV [54%]).

Progression-free survival (PFS) as assessed by IRC according to IWCLL criteria indicated a 77% statistically significant reduction in the risk of death or progression in the Ibrutinib (Imbruvica®) arm. With a median follow-up time on study of 31 months, the median PFS was not reached in the Ibrutinib (Imbruvica®) + obinutuzumab arm and was 19 months in the chlorambucil + obinutuzumab arm. The results from investigator and IRC assessments for PFS and ORR were consistent.

Efficacy results for Study PCYC-1130-CA are shown in Table 4 and the Kaplan-Meier curve for PFS is shown in Figure 6.

Table 4: Efficacy results in Study PCYC-1130-CA

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

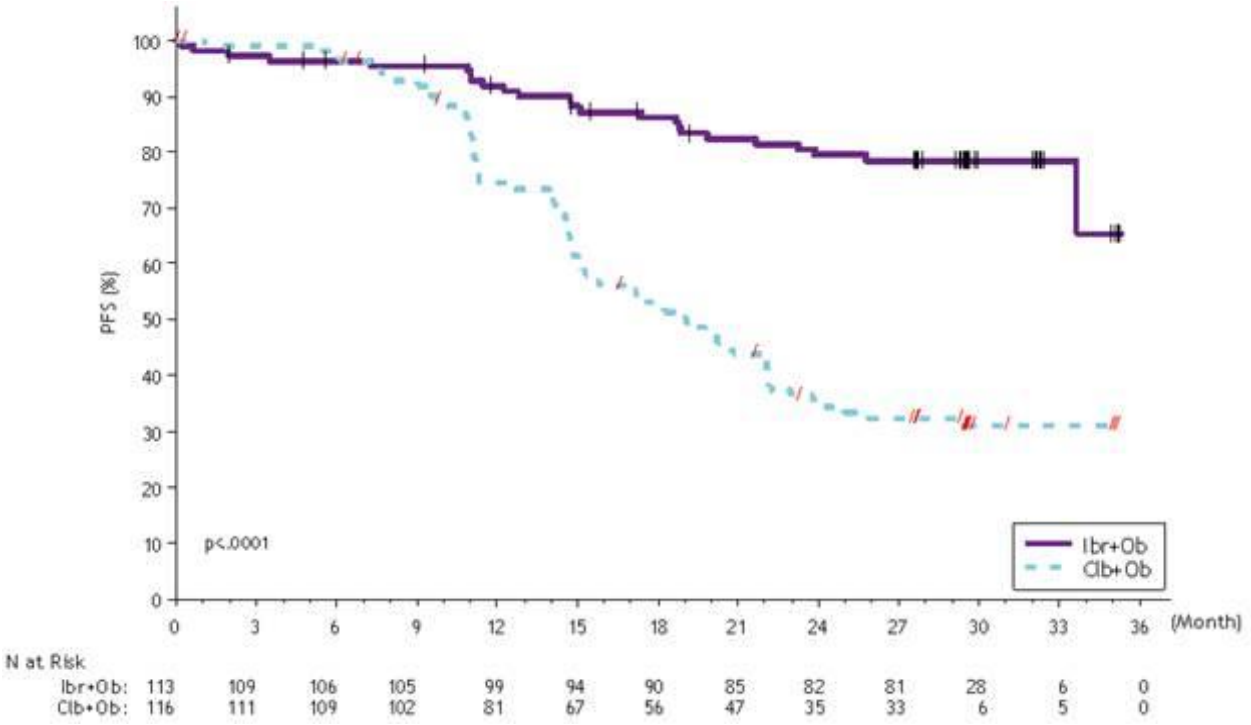
CI = confidence interval; HR = hazard ratio; CR = complete response; PR = partial response.

[a] IRC evaluated.

[b] Includes 1 patient in the Ibrutinib (Imbruvica®) + obinutuzumab arm with a complete response with incomplete marrow recovery (CRi).

[c] PR = PR + nPR.

Figure 6: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1130-CA



The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), with a PFS HR of 0.15 [95% CI (0.09, 0.27)], as shown in Table 5. The 2-year PFS rate estimates for the high-risk CLL/SLL population were 78.8% [95% CI (67.3, 86.7)] and 15.5% [95% CI (8.1, 25.2)] in the Ibrutinib (Imbruvica®) + obinutuzumab and chlorambucil + obinutuzumab arms, respectively.

Table 5: Subgroup Analysis of PFS (Study PCYC-1130-CA)

	N	Hazard Ratio	95% CI
All subjects	229	0.231	0.145, 0.367
High risk (del17p/TP53/del11q/unmutated IGHV)			
Yes	148	0.154	0.087, 0.270
No	81	0.521	0.221, 1.231
Del17p/TP53			
Yes	41	0.109	0.031, 0.380
No	188	0.275	0.166, 0.455
FISH			
Del17p	32	0.141	0.039, 0.506
Del11q	35	0.131	0.030, 0.573
Others	162	0.302	0.176, 0.520
Unmutated IGHV			
Yes	123	0.150	0.084, 0.269
No	91	0.300	0.120, 0.749
Age			
< 65	46	0.293	0.122, 0.705
≥ 65	183	0.215	0.125, 0.372

Bulky disease			
< 5 cm	154	0.289	0.161, 0.521
≥ 5 cm	74	0.184	0.085, 0.398
Rai stage			
0/I/II	110	0.221	0.115, 0.424
III/IV	119	0.246	0.127, 0.477
ECOG per CRF			
0	110	0.226	0.110, 0.464
1-2	119	0.239	0.130, 0.438

Hazard ratio based on non-stratified analysis

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

Study E1912

A randomized, multicenter, open-label, safety and efficacy, Phase 3 study of Ibrutinib (Imbruvica®) in combination with rituximab versus standard fludarabine, cyclophosphamide, and rituximab [FCR] chemoimmunotherapy was conducted in patients with treatment naïve CLL/SLL who were 70 years or younger. Patients (n=529) were randomized 2:1 to receive either IR or FCR. Ibrutinib (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 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, and 59% of patients presented with CLL/SLL with high risk factors (TP53 mutation [6%], del11q [22%], or unmutated IGHV [53%]).

With a median follow-up time on study of 37 months, efficacy results for E1912 are shown in Table 6. The Kaplan-Meier curves for PFS, assessed according to IWCLL criteria, and OS are shown in Figures 7 and 8, respectively.

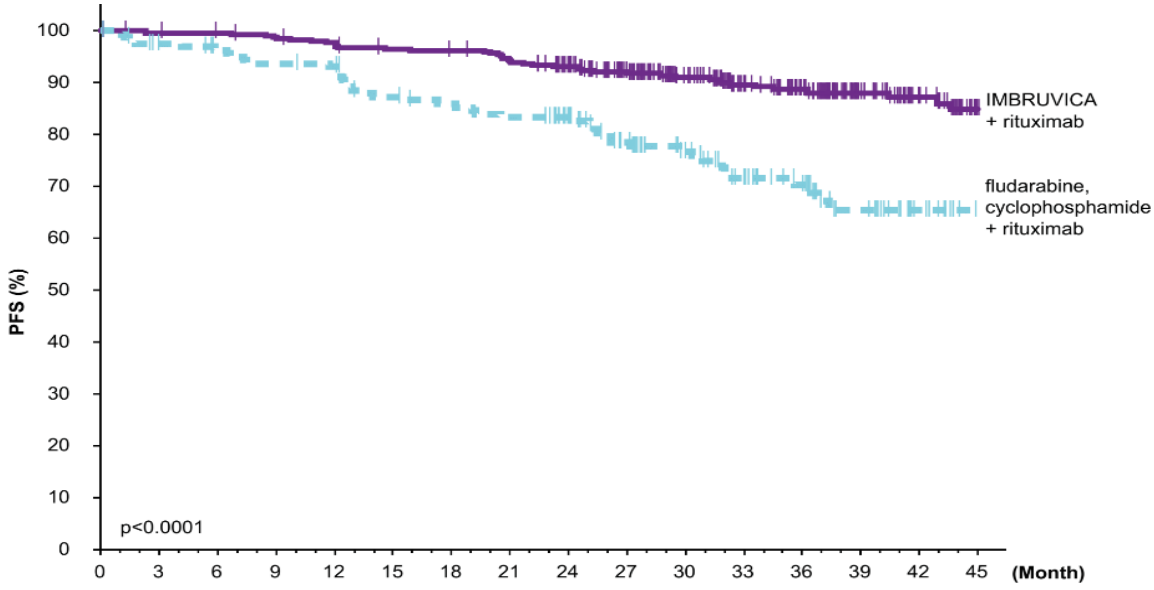
Table 6: Efficacy results in Study E1912

Endpoint	**Ibrutinib+ rituximab (IR) N=354**	**Fludarabine, Cyclophosphamide, and Rituximab (FCR) N=175**
Progression Free Survival		
Number of events (%)	41 (12)	44 (25)
Disease progression	39	38
Death events	2	6
Median (95% CI), months	NE (49.4, NE)	NE (47.1, NE)
HR (95% CI)	0.34 (0.22, 0.52)	

P-value[a]	<0.0001	
Overall Survival		
Number of deaths (%)	4 (1)	10 (6)
HR (95% CI)	0.17 (0.05, 0.54)	
P-value[a]	0.0007	
Overall Response Rate[b] (%)	96.9	85.7

[a] P-value is from unstratified log-rank test.
[b] Investigator evaluated.
HR = hazard ratio; NE = not evaluable

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



The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (del17p/TP53 mutation, del11q, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.40)], p <0.0001, as shown in Table 7. The 3-year PFS rate estimates for the high-risk CLL/SLL population were 90.4% [95% CI (85.4, 93.7)] and 60.3% [95% CI (46.2, 71.8)] in the IR and FCR arms, respectively.

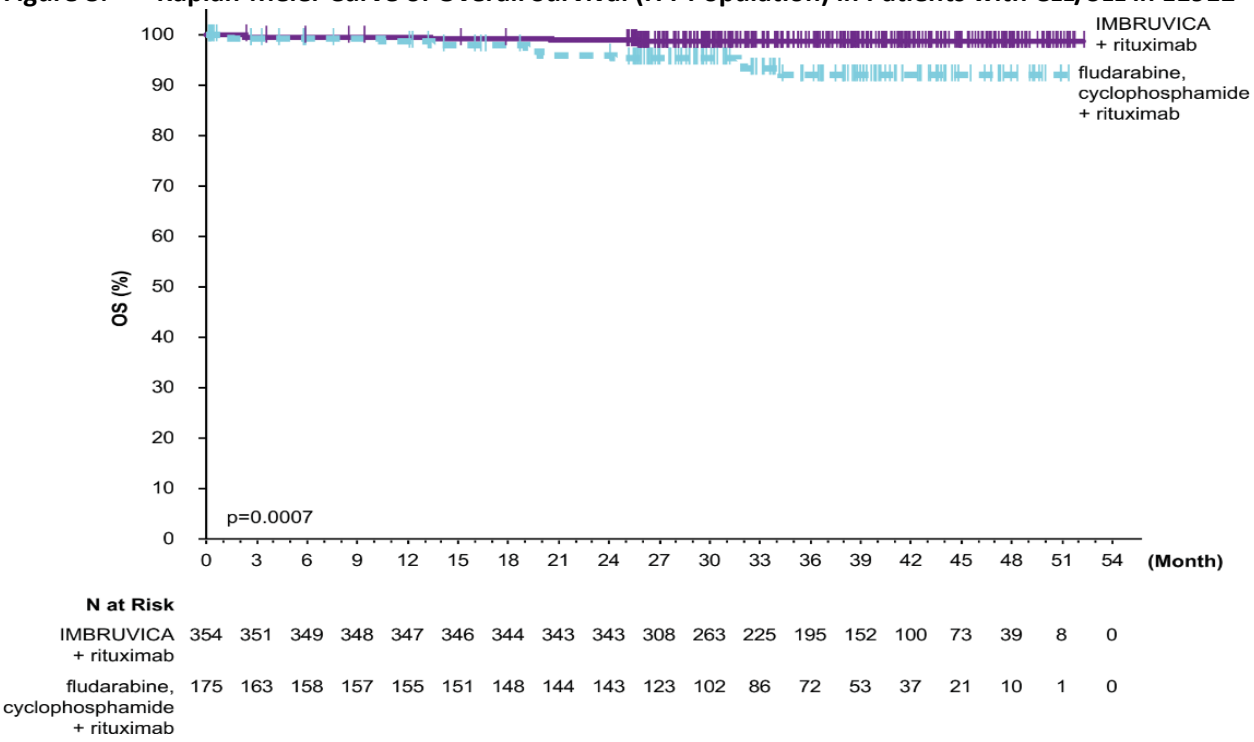
Table 7: Subgroup Analysis of PFS (Study E1912)

	N	Hazard Ratio	95% CI
All subjects	529	0.340	0.222, 0.522
High risk (TP53/del11q/unmutated IGHV)			
Yes	313	0.231	0.132, 0.404
No	216	0.568	0.292, 1.105
del11q			
Yes	117	0.199	0.088, 0.453
No	410	0.433	0.260, 0.722

Unmutated IGHV			
Yes	281	0.233	0.129, 0.421
No	112	0.741	0.276, 1.993
Bulky disease			
<5 cm	316	0.393	0.217, 0.711
≥5 cm	194	0.257	0.134, 0.494
Rai stage			
0/I/II	301	0.398	0.224, 0.708
III/IV	228	0.281	0.148, 0.534
ECOG			
0	335	0.242	0.138, 0.422
1-2	194	0.551	0.271, 1.118

Hazard ratio based on non-stratified analysis

Figure 8: Kaplan-Meier Curve of Overall Survival (ITT Population) in Patients with CLL/SLL in E1912



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

Single agent

PCYC-1102-CA

An open-label, multi-center study was conducted in 51 patients with CLL/SLL, who received 420 mg once daily. Ibrutinib (Imbruvica®) was administered until disease progression or unacceptable toxicity. The median age was 68 (range, 37 to 82 years), median time since diagnosis was 80 months, and median number of prior treatments was 4 (range, 1 to 12 treatments), including 92% with a prior nucleoside analog, 98.0% with prior rituximab, 86% with a prior alkylator, 39% with prior bendamustine and 20% with prior ofatumumab. At baseline, 39% of patients had Rai Stage IV, 45% had bulky disease (≥ 5 cm), 35% had del 17p, 31% had del 11q.

ORR was assessed according to the 2008 International Workshop on CLL (IWCLL) criteria. At a median duration follow up of 16 months, responses to Ibrutinib (Imbruvica®) for the 51 patients are show in Table 8.

Table 8: Overall response rate in patients with chronic lymphocytic leukemia treated with 420 mg Ibrutinib (Imbruvica®) - Study PCYC-1102-CA (N=51)

ORR (CR+PR) (95% CI) (%)	78.4 (64.7, 88.7)
CR (%)	3.9
PR (%)	74.5
ORR including Partial Response with Lymphocytosis (PRL) (%)	92.2
Median DOR (CR+PR)	NR[1]
Median Time to Initial Response, months (range)	1.8 (1.4-12.2)

CI = confidence interval; CR = complete response; PR = partial response

[1] 92.5% of responders were censored (i.e., progression-free and alive) with a median follow up of 16.4 months.

NR: not reached

The efficacy data were further evaluated using IWCLL criteria by an IRC, demonstrating an ORR of 65% (95% CI: 50%; 78%), all partial responses. The DOR ranged from 4 to 24+ months. The median DOR was not reached.

PCYC-1112-CA

A randomized, multi-center, open-label phase 3 study of Ibrutinib (Imbruvica®) versus ofatumumab was conducted in patients with CLL/SLL. Patients (n = 391) were randomized 1:1 to receive either Ibrutinib (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 Ibrutinib (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 tumor ≥5 cm. Thirty-two percent of patients had deletion 17p (with 50% of patients having deletion 17p/TP53 mutation), 24% had 11q deletion and 47% of patients had unmutated IGHV.

Progression-free survival (PFS) as assessed by an IRC according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the Ibrutinib (Imbruvica®) arm. The results from investigator and IRC assessments for PFS were consistent. Analysis of overall survival (OS) demonstrated a 57% statistically significant reduction in the risk of death for patients in the Ibrutinib (Imbruvica®) arm. Efficacy results for Study PCYC-1112-CA are shown in Table 9.

Table 9: Efficacy results in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (Study PCYC-1112-CA)

Endpoint	**Ibrutinib (Imbruvica®) N=195**	**Ofatumumab N=196**
Progression-Free Survival		
Median Progression-Free Survival, months	Not reached	8.1
HR (95% CI)	0.215 (0.146; 0.317)	
Overall Survival[a]		

HR (95% CI)	0.434 (0.238; 0.789)[b]	
HR (95% CI)	0.387 (0.216; 0.695)[c]	
Overall Response Rate[d,e] (%)	42.6	4.1
Overall Response Rate including Partial Response with Lymphocytosis (PRL)[d] (%)	62.6	4.1

HR = hazard ratio; CI = confidence interval; PR = partial response

[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 Ibrutinib (Imbruvica®).

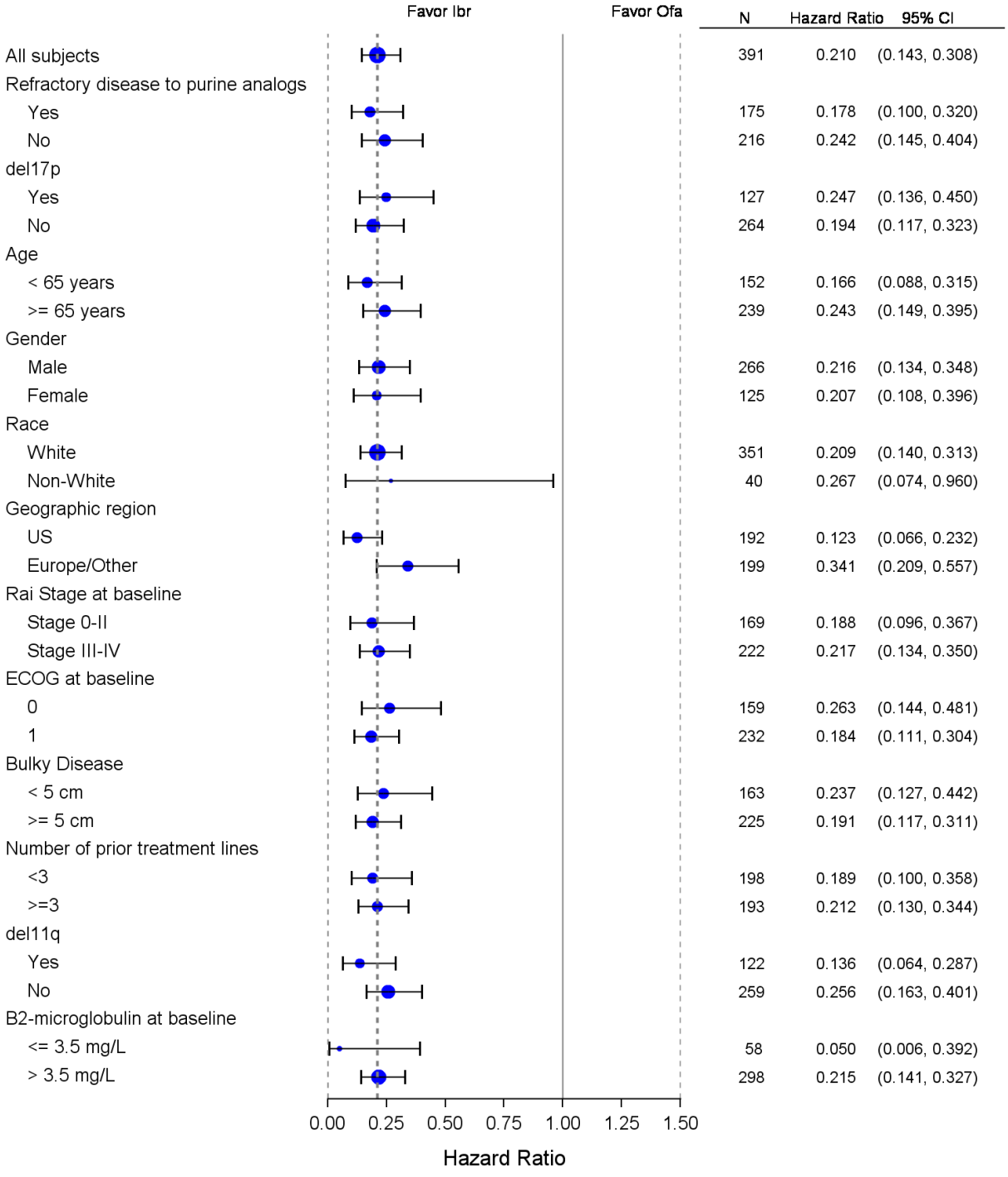
[d] Per IRC. Repeat CT scans required to confirm response.

[e] All PRs achieved. $p < 0.0001$ for ORR.

Median follow-up time on study = 9 months

The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (Figure 9).

Figure 9: Subgroup Analysis of Progression-Free Survival by IRC (Study PCYC-1112; 420 mg)



The Kaplan-Meier curves for PFS and OS are shown in Figures 10 and 11, respectively.

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

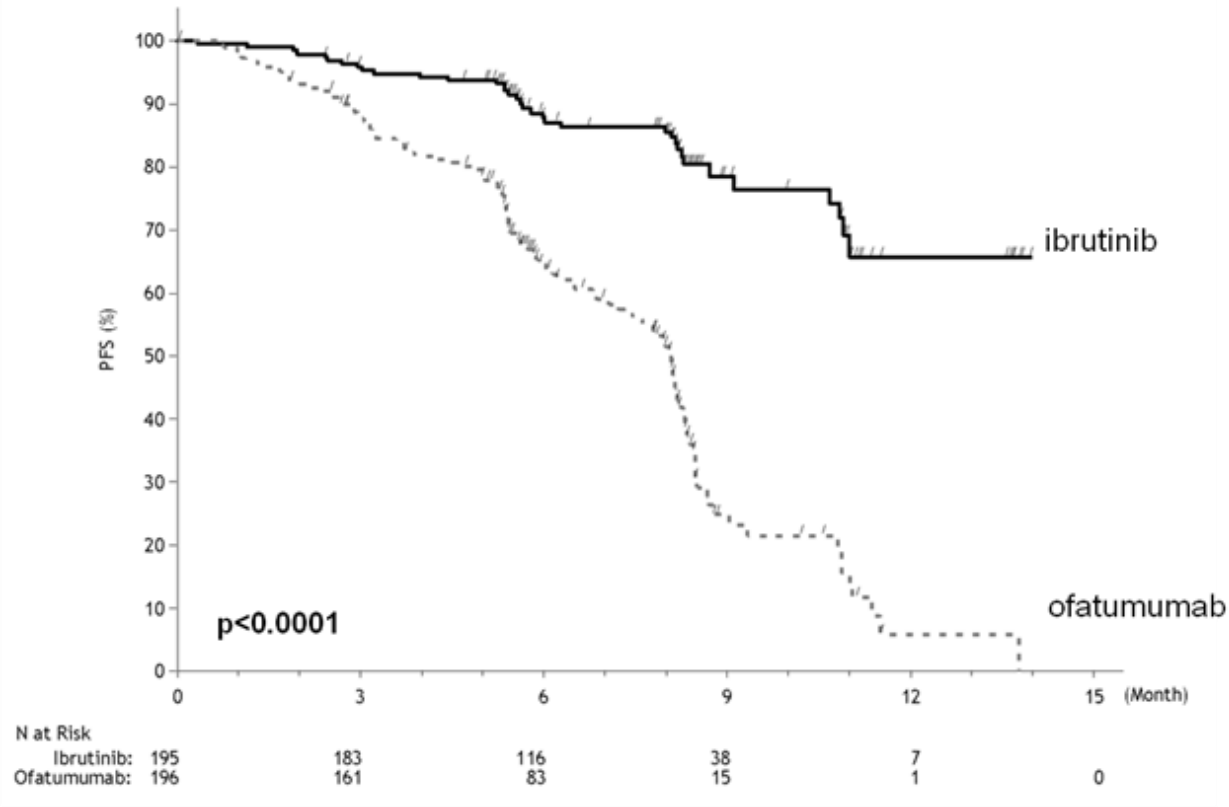
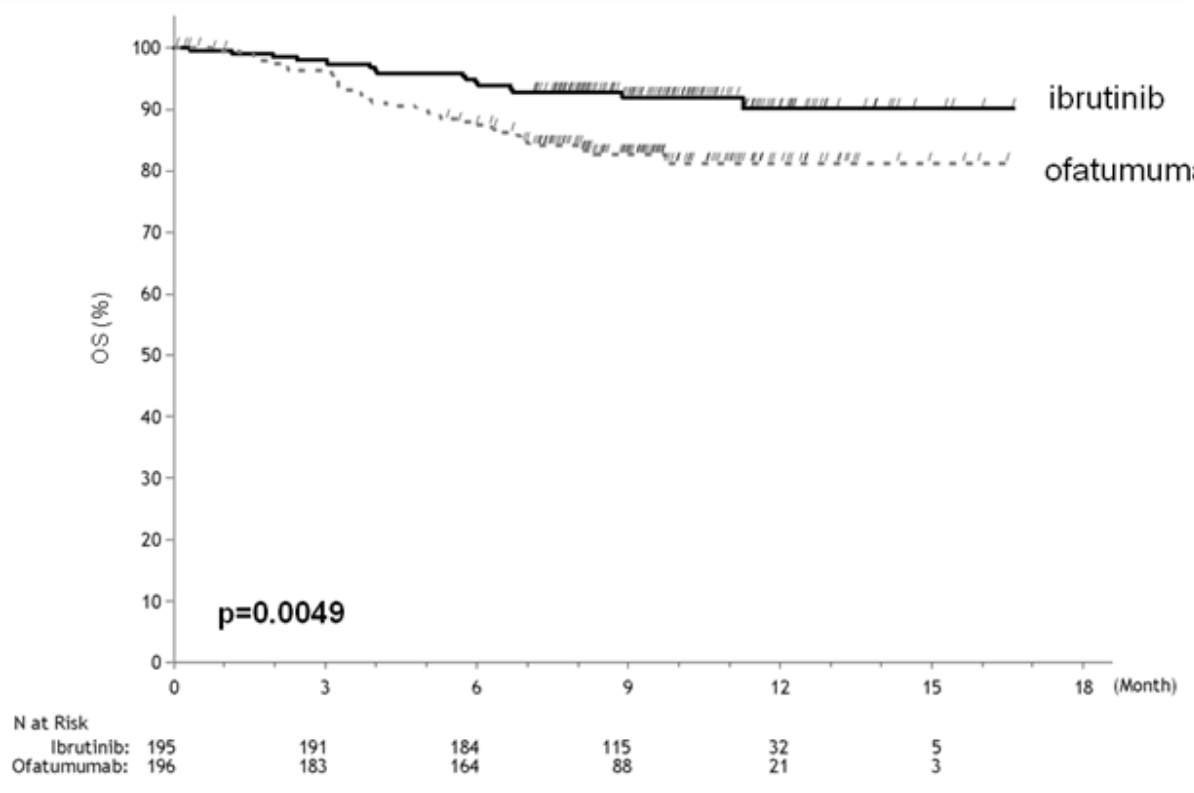


Figure 11: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1112-CA

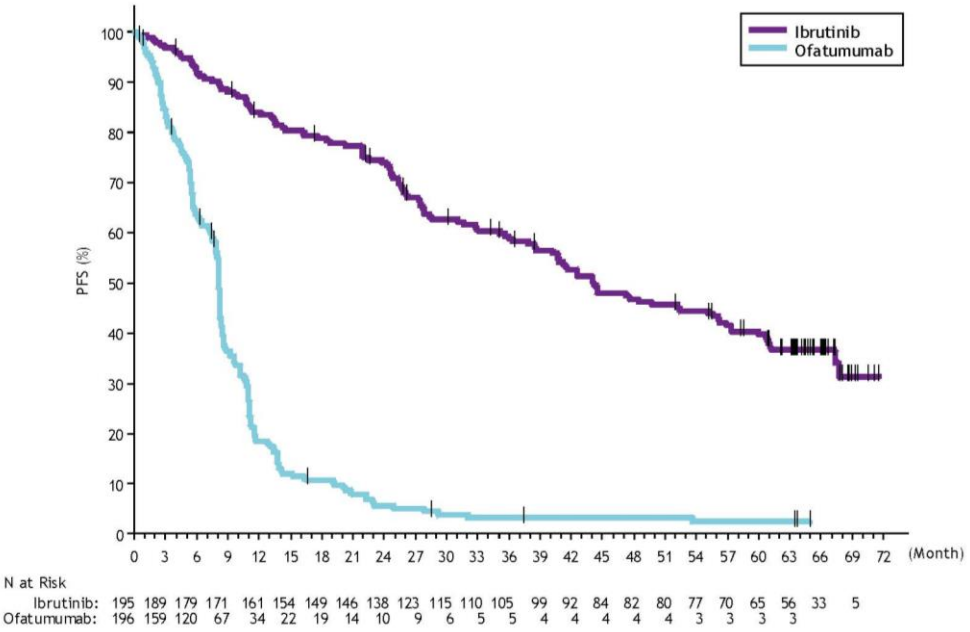


Final Analysis at 65-month Follow-up

With median follow-up time on study of 65 months in Study PCYC-1112-CA, an 85% reduction in the risk of death or progression by investigator assessment was observed for patients in the Ibrutinib (Imbruvica®) arm. The median investigator-assessed PFS according to IWCLL criteria was 44.1 months [95% CI (38.47, 56.18)] in the Ibrutinib (Imbruvica®) arm and 8.1 months [95% CI (7.79, 8.25)] in the ofatumumab arm, respectively; HR = 0.15 [95% CI (0.11, 0.20)]. The updated Kaplan-Meier curve for PFS is shown in Figure 12. The investigator-assessed ORR in the Ibrutinib (Imbruvica®) arm was 87.7% versus 22.4% in the ofatumumab arm. At the time of final analysis, 133 (67.9%) of the 196 subjects originally randomized to the ofatumumab treatment arm had crossed over to ibrutinib treatment. The median investigator-assessed PFS2 (time from randomization until PFS event after first subsequent anti-neoplastic therapy) according to IWCLL criteria was 65.4 months [95% CI (51.61, not estimable)] in the Ibrutinib (Imbruvica®) arm and 38.5 months [95% CI (19.98, 47.24)] in the ofatumumab arm, respectively; HR=0.54 [95% CI (0.41, 0.71)]. The median OS was 67.7 months [95% CI (61.0, not estimable)] in the Ibrutinib (Imbruvica®) arm.

The treatment effect of ibrutinib in Study PCYC-1112-CA was consistent across high-risk patients with del 17p/TP53 mutation, del 11q, and/or unmutated IGHV.

Figure 12: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) by Investigator in Study PCYC-1112-CA at Final Analysis with 65 Months Follow-up



CLL/SLL with deletion 17p

Study PCYC-1112-CA included 127 patients with CLL/SLL with deletion 17p. 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/SLL with deletion 17p are shown in Table 10.

Table 10: Efficacy results in patients with CLL/SLL with deletion 17p

Endpoint	Ibrutinib (Imbruvica®) N=63	Ofatumumab N=64
Progression-Free Survival		
Median Progression-Free Survival, months	Not reached	5.8
HR (95% CI)	0.25 (0.14; 0.45)	
Overall Response Rate[a]	47.6%	4.7%
Overall Response Rate including PRL	66.7%	4.7%

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

HR = hazard ratio; CI = confidence interval; PRL = partial response with lymphocytosis

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

With an overall follow-up of 63 months (median of 56 months) in Study PCYC-1112-CA, the median investigator-assessed PFS in patients with del 17p according to IWCLL criteria was 40.6 months [95% CI (25.36, 44.55)] in the Ibrutinib (Imbruvica®) arm and 6.2 months [95% CI (4.63, 8.11)] in the ofatumumab

arm, respectively; HR = 0.12, ([95% CI (0.07, 0.21)]. The investigator-assessed ORR in patients with del 17p in the Ibrutinib (Imbruvica®) arm was 88.9% versus 18.8% in the ofatumumab arm.

Combination therapy

Study CLL3001

The safety and efficacy of Ibrutinib (Imbruvica®) in patients previously treated for CLL/SLL were further evaluated in a randomized, multicenter, double-blinded phase 3 study of Ibrutinib (Imbruvica®) in combination with BR versus placebo + BR. Patients (n = 578) were randomized 1:1 to receive either Ibrutinib (Imbruvica®) 420 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles. Bendamustine was dosed at 70 mg/m^2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 in the first cycle, Day 1, and 500 mg/m^2 Cycles 2 through 6, Day 1. Ninety patients randomized to placebo + BR crossed over to receive Ibrutinib (Imbruvica®) following IRC confirmed progression. The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumor ≥5 cm, 26% had del11q, and 72% had unmutated IGHV.

Progression free survival (PFS) was assessed by IRC according to IWCLL criteria indicated an 80% statistically significant reduction in the risk of death or progression. Efficacy results for Study CLL3001 are shown in Table 11 and the Kaplan-Meier curve for PFS is shown in Figure 13.

Table 11: Efficacy results in Study CLL3001

Endpoint	Ibrutinib (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	Not reached	13.3 (11.3, 13.9)
HR (95% CI)	0.20 (0.15, 0.28)	
Overall Response Rate[b] (%)	82.7	67.8
CR/CRi	10.4	2.8
Overall Survival[c] HR (95% CI)	0.628 (0.385, 1.024)	
Minimal Residual Disease – negative status[d] (%)	12.8	4.8

CI = confidence interval; HR = hazard ratio; CR = complete response; CRi = complete response with incomplete marrow recovery.

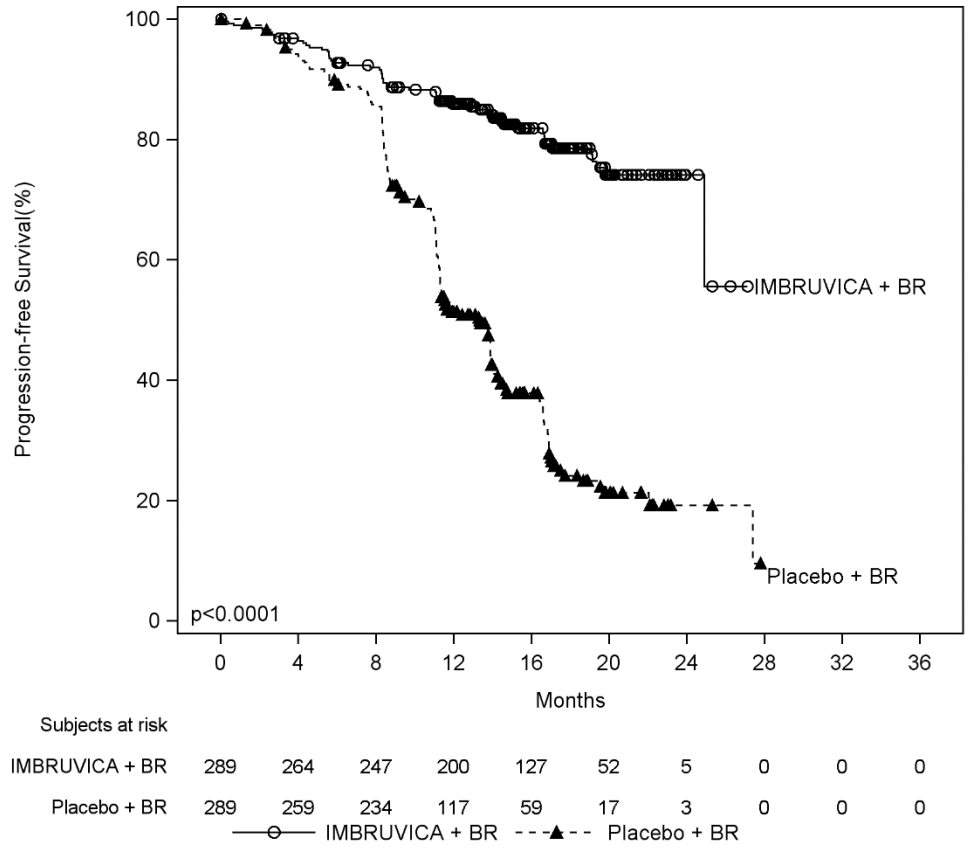
[a] IRC evaluated.

[b] IRC evaluated, ORR (CR, CRi, nodular partial response, partial response).

[c] Median OS not reached for both arms.

[d] MRD was evaluated in patients with suspected complete response; 120 patients for Ibrutinib (Imbruvica®), 57 patients for placebo had MRD samples obtained.

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



Waldenström's macroglobulinemia (WM)

The safety and efficacy of Ibrutinib (Imbruvica®) in WM (IgM-excreting lymphoplasmacytic lymphoma) were evaluated in one single-arm and one randomized, controlled study.

Study PCYC-1118E

An open-label, multi-center, single-arm trial (PCYC-1118E) was conducted in 63 previously-treated patients. The median age was 63 years (range, 44 to 86 years), 76% were male, and 95% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 74 months, and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL (range, 0.7 to 8.4 g/dL), and 60% of patients were anemic (hemoglobin ≤ 11 g/dL).

Ibrutinib (Imbruvica®) was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The primary endpoint in this study was ORR per investigator assessment. The ORR and DOR were assessed using criteria adopted from the Third International Workshop of Waldenström's Macroglobulinemia. Responses to Ibrutinib (Imbruvica®) are shown in Table 12.

Table 12: Overall response rate (ORR) and duration of response (DOR) based on investigator assessment in patients with WM in Study PCYC-1118E

	Total (N = 63)
ORR (%)	87.3
95% CI (%)	(76.5, 94.4)
VGPR (%)	14.3
PR (%)	55.6
MR (%)	17.5
Median DOR months (range)	NR (0.03+, 18.8+)

CI = confidence interval; NR = not reached; MR = minor response; PR = partial response; VGPR = very good partial response; ORR = MR+PR+VGPR
Median follow-up time on study = 14.8 months

The median time to response was 1.0 month (range, 0.7-13.4 months).
Efficacy results were also assessed by an IRC demonstrating an ORR of 82.5%, with a 11% VGPR rate and a 51% PR rate.

Study PCYC-1127-CA
A randomized, multicenter, double-blinded phase 3 study of Ibrutinib (Imbruvica®) in combination with rituximab versus placebo in combination with rituximab (PCYC-1127-CA) was conducted in patients with treatment-naïve or previously treated WM. Patients (n=150) were randomized 1:1 to receive either Ibrutinib (Imbruvica®) 420 mg daily or placebo in combination with rituximab until disease progression or unacceptable toxicity. Rituximab was administered weekly at a dose of 375 mg/m^2 for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 consecutive weeks (weeks 17-20).

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were Caucasian. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were treatment-naïve, and 55% of patients were previously treated. The median time since diagnosis was 52.6 months (treatment-naïve patients = 6.5 months and previously treated patients = 94.3 months). Among previously treated patients, the median number of prior treatments was 2 (range, 1 to 6 treatments). At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), 63% of patients were anemic (hemoglobin ≤11 g/dL) and MYD88 L265P mutations were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status.

Progression free survival (PFS) as assessed by IRC indicated an 80% statistically significant reduction in the risk of death or progression. Efficacy results for Study PCYC-1127-CA are shown in Table 13 and the Kaplan-Meier curve for PFS is shown in Figure 14. PFS hazard ratios for treatment-naïve patients, previously treated patients, and patients with or without MYD88 L265P mutations were consistent with the PFS hazard ratio for the ITT population.

Table 13: Efficacy results in Study PCYC-1127-CA

Endpoint	**Ibrutinib (Imbruvica®) + R N=75**	**Placebo + R N=75**
Progression Free Survival[a]		
Number of events (%)	14 (18.7)	42 (56.0)
Median (95% CI), months	Not reached	20.3 (13.7, 27.6)

HR (95% CI)	0.20 (0.11, 0.38)	
TTnT		
Median (95% CI), months	Not reached	18.1 (11.1, NE)
HR (95% CI)	0.1 (0.04, 0.23)	
Best Overall Response (%)		
CR	2.7	1.3
VGPR	22.7	4.0
PR	46.7	26.7
MR	20.0	14.7
Overall Response Rate (CR, VGPR, PR, MR)[b] (%)	92.0	46.7
Median duration of overall response, months (range)	Not reached (1.9+, 36.4+)	24.8 (1.9, 30.3+)
Response Rate (CR, VGPR, PR)[b] (%)	72.0	32.0
Median duration of response, months (range)	Not reached (1.9+, 36.4+)	21.2 (4.6, 25.8)
Rate of Sustained Hemoglobin Improvement[b, c] (%)	73.3	41.3

CI = confidence interval; CR = complete response; HR = hazard ratio; MR = minor response; NE = not estimable; PR = partial response; R = Rituximab; TTnT = time to next treatment; VGPR = very good partial response

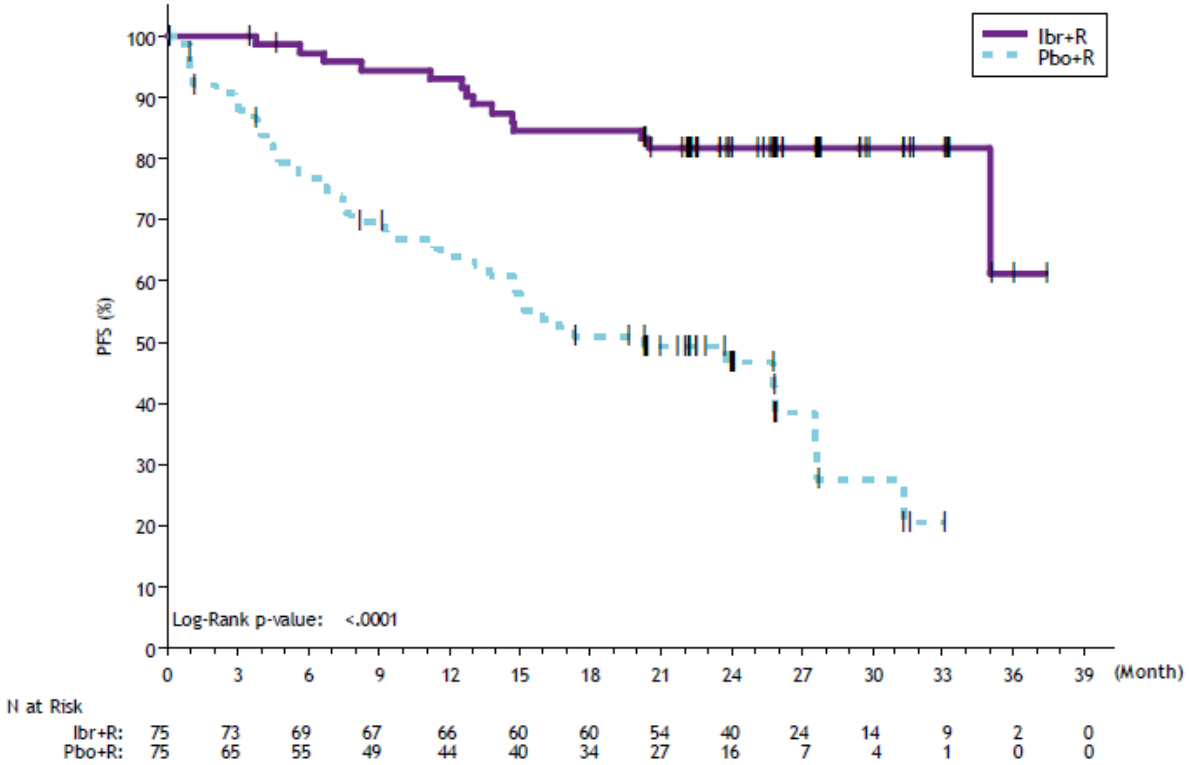
[a] IRC evaluated.

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

[c] Defined as increase of ≥2 g/dL over baseline regardless of baseline value, or an increase to >11 g/dL with a ≥0.5 g/dL improvement if baseline was ≤11 g/dL.

Median follow-up time on study = 26.5 months.

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



Tumor flare in the form of IgM increase occurred in 8.0% of subjects in the Ibrutinib (Imbruvica®) + rituximab arm and 46.7% of subjects in the placebo + rituximab arm.

63-Month Follow-Up (Final Analysis)

With an overall follow-up of 63 months, efficacy results as assessed by an IRC at the time of the final analysis for PCYC-1127-CA are shown in Table 14. PFS hazard ratios for treatment-naïve patients (0.31 [95% CI (0.14, 0.69)]) and previously treated patients (0.22 [95% CI (0.11, 0.43)]) were consistent with the PFS hazard ratio for the ITT population.

Table 14: Efficacy results in Study PCYC-1127-CA (Final Analysis*)

Endpoint	Ibrutinib (Imbruvica®) + R N=75	Placebo + R N=75
Progression Free Survival[a, b]		
Number of events (%)	22 (29)	50 (67)
Median (95% CI), months	Not reached	20.3 (13.0, 27.6)
HR (95% CI)	0.25 (0.15, 0.42)	
P-value	<0.0001	
TTnT		
Median (95% CI), months	Not reached	18.1 (11.1, 33.1)
HR (95% CI)	0.1 (0.05, 0.21)	
Best Overall Response (%)		
CR	1.3	1.3
VGPR	29.3	4.0
PR	45.3	25.3
MR	16.0	13.3
Overall Response Rate[c] (CR, VGPR, PR, MR) (%)	69 (92.0)	33 (44.0)
Median duration of overall response, months (range)	Not reached (2.7, 58.9+)	27.6 (1.9, 55.9+)
Response Rate (CR, VGPR, PR)[c,d] (%)	57 (76.0)	23 (30.7)
Median duration of response, months (range)	Not reached (1.9+, 58.9+)	Not reached (4.6, 49.7+)
Rate of Sustained Hemoglobin Improvement[c,e] (%)	77.3	42.7

CI = confidence interval; CR = complete response; HR = hazard ratio; MR = minor response; PR = partial response; R = Rituximab; TTnT = time to next treatment; VGPR = very good partial response

* Median follow-up time on study = 49.7 months.

[a] IRC evaluated.

[b] 4-year PFS estimates were 70.6% [95% CI (58.1, 80.0)] in the Ibrutinib (Imbruvica®) + R arm versus 25.3% [95% CI (15.3, 36.6)] in the placebo + R arm.

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

[d] Response rate was 76% vs 41% in treatment-naïve patients and 76% vs 22% in previously treated patients for the Ibrutinib (Imbruvica®) + R arm vs the placebo + R arm, respectively.

[e] 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.

Study PCYC-1127-CA had a separate monotherapy arm of 31 patients with previously treated WM who failed prior rituximab-containing therapy and received single agent Ibrutinib (Imbruvica®). The median age was 67 years (range, 47 to 90 years). Eighty-one percent of patients had a baseline ECOG performance status of 0 or 1, and 19% had a baseline ECOG performance status of 2. The median number of prior treatments was 4 (range, 1 to 7 treatments). The response rate per IRC observed in the monotherapy arm was 71% (0% CR, 29% VGPR, 42% PR). The overall response rate per IRC observed in the monotherapy arm was 87% (0% CR, 29% VGPR, 42% PR, 16% MR). With a median follow-up time on study of 34 months (range, 8.6+ to 37.7 months), the median duration of response has not been reached.

61-Month Follow-Up (Final Analysis)

With an overall follow-up of 61 months, the response rate observed in Study PCYC-1127-CA monotherapy arm per IRC assessment was 77% (0% CR, 29% VGPR, 48% PR). The median duration of response was 33 months (range, 2.4 to 60.2+ months). The overall response rate per IRC observed in the monotherapy arm was 87% (0% CR, 29% VGPR, 48% PR, 10% MR). The median duration of overall response was 39 months (range, 2.07 to 60.2+ months).

PHARMACOKINETIC PROPERTIES

Absorption

Ibrutinib is rapidly absorbed after oral administration with a median T_{max} of 1 to 2 hours. Absolute bioavailability in fasted condition (n = 8) was 2.9% (90% CI = 2.1 – 3.9) and doubled when combined with a meal. Pharmacokinetics of ibrutinib does not significantly differ in patients with different B-cell malignancies. Ibrutinib exposure increases with doses up to 840 mg. The steady state AUC observed in patients at 560 mg is (mean ± standard deviation) 953 ± 705 ng•h/mL and in patients at 420 mg with CLL/SLL is 732 ± 521 ng•h/mL (680 ± 517 ng•h/mL in subset of R/R patients) and with cGVHD is 1159 ± 583 ng•h/mL. Administration of ibrutinib in fasted condition resulted in approximately 60% of exposure (AUC_{last}) as compared to either 30 minutes before, 30 minutes after (fed condition) or 2 hours after a high fat breakfast.

Distribution

Reversible binding of ibrutinib to human plasma protein *in vitro* was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution (V_d) was 683 L and the apparent volume of distribution at steady state ($V_{d,ss}$/F) was approximately 10000 L.

Metabolism

Ibrutinib is metabolized primarily by cytochrome P450, CYP3A4/5 to produce a prominent dihydrodiol metabolite with an inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. Systemic steady-state exposure to the dihydrodiol metabolite is comparable to that of the parent drug.

In vitro studies indicated that CYP2D6 involvement in ibrutinib oxidative metabolism is <2%. Moreover, as part of the human mass balance study, subjects genotyped as poor metabolizers for CYP2D6, showed a similar pharmacokinetic profile as extensive metabolizers. Therefore, no precautions are necessary in patients with different CYP2D6 genotypes.

Elimination

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.

After a single oral administration of radiolabeled [^{14}C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and < 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

Elderly (65 years of age and older)

Population pharmacokinetics indicated that in older patients (67 to 81 years), a 14% higher ibrutinib exposure is predicted. Dose adjustment by age is not warranted.

Pediatric population (18 years of age and younger)

No pharmacokinetic studies were performed with Ibrutinib (Imbruvica®) in patients under 18 years of age.

Gender
Population pharmacokinetics data indicated that gender does not significantly influence ibrutinib clearance from the circulation.

Renal impairment
Ibrutinib has minimal renal clearance; urinary excretion of metabolites is < 10% of the dose. No specific studies have been conducted to date in subjects with impaired renal function. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There are no data in patients with severe renal impairment or patients on dialysis.

Hepatic impairment
Ibrutinib is metabolized in the liver. A hepatic impairment trial was performed in non-cancer subjects administered a single dose of 140 mg of Ibrutinib (Imbruvica®) under fasting conditions. Ibrutinib AUC_{last} 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.

NON-CLINICAL INFORMATION
The following adverse effects were seen in studies of 13-weeks duration in rats and dogs. Ibrutinib was found to induce gastrointestinal effects (soft feces/diarrhea and/or inflammation) and lymphoid depletion in rats at human equivalent doses (HEDs) ≥16 mg/kg/day and dogs at HEDs ≥ 32 mg/kg/day. Effects on lymphoid tissue (lymphoid depletion) were also induced at HEDs ≥ 28 mg/kg/day in rats and ≥ 32 mg/kg/day in dogs. In rats, moderate pancreatic acinar cell atrophy was observed at HEDs ≥ 6 mg/kg/day. Mildly decreased trabecular and cortical bone was seen in rats administered HEDs ≥ 16 mg/kg/day for 13 weeks. All notable findings in rats and dogs fully or partially reversed following recovery periods of 6 to 13 weeks.

Carcinogenicity and Mutagenicity
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.

Ibrutinib has no genotoxic properties when tested in bacteria, mammalian cells or in mice**.**

Fertility
No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (HED 16 mg/kg/day).

THERAPEUTIC INDICATIONS
Mantle cell lymphoma (MCL)
Ibrutinib (Imbruvica®) is indicated for the treatment of adult patients with MCL who have received at least one prior therapy.

Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL)

Ibrutinib (Imbruvica®) is indicated for the treatment of patients with CLL/SLL.

Chronic lymphocytic leukemia/Small lymphocytic lymphoma with deletion 17p
Ibrutinib (Imbruvica®) is indicated for the treatment of patients with CLL/SLL with deletion 17p.

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

DOSAGE AND METHOD OF ADMINISTRATION

Dosage
Ibrutinib (Imbruvica®) should be administered orally once daily with a glass of water at approximately the same time each day. The tablets should be swallowed whole with water. Do not break or chew the tablets. Ibrutinib (Imbruvica®) must not be taken with grapefruit juice. Ibrutinib (Imbruvica®) should continue until disease progression or no longer tolerated by the patient.

Mantle cell lymphoma
The recommended dose of Ibrutinib (Imbruvica®) for the treatment of MCL is 560 mg once daily until disease progression or no longer tolerated by the patient.

Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL) and Waldenström's macroglobulinemia (WM)
The recommended dose of Ibrutinib (Imbruvica®) for CLL/SLL or WM is 420 mg once daily until disease progression or no longer tolerated by the patient. For CLL/SLL, Ibrutinib (Imbruvica®) can be administered as a single agent, in combination with anti-CD20 therapy (rituximab or obinutuzumab), or in combination with bendamustine and rituximab (BR). For WM, Ibrutinib (Imbruvica®) can be administered as a single agent or in combination with rituximab. For additional information concerning rituximab, BR, or obinutuzumab see the corresponding local rituximab, bendamustine or obinutuzumab prescribing information. When administering Ibrutinib (Imbruvica®) in combination with anti-CD20 therapy, it is recommended to administer Ibrutinib (Imbruvica®) prior to anti-CD20 therapy when given on the same day.

Dose modification guidelines
Dose modifications are required for the concomitant use of moderate and strong CYP3A inhibitors as these can increase the exposure of ibrutinib (see ***Interactions***).

Ibrutinib (Imbruvica®) therapy should be withheld for any new onset or worsening Grade ≥ 3 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), Ibrutinib (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 Ibrutinib (Imbruvica®).

Recommended dose modifications are described below:

Toxicity occurrence	MCL dose modification after recovery	CLL/SLL/WM dose modification after recovery
First	restart at 560 mg daily	restart at 420 mg daily
Second	restart at 420 mg daily	restart at 280 mg daily
Third	restart at 280 mg daily	restart at 140 mg daily
Fourth	discontinue Ibrutinib (Imbruvica®)	

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

Special populations

Pediatrics (18 years of age and younger)
The safety and efficacy of Ibrutinib (Imbruvica®) in children have not been evaluated.

Renal impairment
Ibrutinib has minimal renal clearance. No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in Ibrutinib (Imbruvica®) clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained and serum creatinine levels monitored periodically. There are no data in patients with severe renal impairment or patients on dialysis (see section ***Pharmacokinetic Properties***).

Hepatic impairment
Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure (see ***Pharmacokinetic Properties***). For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily. For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily. Monitor patients for signs of Ibrutinib (Imbruvica®) toxicity and follow dose modification guidance as needed. It is not recommended to administer Ibrutinib (Imbruvica®) to patients with severe hepatic impairment (Child-Pugh class C).

CONTRAINDICATIONS
Ibrutinib (Imbruvica®) is contraindicated in patients who have known hypersensitivity (e.g. anaphylactic and anaphylactoid reactions) to ibrutinib or to the excipients in its formulation.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
Bleeding-related events
There have been reports of bleeding events in patients treated with Ibrutinib (Imbruvica®), both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae; and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.

In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed (see ***Pharmacodynamic Properties***). Use of either anticoagulant or

antiplatelet agents concomitantly with Ibrutinib (Imbruvica®) increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with Ibrutinib (Imbruvica®). Monitor for signs and symptoms of bleeding.

Supplements such as fish oil and vitamin E preparations should be avoided.

Ibrutinib (Imbruvica®) should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Patients with congenital bleeding diathesis have not been studied.

Leukostasis
There were isolated cases of leukostasis reported in patients treated with Ibrutinib (Imbruvica®). A high number of circulating lymphocytes (> 400000/mcL) may confer increased risk. Consider temporarily holding Ibrutinib (Imbruvica®). Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

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

Cytopenias
Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anemia) were reported in patients treated with Ibrutinib (Imbruvica®). Monitor complete blood counts monthly.

Interstitial lung disease (ILD)
Cases of ILD have been reported in patients treated with Ibrutinib (Imbruvica®). Monitor patients for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt Ibrutinib (Imbruvica®) and manage ILD appropriately. If symptoms persist, consider the risks and benefits of Ibrutinib (Imbruvica®) treatment and follow the dose modification guidelines.

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

Tumor lysis syndrome
Tumor lysis syndrome has been reported with Ibrutinib (Imbruvica®) therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

Non-melanoma skin cancer
Non-melanoma skin cancers have occurred in patients treated with Ibrutinib (Imbruvica®). Monitor patients for the appearance of non-melanoma skin cancer.

Hypertension
Hypertension has occurred in patients treated with Ibrutinib (Imbruvica®). Regularly monitor blood pressure in patients treated with Ibrutinib (Imbruvica®) and initiate or adjust antihypertensive medication throughout treatment with Ibrutinib (Imbruvica®) as appropriate.

PREGNANCY, BREAST-FEEDING AND FERTILITY
Pregnancy
There are no adequate and well-controlled studies of Ibrutinib (Imbruvica®) in pregnant women. Based on findings in animals, Ibrutinib (Imbruvica®) may cause fetal harm when administered to pregnant women.

Ibrutinib (Imbruvica®) should not be used during pregnancy. Women of child-bearing potential must use highly effective contraceptive measures while taking Ibrutinib (Imbruvica®). Women should avoid becoming pregnant while taking Ibrutinib (Imbruvica®) and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. The time period following treatment with Ibrutinib (Imbruvica®) where it is safe to become pregnant is unknown.

Men should be advised not to father a child or donate sperm while receiving Ibrutinib (Imbruvica®), and for 3 months following completion of treatment (see ***Non-clinical Information – Fertility***).

Ibrutinib was studied for effects on embryo-fetal development in pregnant rats given oral doses of 10, 40, and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day (approximately 14 times the AUC of ibrutinib and 9.5 times the AUC of the dihydrodiol metabolite compared to patients at the dose of 560 mg daily) was associated with increased post-implantation loss and increased visceral malformations (heart and major vessels). Ibrutinib at a dose of ≥ 40 mg/kg/day (≥ approximately 5.6 times the AUC of ibrutinib and 4.0 times the AUC of the dihydrodiol metabolite compared to patients at a dose of 560 mg daily) was associated with decreased fetal weights.

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

Breast-feeding
It is not known whether ibrutinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Ibrutinib (Imbruvica®), breast-feeding should be discontinued during Ibrutinib (Imbruvica®) treatment.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Fatigue, dizziness and asthenia have been reported in some patients taking Ibrutinib (Imbruvica®) and should be considered when assessing a patient's ability to drive or operate machines.

INTERACTIONS
Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4 (CYP3A4).

Agents that may increase ibrutinib plasma concentrations
Concomitant use of Ibrutinib (Imbruvica®) and drugs that strongly or moderately inhibit CYP3A4 can increase ibrutinib exposure and strong CYP3A4 inhibitors should be avoided.

Strong CYP3A4 inhibitors
Co-administration of ketoconazole, a very strong CYP3A4 inhibitor, in 18 healthy subjects, increased exposure (C_{max} and $AUC_{0\text{-}last}$) of ibrutinib by 29- and 24-fold, respectively. In a dedicated drug-drug interaction study in patients with B-cell malignancies, co-administration of voriconazole increased C_{max} and AUC by 6.7-fold and 5.7-fold, respectively. In clinical studies, the maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Voriconazole and posaconazole can be used concomitantly with Ibrutinib (Imbruvica®) as per dose recommendations in the table below. All other strong inhibitors of CYP3A4 (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone and cobicistat) should be avoided. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, see recommended dose modifications in the table below.

Moderate and mild CYP3A inhibitors
In patients with B-cell malignancies, co-administration of the CYP3A inhibitor erythromycin increased C_{max} and AUC by 3.4-fold and 3.0-fold, respectively. If a moderate CYP3A inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone and dronedarone) is indicated, reduce Ibrutinib (Imbruvica®) dose as per recommended dose modifications in the table below.

No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during Ibrutinib (Imbruvica®) treatment as these contain moderate inhibitors of CYP3A (see ***Dosage and Method of Administration*** and ***Pharmacokinetic Properties***).

Recommended dose modifications are described below:

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

[a] Monitor for adverse reactions to Ibrutinib (Imbruvica®) and interrupt or modify dose as recommended (see ***Dosage and Method of Administration***).

[b] Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

After discontinuation of a CYP3A inhibitor, resume previous dose of Ibrutinib (Imbruvica®) (see ***Dosage and Method of Administration***).

Agents that may decrease ibrutinib plasma concentrations

Administration of Ibrutinib (Imbruvica®) with strong inducers of CYP3A decreases ibrutinib plasma concentrations by up to 90%.

Avoid concomitant use of strong CYP3A inducers (e.g. carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction.

Drugs that may have their plasma concentrations altered by ibrutinib

In vitro studies indicated that ibrutinib is a weak reversible inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time-dependent CYP450 inhibition. 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*. However, in a drug interaction study in patients with B-cell malignancies, a single 560 mg dose of ibrutinib did not have a clinically meaningful effect on the exposure of the CYP3A4 substrate midazolam. In the same study, 2 weeks of treatment with ibrutinib at 560 mg daily had no clinically relevant effect on the pharmacokinetics

of oral contraceptives (ethinyl estradiol and levonorgestrel), the CYP3A4 substrate midazolam, nor the CYP2B6 substrate bupropion.

In vitro studies indicated that ibrutinib is not a substrate of P-gp nor other major transporters, except OCT2. The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is a mild inhibitor of P-gp and breast cancer resistance protein (BCRP). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. There are no clinical data available. To minimize the potential for an interaction with the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after Ibrutinib (Imbruvica®). Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

ADVERSE REACTIONS

Throughout this section, adverse reactions (AR) are presented. Adverse reactions are adverse events that have been considered to be reasonably causally associated with the use of ibrutinib based on the comprehensive assessment of the available adverse event information. A causal relationship with ibrutinib cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Non-melanoma skin cancer

Based on an integrated analysis of the randomized, controlled phase 3 studies (PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, MCL3001, PCYC-1127-CA, and E1912), the incidence of non-melanoma skin cancer was 6% in IMBRUVICA-treated patients and 3% in comparator-treated patients.

Mantle cell lymphoma

The data described below reflect exposure to Ibrutinib (Imbruvica®) in a phase 2 clinical study (PCYC-1104-CA) and a randomized phase 3 study (MCL3001) in patients with MCL (n=250).

The most commonly occurring adverse reactions for MCL (≥ 20%) were diarrhea, hemorrhage (e.g., bruising), fatigue, musculoskeletal pain, nausea, upper respiratory tract infection, cough, and rash.

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

Discontinuation and dose reduction due to ARs

Of the 250 patients treated with Ibrutinib (Imbruvica®) for MCL, seven (3%) discontinued treatment due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation included hemorrhage, pneumonia, and thrombocytopenia. Adverse reactions leading to dose reduction occurred in 6% of patients.

Adverse reactions from Study 1104 are described below in Table 15 to reflect exposure to Ibrutinib (Imbruvica®) in patients with MCL who received at least one prior therapy with a median treatment duration of 8.3 months.

Table 15: Adverse reactions reported in ≥ 10% of patients with MCL treated with 560 mg Ibrutinib (Imbruvica®) – Study 1104 (N=111)

		Frequency	
System Organ Class	**Adverse Reaction**	**All Grades (%)**	**Grade 3 or 4 (%)**
Infections and infestations	Pneumonia	12	5
	Urinary tract infection	14	3
	Sinusitis	14	1
	Upper respiratory tract infection	26	0
Blood and lymphatic system disorders	Neutropenia	19	17
	Thrombocytopenia	21	12
	Anemia	15	10
Metabolism and nutrition disorders	Dehydration	14	4
	Hyperuricemia	17	5
	Decreased appetite	23	2
Nervous system disorders	Dizziness	14	0
	Headache	12	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	28	4
	Epistaxis	11	0
	Cough	18	0
Gastrointestinal disorders	Diarrhea	53	5
	Abdominal pain	18	5
	Vomiting	23	0
	Stomatitis	13	1
	Constipation	28	0
	Nausea	32	1
	Dyspepsia	11	0
Skin and subcutaneous tissue disorders	Rash	16	2
Musculoskeletal and connective tissue disorders	Muscle spasms	14	0
	Myalgia	14	0
	Arthralgia	14	0
	Back pain	14	1
	Pain in extremity	12	0
General disorders and administration site conditions	Pyrexia	19	1
	Fatigue	43	5
	Asthenia	12	3
	Edema peripheral	30	2
Injury, poisoning and procedural complications	Contusion	18	0

Serious adverse reactions

In the phase 2 study, serious adverse reactions were reported in 60% of patients (treatment-emergent frequencies). Serious adverse reactions that occurred in greater than 2% of patients were atrial fibrillation (6%), pneumonia (5%), urinary tract infection (4%), abdominal pain (3%), subdural hematoma (3%), febrile neutropenia (3%), acute renal failure (3%), peripheral edema (3%), and pyrexia (3%).

Adverse reactions from Study MCL3001 are described below in Table 16 reflecting exposure to Ibrutinib (Imbruvica®) in patients with MCL who received at least one prior therapy, treated with a median treatment duration of 14.4 months.

Table 16: Adverse reactions reported in patients with MCL treated with 560 mg Ibrutinib (Imbruvica®) – Study MCL3001 (n=139)

		Ibrutinib (Imbruvica®) (n=139)		Temsirolimus (n=139)	
System Organ Class	**Adverse Reactions**	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Infections and infestations	Upper respiratory tract infection	19	2	12	1
	Pneumonia*	14	10	19	12
Eye disorders	Conjunctivitis	12	0	5	0
Cardiac disorders	Atrial fibrillation	4	4	2	1
Gastrointestinal disorders	Abdominal pain	8	4	8	1
Musculoskeletal and connective tissue disorders	Muscle spasms	19	0	3	0

* Includes multiple adverse reaction terms.

Chronic lymphocytic leukemia/Small lymphocytic lymphoma

The data described below reflect exposure to Ibrutinib (Imbruvica®) in a single arm, open-label clinical study (Study PCYC-1102-CA) and four randomized clinical studies (Study PCYC-1115-CA, Study PCYC-1112-CA, Study CLL3001, and PCYC-1130-CA) in patients with CLL/SLL (n=781).

The most commonly occurring adverse reactions in studies PCYC-1102-CA, PCYC-1112-CA, PCYC-1115-CA, CLL3001, and PCYC-1130-CA (≥ 20%) were diarrhea, neutropenia, rash, musculoskeletal pain, hemorrhage (e.g., bruising), nausea, thrombocytopenia, and pyrexia.

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

Discontinuation and dose reduction due to ARs

Six percent of patients receiving Ibrutinib (Imbruvica®) in studies PCYC-1102-CA, PCYC-1112-CA, PCYC-1115-CA, CLL3001, and PCYC-1130-CA discontinued treatment due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation included pneumonia, atrial fibrillation, rash, and hemorrhage. Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Patients with previously untreated CLL/SLL

Single agent

Adverse reactions described below in Table 17 reflect exposure to Ibrutinib (Imbruvica®) with a median duration of 17.4 months, which is approximately 2.5 times the median exposure to chlorambucil of 7.1 months in Study PCYC-1115-CA.

Table 17: Adverse reactions reported in previously untreated patients with CLL/SLL treated with 420 mg Ibrutinib (Imbruvica®) - Study PCYC-1115-CA[a]

	Ibrutinib (Imbruvica®) (N=135)		Chlorambucil (N=132)	
System Organ Class **Adverse Reaction**	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Neoplasms benign, malignant, and unspecified (including cysts and polyps)				
Basal cell carcinoma	9	1	2	0
Metabolism and nutrition disorders				
Hyponatremia	7	3	1	0
Eye disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Cardiac disorders				
Atrial fibrillation	6	1	1	0
Vascular disorders				
Hypertension*	14	4	1	0
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Dyspepsia	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0

General disorders and administrative site conditions				
Peripheral edema	19	1	9	0

[a] Subjects with multiple events for a given adverse reaction term are counted once only for each adverse reaction term.

* Includes multiple adverse reaction terms

Combination therapy

Adverse reactions described below in Table 18 reflect exposure to Ibrutinib (Imbruvica®) + obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median duration of 5.1 months in Study PCYC-1130-CA.

Table 18: Adverse reactions reported in previously untreated patients with CLL/SLL treated with Ibrutinib (Imbruvica®) in combination with obinutuzumab in Study PCYC-1130-CA[a]

	Ibrutinib (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 (%)**
Blood and lymphatic system disorders				
Thrombocytopenia*	36	19	28	11
Skin and subcutaneous tissue disorders				
Rash*	36	3	11	0
Bruising*	32	3	3	0
Gastrointestinal disorders				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
Respiratory, thoracic and mediastinal disorders				
Cough	27	1	12	0
Vascular disorders				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3
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
Conjunctivitis	11	0	2	0

Metabolism and nutrition disorders				
Hyperuricemia	13	1	0	0
Cardiac disorders				
Atrial fibrillation	12	5	0	0
General disorders and administration site conditions				
Peripheral edema	12	0	7	0
Psychiatric disorders				
Insomnia	12	0	4	0

[a] Occurring at ≥10% incidence and ≥2% greater in the Ibrutinib (Imbruvica®) + obinutuzumab arm when compared to the chlorambucil + obinutuzumab arm

* Includes multiple adverse reaction terms

Events are sorted by system organ class and by decreasing frequency of adverse reaction term in the Ibrutinib (Imbruvica®) + obinutuzumab arm.

Adverse reactions described below in Table 19 reflect exposure to Ibrutinib (Imbruvica®) in combination with rituximab (IR) or received fludarabine, cyclophosphamide, and rituximab (FCR) with a median duration of 34.3 months for IR and 4.7 months for FCR in Study E1912.

Table 19: Adverse reactions reported in previously untreated patients with CLL/SLL treated with Ibrutinib (Imbruvica®) in combination with Rituximab in Study E1912

System Organ Class	**Ibrutinib (Imbruvica®) + Rituximab (N=352) (%)**		**Fludarabine + Cyclophosphamide + Rituximab (N=158) (%)**	
Adverse Reaction Term	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Gastrointestinal disorders				
Diarrhea	53	4	27	1
Nausea	40	1	64	1
Stomatitis*	22	1	8	1
Vomiting	18	2	28	0
Constipation	17	0	32	0
Abdominal pain	16	1	9	1
Dyspepsia	14	0	3	0
Gastroesophageal reflux disease	13	0	6	0
General disorders and administration site conditions				
Fatigue	80	2	78	3
Edema peripheral	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
Investigations				
Blood creatinine increased	36	1	20	1
Metabolism and nutrition disorders				
Hyperuricemia	18	1	4	0
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
Neuropathy peripheral*	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				
Hypertension*	42	19	22	6
Hemorrhage*	31	2	8	1

Table 20: Treatment-Emergent* Hematologic Laboratory Abnormalities reported in previously untreated patients with CLL/SLL treated with Ibrutinib (Imbruvica®) in combination with Rituximab in Study E1912

	Ibrutinib (Imbruvica®) + Rituximab (N=352)	**Fludarabine + Cyclophosphamide + Rituximab (N=158)**

	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Neutrophils decreased (%)	53	30	70	44
Platelets decreased (%)	43	7	69	25
Hemoglobin decreased (%)	26	0	51	2

* Based on laboratory measurements per iwCLL criteria grade (iwCLL: International Workshop on Chronic Lymphocytic. Leukemia)
Treatment-emergent Grade 4 thrombocytopenia (3% in the Ibrutinib (Imbruvica®) + Rituximab arm and 9% in the Fludarabine + Cyclophosphamide + Rituximab arm) and neutropenia (15% in the Ibrutinib (Imbruvica®) + Rituximab arm and 22% in the Fludarabine + Cyclophosphamide + Rituximab arm) occurred in subjects.

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

Single agent

Adverse reactions described in Table 21 below reflect exposure to Ibrutinib (Imbruvica®) with a median duration of 8.6 months and exposure to ofatumumab with a median duration of 5.3 months in Study PCYC-1112-CA.

Table 21: Adverse reactions reported in patients with CLL/SLL treated with Ibrutinib (Imbruvica®) as single agent in Study PCYC-1112-CA[a]

	Ibrutinib (Imbruvica®) (N=195)		Ofatumumab (N=191)	
System Organ Class Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Infections and infestations				
Upper respiratory tract infection	16	1	10	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin infection*	7	2	3	1
Sepsis*	4	2	4	3
Blood and lymphatic system disorders				
Anemia	23	5	17	8
Neutropenia	22	16	15	14
Thrombocytopenia	17	6	12	4
Lymphocytosis	4	2	3	1
Leukocytosis	4	3	1	0
Febrile neutropenia	2	2	3	3
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Eye disorders				
Vision blurred	10	0	3	0
Cardiac disorders				
Atrial fibrillation	5	3	1	0
Respiratory, thoracic and mediastinal disorders				

Epistaxis	9	0	3	1
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Bruising*	21	0	4	0
Petechiae	14	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Injury, poisoning and procedural complications				
Subdural hematoma	1	0	0	0

[a] Occurring at ≥10% incidence and 5% greater in the Ibrutinib (Imbruvica®) arm when compared to the ofatumumab arm or serious adverse reactions ≥2% incidence and 2% greater in the Ibrutinib (Imbruvica®) arm when compared to the ofatumumab arm or biologically plausible.

* Includes multiple adverse reaction terms.

Patients with multiple events for a given adverse reaction term are counted once only for each adverse reaction term.

Events are sorted by system organ class and by decreasing frequency of adverse reaction term in the Ibrutinib (Imbruvica®) arm.

Combination therapy

Adverse reactions described below in Table 21 reflect exposure to Ibrutinib (Imbruvica®) + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study CLL3001.

Table 21: Adverse reactions reported in patients with CLL/SLL treated with Ibrutinib (Imbruvica®) in combination with BR in Study CLL3001[a]

	Ibrutinib (Imbruvica®) + BR (N=287)		**Placebo + BR (N=287)**	
System Organ Class Adverse Reaction Term	**All Grades %**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
Blood and lymphatic system disorders				
Thrombocytopenia	31	15	24	15
Cardiac disorders				
Atrial fibrillation	7	3	2	1
Vascular disorders				
Hypertension*	10	5	5	2
Gastrointestinal disorders				

Diarrhea	36	2	23	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	18	1
Bruising*	18	<1	6	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0

[a] Occurred at an incidence of at least 5% higher for AEs or 2% higher for SAEs.
Events are sorted by system organ class and by decreasing frequency of adverse reaction term in the Ibrutinib (Imbruvica®) arm.
* Includes multiple adverse reaction terms
<1 used for frequency above 0 and below 0.5%

Waldenström's macroglobulinemia (WM)
The data described below reflect exposure to Ibrutinib (Imbruvica®) in an open-label clinical study that included 63 patients with previously treated WM (PCYC-1118E) and a randomized phase 3 clinical study in 75 patients with treatment-naïve or previously treated WM (PCYC-1127-CA). Study PCYC-1127-CA also had an additional monotherapy arm of 31 patients with previously treated WM who failed prior rituximab-containing therapy. The safety profile of patients included in the PCYC-1127-CA monotherapy arm is consistent with the overall known WM safety profile for Ibrutinib (Imbruvica®)-exposed patients.

The most commonly occurring adverse reactions in the WM studies (PCYC-1118E and PCYC-1127-CA) (≥ 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.

Discontinuation and dose reduction due to ARs
Four percent of patients receiving Ibrutinib (Imbruvica®) in the WM studies (PCYC-1118E and PCYC-1127-CA) discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 11% of patients.

Adverse reactions described below in Table 22 reflect exposure to Ibrutinib (Imbruvica®) with a median duration of 11.7 months in Study PCYC-1118E.

Table 22: Adverse reactions reported in ≥10% of patients with WM treated with 420 mg Ibrutinib (Imbruvica®) - Study 1118E (N=63)

System Organ Class	Adverse Reaction	All Grades (%)	Grades 3-4 (%)
Infections and infestations	Sinusitis	19	0
	Upper respiratory tract infection	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin cancer*	11	0
	Neutropenia	25	17

Blood and lymphatic system disorders	Thrombocytopenia	17	13
	Anemia	16	3
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
General disorders and administration site conditions	Fatigue	21	0

* Includes multiple adverse reaction terms.

Adverse reactions from Study PCYC-1127-CA are described below in Table 23 reflecting exposure to Ibrutinib (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 treatment-naïve or previously treated WM.

Table 23: Adverse reactions reported in patients with WM treated with Ibrutinib (Imbruvica®) in combination with Rituximab in Study PCYC-1127-CA[a]

	Ibrutinib (Imbruvica®) + R (N=75)		**Placebo + R (N=75)**	
System Organ Class Adverse Reaction Term	**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
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
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

[a] Occurring at ≥10% incidence and ≥2% greater in the Ibrutinib (Imbruvica®) + rituximab arm when compared to the placebo + rituximab arm

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

* Includes multiple adverse reaction terms

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

Long-term safety

The long-term safety data over 5 years from 1178 patients (treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, and relapsed/refractory MCL n=370) treated with Ibrutinib (Imbruvica®) were analyzed. The median duration of treatment for CLL/SLL was 51 months (range, 0.2 to 98 months) with 70% and 52% of patients receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for MCL was 11 months (range, 0 to 87 months) with 31% and 17% of patients receiving treatment for more than 2 years and 4 years, respectively. The overall known safety profile of Ibrutinib (Imbruvica®)-exposed patients remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), 8% (year 2-3), and 9% (year 3-4), and 9% (year 4-5). The incidence for the 5-year period was 11%.

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 24). Because these reactions were 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. In the table, the frequencies are provided according to the following convention:

Very common	≥ 1/10 (≥ 10%)
Common	≥ 1/100 and < 1/10 (≥ 1% and < 10%)
Uncommon	≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
Rare	≥ 1/10000 and < 1/1000 (≥ 0.01% and < 0.1%)
Very rare	< 1/10000, including isolated reports (< 0.01%)
Not known	Cannot be estimated from the available data.

In Table 24, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 24: Adverse reactions identified during postmarketing experience with Ibrutinib (Imbruvica®)

System Organ Class Adverse Reaction	Frequency Category Estimated from Spontaneous Reporting Rates
Cardiac disorders	
Ventricular tachyarrhythmias*†	Rare
Immune system disorders	
Interstitial lung disease*†	Uncommon
Metabolism and nutrition disorders	
Tumor lysis syndrome	Very rare
Hepatobiliary disorders	
Hepatic failure*	Uncommon
Skin and subcutaneous tissue disorders	
Angioedema	Very rare
Erythema	Very rare
Onychoclasis	Uncommon
Panniculitis*	Rare
Stevens-Johnson syndrome	Rare
Urticaria	Very rare
Neutrophilic dermatoses*	Rare
Nervous system disorders	
Peripheral neuropathy*	Uncommon
Cerebrovascular accident†	Uncommon
Transient ischemic attack	Rare
Ischemic stroke†	Rare

* Includes multiple adverse reaction terms.

† Includes events with fatal outcome.

OVERDOSE

Symptoms and signs

There are limited data on the effects of Ibrutinib (Imbruvica®) overdose. No Maximum Tolerated Dose was reached in the phase 1 study in which patients received up to 12.5 mg/kg/day (1400 mg/day). In a separate study, one healthy subject who received a dose of 1680 mg experienced reversible grade 4 hepatic enzyme increases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. There is no specific antidote for Ibrutinib (Imbruvica®). Patients who ingested more than the recommended dose should be closely monitored and given appropriate supportive treatment.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Patient must seek medical attention immediately at the first sign of any adverse drug reaction. For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Questions or comments? Email us at Janssendrugsafety_Phil@its.jnj.com.

INCOMPATIBILITIES
Not applicable.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.
Keep out of the sight and reach of children.

AVAILABILITY
PVC/PCTFE/Alu Blister Pack x 14's/Box of 28's

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

MANUFACTURED BY
Cilag AG
Hochstrasse 201
8200 Schaffhausen, Switzerland

PACKED BY
Janssen Cilag S.p.A.
Via C. Janssen
(Loc. Borgo San Michele)
04100 Latina (LT), Italy

Co-developed with Pharmacyclics

IMPORTED BY
Johnson & Johnson (Philippines), Inc.
KM 14 Edison Road
Merville, Parañaque City

REGISTRATION NUMBER

140 mg: DR-XY48675
420 mg: DR-XY48674

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