Original Study

Safety Analysis of Four Randomized Controlled Studies of Ibrutinib in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma or Mantle Cell Lymphoma

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Abstract

Ibrutinib, a Bruton's tyrosine kinase inhibitor, has become a standard treatment for patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The present pooled safety analysis of 4 randomized controlled studies demonstrated a favorable benefit/risk profile for ibrutinib in patients with CLL/SLL and mantle cell lymphoma.

Background: Multiple studies have demonstrated the efficacy and safety of ibrutinib for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL). This first-in-class inhibitor of Bruton's tyrosine kinase has become a standard treatment for patients with CLL and MCL. **Patients and Methods:** We conducted an integrated safety analysis to characterize the frequency, severity, natural history, and outcomes of adverse events (AEs) with ibrutinib versus comparators. Data were pooled from 4 completed randomized controlled studies that had included 756 ibrutinib-treated and 749 comparator-treated patients with CLL/SLL or relapsed/refractory MCL. Safety analyses included reporting of AEs using crude and exposure-adjusted incidence rates. **Results:** The median treatment duration was 13.3 months (maximum, 28.2 months) for ibrutinib and 5.8 months (maximum, 27.3 months) for comparators. When adjusted for exposure, diarrhea, atrial fibrillation, and hypertension were the only common grade $\geq$ 3 AEs more often reported with ibrutinib than with the comparators. Dose reductions (7% vs. 14%) and discontinuation (12% vs. 16%) because of AEs occurred less often with ibrutinib, and deaths due to AEs occurred at similar rates (6% vs. 7%). When adjusted for exposure, the corresponding data were all lower with ibrutinib than with the comparators (0.06 vs. 0.22, 0.11 vs. 0.22, and 0.06 vs. 0.09 patient-exposure-years, respectively). The prevalence of common grade 3/4 AEs with ibrutinib generally decreased over time, with the exception of

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hypertension. **Conclusion:** These results from an integrated analysis support a favorable benefit/risk profile of ibrutinib in patients with CLL/SLL and MCL.

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Introduction

Ibrutinib, a first-in-class, once-daily inhibitor of Bruton's tyrosine kinase, has been approved by the US Food and Drug Administration for the treatment of patients with mantle cell lymphoma (MCL) who have received ≥ 1 prior therapy, patients with marginal zone lymphoma who require systemic therapy and have received ≥ 1 prior anti-CD20–based therapy, and patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Waldenström's macroglobulinemia, and chronic graft-versus-host disease after failure of ≥ 1 lines of systemic therapy.[1] Although chemotherapy is given for a finite number of cycles, ibrutinib is continued until progressive disease or unacceptable toxicity, leading to prolonged ibrutinib exposure.

The superiority of ibrutinib versus comparators has been reported in 4 phase III randomized controlled trials (RCTs) in patients with CLL/SLL or MCL (Supplemental Table 1; available in the online version).[2-5] The results from each of these RCTs, including detailed safety information, have been previously reported.[2-5] The aim of the present analysis was to expand on the previous findings and further characterize the adverse event (AE) profile of ibrutinib using safety data pooled across 4 RCTs involving previously untreated and relapsed/refractory patients who had received ≥ 1 therapy for CLL/SLL or ≥ 1 rituximab-containing therapy for MCL. The pooling of these studies increased the sample size and allowed for the inclusion of a comparator group for comprehensive analysis of the incidence and outcomes of common AEs and AEs of clinical interest with ibrutinib.

Patients and Methods

Study Design and Patients

The methods for each study have been previously reported in detail.[2-5] Briefly, RESONATE (PCYC-1112) included adult patients with CLL/SLL requiring treatment[6] who received ≥ 1 previous line of therapy.[2] RESONATE-2 (PCYC-1115) included patients aged ≥ 65 years with previously untreated CLL/SLL requiring treatment[6] (del[17p] excluded).[3] The HELIOS (CLL3001) included adult patients with CLL/SLL requiring treatment[6] (del[17p] excluded) who had received ≥ 1 previous line of systemic therapy.[4] The RAY study (MCL3001) included adult patients with MCL who had received ≥ 1 previous rituximab-containing chemotherapy.[5] The cutoff dates for each study included in the present analysis were November 6, 2013, for RESONATE; January 12, 2015, for HELIOS; April 22, 2015, for RAY; and May 4, 2015, for RESONATE-2. All studies were approved by the institutional review boards at each participating institution and conducted in accordance with the Declaration of Helsinki, and all patients provided written informed consent.

Randomization and Masking

In each of the RCTs, patients were randomly allocated 1:1 to the 2 treatment groups (additional information on randomization and masking has been provided in the Supplemental Appendix; available in the online version).

Procedures

In RESONATE, the patients were randomly assigned to oral ibrutinib versus intravenous (IV) ofatumumab. In RESONATE-2, patients were randomly assigned to oral ibrutinib versus oral chlorambucil. In HELIOS, all patients received IV bendamustine plus rituximab (BR) and were randomly assigned to oral ibrutinib or placebo starting on day 2 of cycle 1. In RAY, patients were randomly assigned to oral ibrutinib versus IV temsirolimus. In all 4 RCTs, crossover to the ibrutinib-containing arm was allowed after the development of progressive disease (PD; additional dosing information can be found in the Supplemental Appendix; available in the online version).

Outcomes

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA; version 19.0). Using the MedDRA hierarchy, the preferred terms for AEs were reported, and related preferred terms grouped into high-level terms (HLTs) were also reported for specific safety topics such as infections and cardiac events. In addition, the related HLTs were grouped into high-level group terms were reported for infections. AEs were also reported at the system organ class (SOC) level, which included the related high-level group terms. In RESONATE, data were collected according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0; version 4.03 was used in RESONATE-2, HELIOS, and RAY. In RESONATE, RESONATE-2, and HELIOS, hematologic AEs were graded according to the International Workshop on Chronic Lymphocytic Leukemia recommendations.[6] The following safety topics of interest with ibrutinib were examined (defined in the Supplemental Appendix; available in the online version): hematologic toxicities, diarrhea, infections, interstitial lung disease (ILD), atrial fibrillation, major hemorrhage, hypertension, second primary malignancies, and hepatobiliary disorders. Complete resolution was defined as resolution of all such AEs during the assessment period. Partial improvement was

defined as any ongoing AE with a decrease in toxicity grade compared with the first occurring event.

Statistical Analysis

Treatment-emergent AEs were examined using both crude (%) and exposure-adjusted incidence rates (EAIRs). EAIRs lend some perspective to comparisons between ibrutinib and comparators by accounting for differences in treatment duration or follow-up time between groups. The EAIR is defined as the number of patients with a specific event or group of events divided by the total exposure time among the patients in the treatment group at risk of an initial occurrence of the event. EAIRs are expressed in "patient-exposure-years" and as the difference (Δ) in EAIRs for ibrutinib versus comparators. Negative values for ΔEAIR indicate higher rates with comparators.

Results

In the present pooled analysis, 756 patients were treated with ibrutinib (469 as a single agent, 287 combined with BR), and 749 patients were treated with comparators (191 with ofatumumab, 132 with chlorambucil, 287 with placebo plus BR, 139 with temsirolimus). The baseline characteristics were similar between the 2 groups (Table 1). The median follow-up was similar for the 2 groups (≈16 months), although the median duration of study treatment was longer with ibrutinib (13.3 vs. 5.8 months; Table 2). Most patients continued receiving ibrutinib, with a low rate of treatment discontinuation compared with that reported for comparators (27% vs. 85%). The most common reason for discontinuation in both groups was PD (Table 2). The baseline characteristics and patient disposition for the individual studies are shown in Supplemental Tables 2 and 3; available in the online version.

Table 1 Baseline Disease Characteristics

Characteristic	Ibr (n = 756)	Comp (n = 749)
Age, y		
Median	67	67
Range	30-89	34-90
Age group, y		
≥ 65	482 (64)	461 (62)
≥ 75	158 (21)	152 (20)
Male gender	508 (67)	506 (68)
Race		
White	670 (89)	686 (92)
Black	21 (3)	18 (2)
Asian	29 (4)	12 (2)
Other	36 (5)	33 (4)
Region		
United States	165 (22)	148 (20)
Europe	434 (57)	430 (57)
Other	157 (21)	171 (23)
Histologic type		
CLL/SLL	617 (82)	610 (81)
MCL	139 (18)	139 (19)
Previous lines of therapy		
Median	2	2
Range	0-12	0-13
Medical history of cardiac disorders	17 (2)	18 (2)
ECOG PS		
0-1	743 (98)	736 (98)
> 1	13 (2)	13 (2)
CrCl < 60 mL/min	208 (28)	220 (29)
Hepatic impairment	120 (16)	107 (14)
Cytopenia (any of those listed)	456 (60)	485 (65)
Absolute neutrophil count ≤ 1.5 × 10^9/L	78 (10)	77 (10)
Hemoglobin ≤ 11 g/dL	253 (33)	271 (36)
Platelet count ≤ 100 × 10^9/L	208 (28)	199 (27)

Data presented as n (%) unless otherwise specified.
Abbreviations: CLL = chronic lymphocytic leukemia; Comp = comparator; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; Ibr = ibrutinib; MCL = mantle cell lymphoma; PS = performance status; SLL = small lymphocytic lymphoma.

Common AEs

The 3 most common SOCs of AEs reported with both ibrutinib and comparators were infections, gastrointestinal disorders, and general disorders/administration-site conditions (Table 3). Of the 22 most common AEs (≥ 10% of patients in either group based on individual preferred terms; Table 4), the rates of diarrhea, muscle spasms, and arthralgia were higher with ibrutinib than with the comparators when adjusted for exposure. The prevalence of the most common all-grade AEs with ibrutinib generally decreased over time, with the highest prevalence rates during months 0 to 3 (Supplemental Figure 1; available in the online version). The most common SOC of the AEs for the individual studies is shown in Supplemental Table 4 (available in the online version). The prevalence of all-grade AEs for the individual studies has been reported and was generally consistent with the findings of the present analysis.[2-5]

Grade 3/4 AEs

The 3 most common grade 3/4 AEs reported with ibrutinib and comparators were neutropenia, thrombocytopenia, and pneumonia (Table 5). Of the 11 most common grade 3/4 AEs (≥ 3% of patients in either group), the rate of diarrhea, atrial fibrillation, and hypertension were higher with ibrutinib than with the comparators when adjusted for exposure. The prevalence of grade 3/4 AEs with ibrutinib generally decreased over time, with the highest prevalence rates for most common grade 3/4 AEs during months 0 to 3, except for hypertension, with a prevalence of ~1% to 2% throughout the time periods examined, and neutropenic events, with a slightly higher prevalence during months 3 to 6 (Supplemental Figure 2; available in the online version). The most common grade 3/4 AEs from the individual studies have been previously reported, and the findings were generally consistent with those from the present analysis.[2-5]

Serious AEs

The most common serious AEs (SAEs) reported with ibrutinib and comparators were pneumonia and febrile neutropenia in both groups and atrial fibrillation with ibrutinib and pyrexia with

Table 2 Patient Disposition

Variable	Ibr (n = 756)	Comp (n = 749)
Continued treatment	554 (73)	116 (15)
Discontinued treatment	202 (27)	633 (85)
Progressive disease	80 (11)	232 (31)
Adverse event	69 (9)	106 (14)
Death	25 (3)	25 (3)
Investigator decision	4 (1)	58 (8)
Consent withdrawal	23 (3)	39 (5)
Completion of study treatment	0	172 (23)
Lost to follow-up	1 (< 1)	1 (< 1)
Follow-up duration, mo		
Median	16.6	16.1
Range	0.2-28.2	0.3-27.8
Treatment duration, mo		
Median	13.3	5.8
Range	0-28.2	0-27.3

Data are n (%) unless otherwise specified.
Abbreviations: Comp = comparator; Ibr = ibrutinib.

comparators (Table 6). SAEs generally reflected AEs requiring hospitalization/causing prolongation of existing hospitalization, causing permanent impairment/requiring intervention to avoid permanent impairment, could be life-threatening, or result in death. Of the 6 most common SAEs (≥ 2% of patients in either group), only the rate of atrial fibrillation was higher with ibrutinib than with the comparators when adjusted for exposure. The most common SAEs for the individual studies are shown in Supplemental Table 5 (available in the online version).

Dose Reductions, Discontinuations, and Deaths From AEs

In accordance with the US prescribing information, for management of grade ≥ 3 nonhematologic toxicities, grade ≥ 3 neutropenia with infection or fever, or grade 4 hematologic toxicities, ibrutinib should be interrupted until the AE has recovered to grade 1 or baseline. For recurring events, dose reductions are recommended for the second and third occurrence, and discontinuation for the fourth occurrence (dose modification guidance provided in Supplemental Table 6; available in the online version). Dose reductions due to AEs were less frequent for the ibrutinib-treated patients than for the comparator-treated patients (7% [n = 53] vs. 14% [n = 107]; EAIR, 0.06 vs. 0.22). The most common AEs leading to dose reductions (> 3 in either group) were neutropenia (n = 10) and diarrhea (n = 5) in ibrutinib-treated patients. In comparator-treated patients, the most common AEs leading to dose reductions included hematologic toxicities (neutropenia [n = 31], thrombocytopenia [n = 27], anemia [n = 10], platelet count decrease [n = 8], neutrophil count decrease [n = 4]), fatigue (n = 8), pyrexia (n = 4), and maculopapular rash (n = 4).

Discontinuations due to AEs were also less frequent in ibrutinib-treated than in comparator-treated patients (12% [n = 89] vs. 16% [n = 120]; EAIR, 0.11 vs. 0.22). The most common AEs leading to discontinuations (> 3 in either group) were pneumonia (n = 11), atrial fibrillation (n = 6), neutropenia (n = 5), and thrombocytopenia

Table 3 Most Common (≥ 10% in Either Pool) System Organ Classes of Adverse Events: Cumulative and Exposure-adjusted Incidence Rates

	Ibr (n = 756)		Comp (n = 749)			
Variable	%	EAIR	%	EAIR	Δ, %[a]	Δ, EAIR[a]
Any treatment-emergent adverse event	98	11.9532	97	15.1488	1.1	−3.1956
Musculoskeletal and connective tissue disorders	44	0.6264	32	0.5784	12.4	0.048
Eye disorders	31	0.3672	21	0.3372	10.3	0.03
Skin and subcutaneous tissue disorders	51	0.7656	43	0.888	8.4	−0.1224
Gastrointestinal disorders	69	1.5516	62	1.7568	7.3	−0.2052
Infections	70	1.3296	63	1.5996	6.7	−0.27
Vascular disorders	20	0.2112	14	0.222	5.9	−0.0108
Cardiac disorders	15	0.1488	10	0.1392	5.7	0.0096
Neoplasms, benign, malignant, and unspecified	11	0.1068	6	0.0876	4.9	0.0192
Renal and urinary disorders	13	0.1284	10	0.1428	3.4	−0.0144
Investigations	28	0.3228	26	0.4464	2.4	−0.1236
Psychiatric disorders	17	0.1680	15	0.2364	1.2	−0.0684
Injury, poisoning, and procedural complications	27	0.3048	26	0.4524	0.8	−0.1476
Respiratory, thoracic, and mediastinal disorders	47	0.6276	46	0.9576	0.6	−0.33
Metabolism and nutrition disorders	34	0.4116	34	0.636	0.2	−0.2244
Nervous system disorders	33	0.3996	33	0.606	−0.2	−0.2064
General disorders and administration site conditions	58	0.9720	59	1.5516	−1	−0.5796
Blood and lymphatic system disorders	55	0.9216	58	1.5276	−2.7	−0.606

Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib.
[a]Negative numbers indicate higher rates with comparator.

Table 4 Most Common (≥ 10% in Either Pool) All-grade Adverse Events: Cumulative and Exposure-adjusted Incidence Rates[a]

Variable	Ibr (n = 756)		Comp (n = 749)		Δ, %[a]	Δ, EAIR[a]
	%	EAIR	%	EAIR		
Hematologic adverse events						
Neutropenia	33	0.4116	34	0.6744	−0.2	−0.2628
Thrombocytopenia	21	0.222	25	0.4104	−4.2	−0.1884
Anemia	21	0.2244	27	0.4464	−6.1	−0.222
Nonhematologic adverse events						
Diarrhea	39	0.5172	22	0.36	16.7	0.1572
Muscle spasms	13	0.1308	5	0.078	7.7	0.0528
Arthralgia	13	0.1236	8	0.1128	4.7	0.0108
Back pain	11	0.1092	8	0.1092	3.6	0
Rash	12	0.1164	9	0.132	3.1	−0.0156
Pyrexia	22	0.2256	19	0.2988	2.8	−0.0732
Upper respiratory tract infection	17	0.1704	15	0.2208	2.2	−0.0504
Edema peripheral	13	0.1296	11	0.1692	1.6	−0.0396
Pneumonia	12	0.114	11	0.1524	1.5	−0.0384
Abdominal pain	10	0.0972	9	0.126	1.4	−0.0288
Headache	13	0.1284	12	0.1752	1.4	−0.0468
Vomiting	13	0.1332	13	0.1956	0.7	−0.0624
Constipation	15	0.1548	15	0.2256	0.6	−0.0708
Dyspnea	9	0.0864	11	0.1536	−1.6	−0.0672
Nausea	27	0.3192	29	0.5496	−1.7	−0.2304
Decreased appetite	11	0.1092	13	0.2004	−2.2	−0.0912
Pruritus	8	0.0708	10	0.1524	−2.8	−0.0816
Fatigue	25	0.2796	28	0.4836	−3.4	−0.204
Infusion-related reaction	6	0.0564	15	0.2436	−9.4	−0.1872

Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib.
[a]Based on individual preferred terms; negative numbers indicate higher rates with comparator.

Table 5 Most Common (≥ 3% in Either Pool) Grade 3/4 Adverse Events: Cumulative and Exposure-adjusted Incidence Rates

Variable	Ibr (n = 756)		Comp (n = 749)		Δ, %[a]	Δ, EAIR[a]
	%	EAIR	%	EAIR		
Grade 3/4 adverse events	70	1.3212	67	2.0496	2.3	−0.7284
Hematologic adverse events						
Febrile neutropenia	6	0.054	4	0.0612	1.4	−0.0072
Neutrophil count decreased	4	0.0324	3	0.0372	0.9	−0.0048
Neutropenia	29	0.336	29	0.54	−0.3	−0.204
Platelet count decreased	2	0.0156	3	0.0456	−1.6	−0.03
Anemia	5	0.0468	10	0.1464	−5.3	−0.0996
Thrombocytopenia	9	0.0888	16	0.2352	−6.6	−0.1464
Nonhematologic adverse events						
Hypertension	3	0.03	1	0.0132	2.4	0.0168
Atrial fibrillation	3	0.0252	1	0.0072	2.3	0.018
Pneumonia	8	0.0732	6	0.0876	1.6	−0.0144
Diarrhea	3	0.0276	2	0.024	1.3	0.0036
Fatigue	3	0.024	4	0.0552	−1.4	−0.0312

Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib.
[a]Negative numbers indicate higher rates with comparator.

Table 6 Most Common (≥ 2% in Either Pool) Serious Adverse Events: Cumulative and Exposure-adjusted Incidence Rates

	Ibr (n = 756)		Comp (n = 749)			
SAE	%	EAIR	%	EAIR	Δ, %[a]	Δ, EAIR[a]
Any SAE	47	0.5616	40	0.6792	7.2	−0.1176
Atrial fibrillation	3	0.0252	1	0.0108	2.0	0.0144
Pneumonia	8	0.078	7	0.0912	2.0	−0.0132
Febrile neutropenia	4	0.0408	4	0.054	0.6	−0.0132
Sepsis	2	0.0144	1	0.0204	0.1	−0.006
Pyrexia	3	0.024	3	0.0444	−0.6	−0.0204
Anemia	1	0.012	2	0.0336	−1.1	−0.0216

Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib; SAE = serious adverse event.
[a]Negative numbers indicate higher rates with comparator.

(n = 4) in ibrutinib-treated patients. In the comparator-treated patients, the most common AEs leading to discontinuations were neutropenia (n = 15), thrombocytopenia (n = 10), autoimmune hemolytic anemia (n = 5), fatigue (n = 8), pneumonia (n = 6), pyrexia (n = 5), peripheral edema (n = 4), pneumonitis (n = 4), and rash (n = 4). Grade 1/2 AEs accounted for 2% (n = 18) and 4% (n = 32) of maximum-grade ibrutinib and comparator discontinuations, respectively.

Deaths due to AEs were reported in 49 ibrutinib-treated patients (6%) and 49 comparator-treated patients (7%; EAIR, 0.06 vs. 0.09, respectively). The most common AEs leading to death (> 1 in either group) were sepsis (n = 6), pneumonia (n = 3), septic shock (n = 3), multiple organ dysfunction syndrome (n = 3), death (n = 3), cardiac arrest (n = 2), CLL (n = 2), myelodysplastic syndrome (n = 2), and renal failure (n = 2) in ibrutinib-treated patients. The most common AEs leading to death (> 1 in either group) were pneumonia (n = 6), sepsis (n = 4), CLL (n = 4), septic shock (n = 2), multiple organ dysfunction syndrome (n = 2), and ischemic stroke (n = 2) in the comparator-treated patients. Select safety topics of interest with ibrutinib were examined in detail for the pooled studies (Supplemental Table 7; available in the online version).

Hematologic Toxicities

Pooled hematologic toxicities were reported in 49% of ibrutinib-treated and 55% of comparator-treated patients (Supplemental Table 7; available in the online version). In ibrutinib-treated patients, the prevalence of hematologic toxicities was highest during months 0 to 3 (35%, all-grade; 23%, grade 3/4) and decreased over time. The median time to onset of the first hematologic toxicity was 1.0 month (median, 1.9 and 3.3 months to the first grade 3 and 4 event, respectively); 72% had complete resolution and 5% had partial improvement, with a median time from onset to resolution or improvement of 0.5 month. In the ibrutinib-treated patients, hematologic toxicities rarely led to discontinuation (n = 9 [1%]; most commonly, neutropenia [n = 5] and thrombocytopenia [n = 4]) and did not result in death. In the comparator-treated patients, hematologic toxicities led to treatment discontinuation in 27 patients (4%; most commonly, neutropenia [n = 15] and thrombocytopenia [n = 10]) and death for 1 patient (1%; febrile neutropenia).

The supportive measures for cytopenias in ibrutinib- and comparator-treated patients included growth factor support in 28% and 30%, red blood cell transfusions in 26% and 31%, immunoglobulin in 8% and 5%, and platelet transfusions in 6% and 8%, respectively. Among the ibrutinib-treated patients, most growth factor and blood support occurred in those treated with ibrutinib plus BR. In both groups, the mean platelet counts and hemoglobin levels increased over time, with a trend toward higher hemoglobin levels with ibrutinib throughout the study period evaluated. In comparator-treated patients, the mean neutrophil counts rapidly decreased by month 1 and did not improve to baseline levels through the last assessment (month 11). In the ibrutinib-treated patients, the mean neutrophil counts had decreased to less than the baseline levels beginning at month 3 but showed a trend toward returning to near baseline levels by month 11 (Supplemental Figure 3; available in the online version).

Infections

Infections were reported in 70% of ibrutinib-treated versus 63% of comparator-treated patients and were grade 3/4 in 23% versus 22%, respectively (Supplemental Table 7; available in the online version). In ibrutinib-treated patients, the prevalence of infections was highest during months 0 to 3 (41%, all-grade; 11%, grade 3/4) and generally decreased over time. The median time to the onset of first infection was 2.4 months (median, 3.5 and 3.7 months to the first grade 3 and 4 event, respectively); 76% had complete resolution, and 4% had partial improvement, with a median time from onset to resolution or improvement of 0.5 month. Despite prolonged treatment with ibrutinib, the rates of dose reductions (1% vs. 1%), discontinuation (4% vs. 3%), and death (2% vs. 3%) due to infection were similar with ibrutinib versus comparators (Supplemental Table 7; available in the online version).

Infections were further evaluated on a pathogen level, which showed that only mycobacterial infections occurred at a higher rate with ibrutinib than with comparators when adjusting for exposure (Supplemental Table 8; available in the online version). Hepatitis B virus reactivation occurred in 2 ibrutinib-treated patients (< 1%) and 3 comparator-treated patients (< 1%). Infections caused by atypical organisms were reported infrequently in both ibrutinib and comparator groups (Supplemental Table 8; available in the online version).

Diarrhea

Diarrhea was reported in 39% of ibrutinib-treated and 22% of comparator-treated patients. The prevalence of grade 3/4 diarrhea was uncommon (Supplemental Table 7; available in the online

version). In the ibrutinib-treated patients, the prevalence of all-grade diarrhea was highest during 0 to 3 months (29%) and markedly decreased over time (Supplemental Figure 1; available in the online version). The median time to the onset of first diarrhea was 0.7 month; 83% had complete resolution, and < 1% had partial improvement, with a median time from onset to resolution or improvement of 0.2 month. Dose reductions and discontinuation because of diarrhea were rare with ibrutinib (1% and < 1%) and comparators (< 1% and < 1%).

Hypertension

Hypertension was more frequently reported in ibrutinib-treated patients than in the comparator group. Grade 3/4 hypertension was reported in 4% versus 1%, respectively (Supplemental Table 7; available in the online version). In the ibrutinib-treated patients, the prevalence of all-grade hypertension (1%-4%) and grade 3/4 hypertension (1%-2%) fluctuated over time (Supplemental Figures 1 and 2; available in the online version). The median time to onset of first hypertension was 4.6 months; 38% had complete resolution and 1% had partial improvement, with a median time from onset to resolution of 0.4 month. Of 69 hypertension events that resolved or improved, 54 (78%) had resolved or improved after the patients had received medication for hypertension. No patient required a dose reduction for hypertension, and hypertension rarely resulted in discontinuation (n = 1; < 1% ibrutinib-treated patients; and no comparator-treated patient).

Cardiac AEs

Cardiac disorders were reported in 15% of ibrutinib-treated and 10% of comparator-treated patients (Table 3). In the ibrutinib-treated patients, the most common cardiac AEs were reported under the MedDRA HLT "supraventricular arrhythmias" (Supplemental Table 9; available in the online version). Atrial fibrillation comprised most of these supraventricular arrhythmias. Atrial fibrillation was reported in 6% of ibrutinib-treated versus 2% of comparator-treated patients; grade 3/4 atrial fibrillation occurred in 3% versus < 1%, respectively (Supplemental Table 7; available in the online version). In ibrutinib-treated patients, the prevalence of atrial fibrillation was greatest during months 0 to 3 (3%, all grade; 2%, grade 3/4) and generally decreased over time (Supplemental Figure 1; available in the online version). However, atrial fibrillation was observed during months ≥ 18 (1%, all-grade; 1%, grade 3/4). The median time to the onset of first atrial fibrillation was 2.8 months; 69% had complete resolution and 4% had partial improvement, with a median time from onset to resolution or improvement of 0.1 month. Atrial fibrillation infrequently resulted in discontinuation in ibrutinib-treated patients (n = 6 [1%] vs. no comparator-treated patient). No deaths or strokes resulted from atrial fibrillation.

Hepatobiliary Disorders

Hepatobiliary disorders were reported in 4% of ibrutinib-treated and 3% of comparator-treated patients (Supplemental Table 7; available in the online version). The median time to the onset of a first hepatobiliary disorder was 2.9 months; 59% had complete resolution, with a median time from onset to resolution of 0.5 month.

Grade 3/4 alanine transaminase, aspartate transaminase, and bilirubin (TBIL) increases were reported in 1% to 2% of patients in both groups. The grade 3/4 hepatobiliary AEs reported in > 1 ibrutinib-treated patients were hyperbilirubinemia (n = 5), toxic hepatitis (n = 2), and abnormal hepatic function (n = 2). Hepatobiliary disorders did not result in discontinuation or death in the ibrutinib-treated patients (Supplemental Table 7; available in the online version). Graphs of liver function laboratory values (alanine transaminase, aspartate transaminase, and TBIL) over time for each of the 4 RCTs are shown in Supplemental Figure 4 (available in the online version). The findings with TBIL did not translate into clinically significant outcomes, with the reported hepatic events similar between the ibrutinib and comparator arms.

Bleeding Events

Grade 1/2 and 3/4 bleeding (pooled individual AEs) was reported in 35% and 3% of ibrutinib-treated patients and 15% and 2% of comparator-treated patients, respectively (Table 7). The most common types of bleeding with ibrutinib were contusion (8%), epistaxis (7%), petechiae (6%), and hematoma (5%) and were primarily low grade.

Major hemorrhage (any preferred term in the substandardized MedDRA, query hemorrhage terms [excluding laboratory terms] that was grade ≥ 3, serious, or any grade central nervous system hemorrhage/hematoma) was infrequent and occurred at similar frequencies in both groups, with no differences between groups when adjusted for exposure (Table 7). The most common events of major hemorrhage included epistaxis (n = 2, ibrutinib; n = 6 comparator), postprocedural hematoma (n = 4, ibrutinib; n = 1,

Table 7 Bleeding Events: Cumulative and Exposure-adjusted Incidence Rates

Event	Ibr (n = 756)		Comp (n = 749)		Δ, %[a]	Δ, EAIR[a]
	%	EAIR	%	EAIR		
Any bleeding event[b]	38	0.486	17	0.2628	21.3	0.2232
Grade 3/4 bleeding event	3	0.0252	2	0.0276	0.8	−0.0024
Major hemorrhage	4	0.0348	3	0.0348	1.3	0
Grade 3/4 major hemorrhage	3	0.0252	2	0.0276	0.8	−0.0024

Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib.
[a]Negative numbers indicate higher rates with comparator.
[b]Based on the number of patients with any bleeding event by preferred term.

comparators), gastrointestinal hemorrhage (n = 2, ibrutinib; n = 3 comparators), subdural hematoma (n = 4, ibrutinib), and vitreous hemorrhage (n = 3, ibrutinib). In ibrutinib-treated patients, the prevalence of all-grade and grade 3/4 major hemorrhage remained stable over time (0.5%-2% for both all-grade and grade 3/4 events). The median time to onset of first major hemorrhage was 5.7 months, and 83% had complete resolution with a median time from onset to resolution or improvement of 0.2 month. Major hemorrhage infrequently resulted in discontinuation (1%) or death (< 1%) in ibrutinib-treated patients (Supplemental Table 7; available in the online version).

The results of a univariate Cox proportional hazards model showed that ibrutinib versus comparator treatment was not associated with major hemorrhage ($P = .6$; hazard ratio, 1.1; 95% confidence interval [CI], 0.7-1.9) in this data set. Anticoagulant and antiplatelet agents were used during treatment for 22% and 39% of ibrutinib-treated patients and 19% and 37% of comparator-treated patients, respectively. The rate of major hemorrhage with anticoagulant and/or antiplatelet use compared with no use of either agent was 5% versus 4% with ibrutinib (relative risk, 1.4; 95% CI, 0.7-2.7) and 3% versus 3% with comparators (relative risk, 1.2; 95% CI, 0.5-2.8), respectively. The risk of major hemorrhage was not significantly increased with anticoagulant/antiplatelet use in either the ibrutinib or comparator groups.

Interstitial Lung Disease

ILD was reported in 2% of ibrutinib-treated and 3% of comparator-treated patients (Supplemental Table 7; available in the online version). In the ibrutinib-treated patients, the prevalence of ILD was < 1% during each period examined. The median time to onset of first ILD was 6.0 months, and 40% had complete resolution, with a median time from onset to resolution of 0.4 month. ILD resulted in discontinuation or death in 0 and 1 (< 1%) ibrutinib-treated patients, respectively (vs. 6 [1%; most often pneumonitis] and 0 comparator-treated patients, respectively).

Second Primary Malignancies

The rate of second primary malignancies in the ibrutinib- and comparator-treated patients was 6% versus 2% for nonmelanoma skin cancer (most commonly basal cell carcinoma or squamous cell carcinoma with ibrutinib [n = 26 and n = 18, respectively] and comparator [n = 7 and n = 9, respectively]), 2% versus 1% for non-skin cancer (most commonly prostate cancer or myelodysplastic syndromes with ibrutinib [n = 3 and n = 2, respectively] and comparator [both, n = 2]), and < 1% each for melanoma (Supplemental Table 7; available in the online version).

Discussion

In the 4 RCTs, the superiority of ibrutinib versus the comparators was demonstrated in patients with CLL/SLL or MCL[2-5] and led to global approvals for these patient populations. Although AE data for each study have been reported separately, the present pooled analysis allowed for an in-depth assessment of the frequency and severity of common AEs and additional AEs of clinical interest. The most common AEs (≥ 20%) reported with ibrutinib were diarrhea, neutropenia, nausea, fatigue, pyrexia, anemia, and thrombocytopenia, all of which have been included in the ibrutinib prescribing information as common adverse reactions.[1] Although diarrhea was commonly reported with ibrutinib, it rarely resulted in ibrutinib discontinuation (< 1%), and most patients (83%) experienced complete resolution. The most common grade 3/4 AEs (≥ 5%) reported with ibrutinib were neutropenia, thrombocytopenia, pneumonia, febrile neutropenia, and anemia (the ibrutinib prescribing information also includes warnings and precautions for cytopenias and infections[1]). Although cytopenias (hematologic toxicities) were common in both groups, when adjusting for treatment exposure, the rates of all-grade and grade 3/4 hematologic toxicities with the comparators were nearly double those with ibrutinib (ΔEAIR, −0.66 and −0.44, respectively). Most hematologic events began in the first month of treatment, and the mean platelet counts and hemoglobin levels increased over time in both groups. Most ibrutinib-treated patients with hematologic toxicities had complete resolution (72%) and discontinuation was rare (1%). During ibrutinib therapy, patients should be monitored for cytopenias by monthly assessments of the complete blood count.

Pneumonia was the only grade 3/4 infection that occurred in ≥ 3% in either group. When pooled, all-grade infections were commonly reported with both ibrutinib and comparators. When adjusting for treatment exposure, the rates of all-grade and grade 3/4 infections were lower with ibrutinib (ΔEAIR, −0.27 and −0.09, respectively). Hepatitis B virus reactivations have been reported in patients treated with ibrutinib, although our analysis showed that these events are rare (< 1%) in the clinical trial setting for both ibrutinib and comparator groups. Recent reports have focused on select cases of severe fungal infections in ibrutinib-treated patients.[7-9] In our analysis, severe fungal infections were rare, with a similar incidence of all fungal infections between ibrutinib and the comparators. Only mycobacterial infections were higher with ibrutinib when adjusting for exposure (ΔEAIR, < 0.01). In patients with an increased risk of opportunistic infections, prophylaxis should be considered according to standard institutional practices. Most ibrutinib-treated patients with infections had complete resolution. Despite prolonged treatment with ibrutinib, the rates of discontinuation (4% vs. 3%) or death (2% vs. 3%) due to infections were similarly low with ibrutinib compared with the comparators.

Higher crude incidence rates and EAIRs were reported with ibrutinib than with comparators for grade 3/4 diarrhea (3% vs. 2%; ΔEAIR, < 0.01), atrial fibrillation (3% vs. 1%; ΔEAIR, 0.02), and hypertension (3% vs. 1%; ΔEAIR, 0.02). Atrial fibrillation and hypertension are also included in the ibrutinib prescribing information warnings and precautions.[1] It has been demonstrated in population-based studies that patients with cancer have an increased risk of atrial fibrillation compared with age- and gender-matched control cohorts.[10,11] A retrospective analysis of a general cohort of patients with CLL showed that 6% of patients with newly diagnosed CLL had a history of atrial fibrillation and that another 6% without such a history developed atrial fibrillation during the subsequent follow-up period.[12] Although this previously published retrospective analysis included patients with CLL and did not include patients with MCL, it highlights the underlying risk of atrial fibrillation based on patient- and disease-related factors. The incidence of all-grade atrial fibrillation in the present analysis was reported more often in the ibrutinib- than in the comparator-treated

patients (6% vs. 2%; ΔEAIR, 0.03). However, most ibrutinib-treated patients with atrial fibrillation had complete resolution, and discontinuation (1%) because of atrial fibrillation was uncommon. Reports have shown higher discontinuation rates (46%) in patients receiving ibrutinib; however, it is important to consider that more than one fourth of patients experiencing atrial fibrillation had a history of atrial fibrillation and risk factors for atrial fibrillation (eg, hypertension, valvular dysfunction, clinical congestive heart failure, angina, and recent infection).[13] A detailed analysis of atrial fibrillation from the 4 RCTs with ibrutinib has recently been reported and suggested that, in the clinical trial setting, atrial fibrillation was manageable with commonly used anticoagulant and/or antiplatelet agents and without ibrutinib discontinuation for most patients with atrial fibrillation.[14] Patients treated with ibrutinib should be monitored clinically for atrial fibrillation, and electrocardiography should be performed for those who develop arrhythmic symptoms or new-onset dyspnea. Dose modifications in accordance with the US prescribing information guidelines should be considered for patients with persistent atrial fibrillation. Studies have shown that approximately one half of patients with CLL have hypertension at the time of CLL diagnosis,[15,16] and management of hypertension is common for such patients.[17] In the present pooled analysis, the prevalence of all-grade and grade 3/4 hypertension in ibrutinib-treated patients fluctuated over time; 1 patient discontinued because of hypertension. However, approximately one third of patients experienced complete resolution. Patients should be monitored for new-onset hypertension or existing hypertension during ibrutinib therapy, and antihypertensive treatments should be initiated or adjusted, as appropriate, for individual patients.

Hemorrhage has been cited as both a common adverse reaction and included in the warnings and precautions in the ibrutinib prescribing information.[1] In the present analysis, the incidence of any-grade bleeding was higher with ibrutinib than with comparator-treated patients. However, such an increase was only apparent with low-grade bleeding events. Major hemorrhage was infrequent in both ibrutinib- and comparator-treated patients (4% vs. 3%). After adjusting for exposure, the rate of major hemorrhage was the same. A recent retrospective analysis of the Surveillance, Epidemiology, End Results—Medicare database demonstrated that the risk of major hemorrhage for patients with CLL/SLL or MCL is ≈8 times higher than that in age- and gender-matched general population.[18] Most ibrutinib-treated patients who experienced major hemorrhage had complete resolution (83%), and discontinuation (1%) or death (< 1%) because of major hemorrhage was uncommon. When assessing the crude incidence rates, the association did not reach statistical significance between the concomitant use of anticoagulant and/or antiplatelet agents and an increased risk of major hemorrhage for either ibrutinib or the comparators. These findings are consistent with previous reports showing that major hemorrhage is infrequent in patients receiving concomitant anticoagulants and/or antiplatelet agents.[4,19] Additionally, the risk of major hemorrhage was not different between patients receiving ibrutinib and those receiving a comparator on univariate analysis.[20] Patients receiving these agents during ibrutinib therapy should be monitored closely for signs of bleeding. In addition, withholding ibrutinib for ≥ 3 to 7 days before and after surgery should be considered, depending on the type of procedure and the potential risks of bleeding.

The potential limitations of the present analysis included pooling of studies across different disease states, doses, and treatment regimens, limiting the applicability of the data. Additionally, including the EAIR lends perspective to comparisons between groups by accounting for differences in drug exposure for ibrutinib versus comparators (median, 13.3 vs. 5.8 months). However, it is limited in that it restricts the analysis to the first event and ignores the existence of later (multiple) events, because these cannot be assumed to have occurred independently of previous events.[21] Thus, the EAIR assumes the risk of an event occurring is constant over time, which might or might not have been the case for all events described.

Conclusion

Overall, the results from the present pooled safety analysis from 4 RCTs of ibrutinib in patients with CLL/SLL and MCL indicate a favorable safety profile compared with that of other standard treatments, despite prolonged ibrutinib therapy. Reported AEs with ibrutinib were primarily grade 1/2 and generally decreased in prevalence during the treatment course. With the exception of hypertension, the AEs of clinical interest resolved in most ibrutinib-treated patients with limited treatment discontinuations, dose reductions, or deaths from AEs.

Clinical Practice Points

- Ibrutinib, a first-in-class inhibitor of Bruton's tyrosine kinase, has become a standard treatment for patients with CLL/SLL and MCL.
- The present comprehensive safety analysis comprising pooled data from 4 RCTs involving patients with CLL/SLL or relapsed/refractory MCL has demonstrated a favorable safety profile for ibrutinib compared with that of other standard treatments, despite prolonged treatment.
- AEs with ibrutinib were primarily grade 1/2 and generally decreased in prevalence during the treatment course.
- Except for hypertension, the AEs of clinical interest resolved in most ibrutinib-treated patients, with limited treatment discontinuations, dose reductions, or deaths from AEs.

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Supplemental Data

Supplemental data accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2018.06.016.

References

1. *IMBRUVICA® (ibrutinib) prescribing information*. Sunnyvale, CA: Pharmacyclics, LLC; 2018.
2. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* 2014; 371:213-23.
3. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med* 2015; 373:2425-37.
4. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol* 2016; 17: 200-11.
5. Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet* 2016; 387:770-8.
6. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008; 111:5446-56.
7. Ahn IE, Jerussi T, Farooqui M, Tian X, Wiestner A, Gea-Banacloche J. Atypical *Pneumocystis jirovecii* pneumonia in previously untreated patients with CLL on single-agent ibrutinib. *Blood* 2016; 128:1940-3.
8. Okamoto K, Proia LA, Demarais PL. Disseminated cryptococcal disease in a patient with chronic lymphocytic leukemia on ibrutinib. *Case Rep Infect Dis* 2016; 2016:1-3.
9. Kreiniz N, Bejar J, Polliack A, Tadmor T. Severe pneumonia associated with ibrutinib monotherapy for CLL and lymphoma. *Hematol Oncol* 2018; 36:349-54.
10. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol* 2014; 63:945-53.
11. Erichsen R, Christiansen CF, Mehnert F, Weiss NS, Baron JA, Sorensen HT. Colorectal cancer and risk of atrial fibrillation and flutter: a population-based case-control study. *Intern Emerg Med* 2012; 7:431-8.
12. Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). *Leuk Lymphoma* 2017; 58:1630-9.
13. Thompson PA, Levy V, Tam CS, et al. Atrial fibrillation in CLL patients treated with ibrutinib: an international retrospective study. *Br J Haematol* 2016; 175:462-6.
14. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. *Haematologica* 2017; 102:1796-805.
15. Thurmes P, Call T, Slager S, et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. *Leuk Lymphoma* 2008; 49:49-56.
16. Blankart CR, Koch T, Linder R, Verheyen F, Schreyogg J, Stargardt T. Cost of illness and economic burden of chronic lymphocytic leukemia. *Orphanet J Rare Dis* 2013; 8:32.
17. Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. *Br J Haematol* 2007; 139:255-64.
18. Gifkins DM, Matcho A, Yang H, Xu Y, Gooden MA, Wildgust M. Incidence of major hemorrhage among CLL and MCL patients compared to the general elderly population: an analysis of the US SEER-Medicare linked database. *Blood* 2015; 126:3268.
19. Jones JA, Hillmen P, Coutre S, et al. Use of anticoagulants and antiplatelet in patients with chronic lymphocytic leukaemia treated with single-agent ibrutinib. *Br J Haematol* 2017; 178:286-91.
20. Brown JR, Moslehi J, Ewer MS, et al. Incidence of and risk factors for major hemorrhage in patients treated with ibrutinib: results from an integrated analysis. *Blood* 2017; 130:1743.
21. He X, Chen L, Lei L, Xia HA, Lee MLT. A simple method for estimating confidence intervals for exposure adjusted incidence rate and its applications to clinical trials. *J Biom Biostat* 2015; 6:238.

Supplemental Appendix

Randomization and Masking

In RESONATE, the patients were stratified by resistance to purine analogue chemoimmunotherapy (yes vs. no) and del(17p) (yes vs. no). In RESONATE-2, patients were stratified by Eastern Cooperative Oncology Group performance status (0-1 vs. 2), and Rai stage (0-II vs. III-IV). In HELIOS, patients were stratified by purine analogue refractory status (yes vs. no) and the number of previous lines of therapy (1 vs. $>$ 1). In RAY, patients were stratified by the number of previous lines of therapy (1 vs. 2 vs. $>$ 2) and the simplified mantle cell lymphoma international prognostic index score (0-3 vs. 4-5 vs. 6-11).

Additional dosing information for each study follows:

- RESONATE

  Oral ibrutinib 420 mg/d until progressive disease (PD) or unacceptable toxicity compared with intravenous (IV) ofatumumab for $\leq$ 24 weeks at an initial dose of 300 mg at week 1, followed by 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks (approved dosing)
- RESONATE-2

  Oral ibrutinib 420 mg/d until PD or unacceptable toxicity compared with oral chlorambucil for $\leq$ 12 cycles of 28 days (0.5 mg/kg on days 1 and 15, increased to a maximum of 0.8 mg/kg as tolerated)
- HELIOS

  All patients received IV BR (bendamustine plus rituximab) for a maximum of six 28-day cycles (B, 70 mg/m^2 on days 2-3 of cycle 1 and days 1-2 of cycles 2-6; R, 375 mg/m^2 on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2-6)

  The patients were randomized to also receive either oral ibrutinib 420 mg/d or placebo starting on day 2 of cycle 1 until PD or unacceptable toxicity (single-agent ibrutinib or placebo after the end of BR treatment)
- RAY

  Oral ibrutinib 560 mg/d compared with IV temsirolimus on days 1, 8, and 15 of 21-day cycles (175 mg in cycle 1; 75 mg in cycles $\geq$ 2) until PD or unacceptable toxicity

The safety topics of interest were defined as follows:

- Hematologic toxicities: preferred terms (PTs) of anemia, thrombocytopenia, neutropenia, or febrile neutropenia
- Diarrhea: PT
- Infections: system organ class
- Interstitial lung disease: narrow standardized Medical Dictionary for Regulatory Activities query defined as PTs of pneumonitis, interstitial lung disease, bronchiolitis, pulmonary fibrosis, and lung infection
- Atrial fibrillation: PT
- Major hemorrhage: any PT in the sub standardized Medical Dictionary for Regulatory Activities query hemorrhage terms (excluding laboratory terms) that was grade $\geq$ 3, serious, and/or central nervous system hemorrhage/hematoma
- Hypertension: PTs of hypertension, essential hypertension, hypertensive crisis, blood pressure increase, systolic hypertension, retinopathy hypertensive
- Second primary malignancies: nonmelanoma skin cancer (grouped PT terms); melanoma skin cancer (grouped PT terms); non-skin cancer (grouped PT terms)
- Hepatobiliary disorders: system organ class

Supplemental Table 1 Phase III Studies of CLL/SLL and MCL—Key Efficacy Results From Primary Analysis

Variable	PCYC-1112[a]	PCYC-1115[b]	CLL3001[c]	MCL3001[d]
Patient population	R/R CLL/SLL	TN CLL/SLL; age ≥65 y	R/R CLL	R/R MCL
Comparators	Ibr vs. Ofa	Ibr vs. Cbl	BR + Ibr vs. BR	Ibr vs. Tem
Progression-free survival	HR, 0.22; $P < .01$	HR, 0.16; $P < .01$	HR, 0.203; $P < .01$	HR, 0.43; $P < .01$
Overall survival	HR, 0.43; $P < .01$	HR, 0.16; $P < .01$	NR	NR

Abbreviations: BR = bendamustine, rituximab; Cbl = chlorambucil; CLL = chronic lymphocytic leukemia; HR = hazard ratio; Ibr = ibrutinib; MCL = mantle cell lymphoma; NR = not reported; Ofa = ofatumumab; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma; Tem = temsirolimus; TN = treatment naive.

[a]Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* 2014; 371:213-23.
[b]Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med* 2015; 373:2425-37.
[c]Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol* 2016; 17:200-11.
[d]Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet* 2016; 387:770-8.

Supplemental Table 2 Baseline Disease Characteristics in Individual Studies

Characteristic	PCYC-1112		PCYC-1115		CLL3001		MCL3001	
	Ibr (n = 195)	Ofa (n = 191)	Ibr (n = 135)	Cbl (n = 132)	Ibr + BR (n = 287)	BR (n = 287)	Ibr (n = 139)	Tem (n = 139)
Age, y								
Median	67	67	73	72.5	64	63	67	68
Range	30-86	37-88	65-89	65-90	31-86	36-83	39-84	34-88
Age group, y								
≥ 65	118 (61)	117 (61)	135 (100)	132 (100)	143 (50)	127 (44)	86 (62)	85 (61)
≥ 75	43 (22)	36 (19)	46 (34)	47 (36)	40 (14)	36 (13)	29 (21)	33 (24)
Male gender	129 (66)	132 (69)	88 (65)	80 (61)	191 (67)	188 (66)	100 (72)	106 (76)
Race								
White	174 (89)	172 (90)	119 (88)	125 (95)	262 (91)	262 (91)	115 (83)	127 (91)
Black	8 (4)	9 (5)	5 (4)	3 (2)	8 (3)	6 (2)	0 (0)	0 (0)
Asian	3 (2)	2 (1)	9 (7)	3 (2)	1 (<1)	2 (1)	16 (12)	5 (4)
Other	10 (5)	8 (4)	2 (1)	1 (1)	16 (6)	17 (6)	8 (6)	7 (5)
Region								
United States	96 (49)	93 (49)	31 (23)	29 (22)	38 (13)	26 (9)	0 (0)	0 (0)
Non—United States	99 (51)	98 (51)	104 (77)	103 (78)	249 (87)	261 (91)	139 (100)	139 (100)
Histologic type								
CLL/SLL	195 (100)	191 (100)	135 (100)	132 (100)	287 (100)	287 (100)	0 (0)	0 (0)
MCL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	139 (100)	139 (100)
Previous lines of therapy								
Median	3	2	0	0	2	2	2	2
Range	1-12	1-13	0-0	0-0	1-11	1-9	1-9	1-9
Medical history of cardiac disorders	4 (2)	6 (3)	2 (1)	4 (3)	7 (2)	4 (1)	4 (3)	4 (3)
ECOG PS								
0-1	195 (100)	191 (100)	123 (91)	121 (92)	287 (100)	287 (100)	138 (99)	137 (99)
> 1	0 (0)	0 (0)	12 (9)	11 (8)	0 (0)	0 (0)	1 (1)	2 (1)
CrCl < 60 mL/min	62 (32)	59 (31)	60 (44)	67 (51)	56 (20)	54 (19)	30 (22)	40 (29)
Hepatic impairment	45 (23)	40 (21)	15 (11)	4 (3)	40 (14)	44 (15)	20 (14)	19 (14)

Data presented as n (%) unless otherwise specified.
Abbreviations: BR = bendamustine, rituximab; Cbl = chlorambucil; CLL = chronic lymphocytic leukemia; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; Ibr = ibrutinib; MCL = mantle cell lymphoma; Ofa = ofatumumab; PS = performance status; SLL = small lymphocytic lymphoma; Tem = temsirolimus.

Supplemental Table 3 Patient Disposition in Individual Studies

	PCYC-1112		PCYC-1115		CLL3001		MCL3001	
Variable	**Ibr (n = 195)**	**Ofa (n = 191)**	**Ibr (n = 135)**	**Cbl (n = 132)**	**Ibr + BR (n = 287)**	**BR (n = 287)**	**Ibr (n = 139)**	**Tem (n = 139)**
Continued treatment	168 (86)	1 (1)	118 (87)	0 (0)	203 (71)	100 (35)	65 (47)	15 (11)
Discontinued treatment	27 (14)	190 (99)	17 (13)	132 (100)	84 (29)	187 (65)	74 (53)	74 (89)
Progressive disease	9 (5)	38 (20)	2 (1)	6 (5)	14 (5)	130 (45)	55 (40)	58 (42)
Adverse event	8 (4)	7 (4)	12 (9)	30 (23)	40 (14)	33 (11)	9 (6)	36 (26)
Death	8 (4)	9 (5)	2 (1)	0 (0)	9 (3)	8 (3)	6 (4)	8 (6)
Investigator decision	1 (1)	11 (6)	0 (0)	37 (28)	3 (1)	4 (1)	0 (0)	6 (4)
Consent withdrawal	1 (1)	6 (3)	1 (1)	6 (5)	17 (6)	11 (4)	4 (3)	16 (12)
Completion of study treatment	0 (0)	119 (62)	0 (0)	53 (40)	0 (0)	0 (0)	0 (0)	0 (0)
Lost to follow-up	0 (0)	0 (0)	0 (0)	0 (0)	1 (< 1)	1 (< 1)	0 (0)	0 (0)
Time in study, mo								
Median	9.6	9.3	18.5	18.4	17.1	16.9	20.4	19.7
Range	0.3-16.6	0.5-16.5	0.7-24.8	0.9-24.2	0.2-27.1	1.0-27.8	0.2-28.2	0.3-27.7
Treatment duration, mo								
Median	8.6	5.3	17.4	7.1	14.7	12.8	14.4	3.0
Range	0.2-16.1	0-7.4	0.7-24.7	0.5-11.7	0.2-27.1	0.2-27.3	0-28.2	0-27.0

Data presented as n (%) unless otherwise specified.
Abbreviations: BR = bendamustine, rituximab; Cbl = chlorambucil, Ibr = ibrutinib; Ofa = ofatumumab; Tem = temsirolimus.

Supplemental Table 4 Most Common (≥ 10% With Either Arm in Pooled Analysis) System Organ Classes of Adverse Events in Individual Studies: Cumulative Rates

	PCYC-1112		PCYC-1115		CLL3001		MCL3001	
Variable	Ibr (n = 195)	Ofa (n = 191)	Ibr (n = 135)	Cbl (n = 132)	Ibr + BR (n = 287)	BR (n = 287)	Ibr (n = 139)	Tem (n = 139)
Any adverse event	99	98	99	94	97	97	99	99
Infections and infestations	71	55	66	51	70	70	70	71
GI disorders	79	54	72	63	67	59	57	79
General disorders and administration site conditions	58	54	62	56	57	59	55	71
Blood and lymphatic system disorders	50	35	43	48	73	70	40	75
Skin and subcutaneous tissue disorders	56	47	55	30	50	43	43	50
Respiratory, thoracic, and mediastinal disorders	49	43	46	39	44	47	46	44
Musculoskeletal and connective tissue disorders	48	36	53	27	41	31	37	35
Metabolism and nutrition disorders	27	19	33	23	38	34	37	63
Nervous system disorders	33	30	35	33	34	33	27	37
Eye disorders	34	18	55	23	23	23	22	19
Investigations	18	16	31	23	30	24	38	45
Injury, poisoning, and procedural complications	21	37	34	16	30	28	23	19
Vascular disorders	11	10	23	13	25	18	21	14
Psychiatric disorders	16	14	18	14	19	15	12	20
Cardiac disorders	12	8	19	5	19	11	9	14
Renal and urinary disorders	9	6	19	14	14	8	12	14
Neoplasms, benign, malignant, and unspecified	11	6	21	7	9	9	6	1

Data presented as percentages.
Abbreviations: BR = bendamustine, rituximab; Cbl = chlorambucil; GI = gastrointestinal; Ibr = ibrutinib; Ofa = ofatumumab; Tem = temsirolimus.

Supplemental Table 5 Most Common (≥ 2% With Either Arm in Pooled Analysis) Serious Adverse Events in Individual Studies: Cumulative Rates

	PCYC-1112		PCYC-1115		CLL3001		MCL3001	
SAE	Ibr (n = 195)	Ofa (n = 191)	Ibr (n = 135)	Cbl (n = 132)	Ibr + BR (n = 287)	BR (n = 287)	Ibr (n = 139)	Tem (n = 139)
Any SAE	42	30	41	25	52	44	48	58
Pneumonia	9	7	6	1	9	9	9	6
Febrile neutropenia	2	2	1	1	9	8	1	1
Atrial fibrillation	3	1	1	1	3	1	4	1
Pyrexia	4	2	1	4	3	3	2	5
Sepsis	1	1	0	0	2	1	3	4
Anemia	1	2	1	1	1	2	2	4

Data presented as percentages.
Abbreviations: BR = bendamustine, rituximab; Cbl = chlorambucil; Ibr = ibrutinib; Ofa = ofatumumab; SAE = serious adverse event; Tem = temsirolimus.

Supplemental Table 6 Recommended Dose Modifications From Ibrutinib Prescribing Information

Toxicity Occurrence	MCL and MZL Dose Modification After Recovery (Starting Dose, 560 mg)	CLL/SLL and WM Dose Modification After Recovery (Starting Dose, 420 mg)
First	Restart at 560 mg/d	Restart at 420 mg/d
Second	Restart at 420 mg/d	Restart at 280 mg/d
Third	Restart at 280 mg/d	Restart at 140 mg/d
Fourth	Discontinue ibrutinib	Discontinue ibrutinib

Abbreviations: CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; SLL = small lymphocytic lymphoma; WM = Waldenström's macroglobulinemia.

Supplemental Table 7 Adverse Events of Interest in Pooled Analysis: Cumulative and Exposure-adjusted Incidence Rates

Variable	Ibr (n = 756)		Comp (n = 749)		Δ, %[a]	Δ, EAIR[a]
	%	EAIR	%	EAIR		
Hematologic toxicity	49	0.7332	55	1.3896	−5.9	−0.6564
Grade 3/4	36	0.456	43	0.8976	−7.0	−0.4416
SAE	7	0.0636	8	0.1104	−0.8	−0.0468
Led to dose reduction	2	0.0168	8	0.1188	−6.4	−0.102
Led to discontinuation	1	0.0108	4	0.0492	−2.4	−0.0384
Death	0	0	< 1	0.0024	−0.1	−0.0024
Diarrhea	39	0.5172	22	0.36	16.7	0.1572
Grade 3/4	3	0.0276	2	0.024	1.3	0.0036
SAE	1	0.0096	1	0.0108	0.3	−0.0012
Led to dose reduction	1	0.006	< 1	0.0036	0.4	0.0024
Led to discontinuation	< 1	0.0024	< 1	0.0024	0.2	0
Death	0	0	0	0	0	0
Infection	70	1.3296	63	1.5996	6.6	−0.27
Grade 3/4	23	0.24	22	0.3336	1.5	−0.0936
SAE	22	0.2196	20	0.2964	2.0	−0.0768
Led to dose reduction	1	0.006	1	0.0132	−0.2	−0.0072
Led to discontinuation	4	0.0312	3	0.0396	0.7	−0.0084
Death	2	0.0216	3	0.036	−0.3	−0.0144
Interstitial lung disease	2	0.018	3	0.0384	−0.8	−0.0204
Grade 3/4	1	0.0048	1	0.0144	−0.6	−0.0096
SAE	< 1	0.0036	1	0.0168	−0.8	−0.0132
Led to dose reduction	< 1	0.0012	< 1	0.006	−0.3	−0.0048
Led to discontinuation	0	0	1	0.0108	−0.8	−0.0108
Death	< 1	0.0012	0	0	0.1	0.0012
Atrial fibrillation	6	0.0552	2	0.0216	4.4	0.0336
Grade 3/4	3	0.0252	< 1	0.0072	2.3	0.018
SAE	3	0.0252	1	0.0252	2.0	0
Led to dose reduction	0	0	0	0	0	0
Led to discontinuation	1	0.0072	0	0	0.8	0.0072
Death	0	0	0	0	0	0
Major hemorrhage	4	0.0348	3	0.0348	1.3	0
Grade 3/4	3	0.0252	2	0.0276	0.8	−0.0024
SAE	3	0.0312	2	0.0216	1.8	0.0096
Led to dose reduction	< 1	0.0012	0	0	0.1	0.0012
Led to discontinuation	1	0.0084	< 1	0.0036	0.6	0.0048
Death	< 1	0.0036	0	0	0.4	0.0036
Hypertension	10	0.0912	3	0.048	6.0	0.0432
Grade 3/4	4	0.0336	1	0.0168	2.5	0.0168
SAE	1	0.0072	0	0	0.8	0.0072
Led to dose reduction	0	0	0	0	0	0
Led to discontinuation	< 1	0.0012	0	0	0.1	0.0012
Death	0	0	0	0	0	0
Nonmelanoma skin cancer	6	0.0588	2	0.0312	4.0	0.0276
Grade 3/4	1	0.012	< 1	0.0072	0.8	0.0048
SAE	2	0.0168	1	0.0108	1.1	0.006
Led to dose reduction	0	0	0	0	0	0
Led to discontinuation	< 1	0.0024	< 1	0.006	−0.1	−0.0036
Death	0	0	< 1	0.0024	−0.1	−0.0024

Supplemental Table 7 Continued

Variable	Ibr (n = 756)		Comp (n = 749)		Δ, %[a]	Δ, EAIR[a]
	%	EAIR	%	EAIR		
Melanoma skin cancer	< 1	0.0012	< 1	0.0024	0	−0.0012
Grade 3/4	< 1	0.0012	0	0	0.1	0.0012
SAE	< 1	0.0012	< 1	0.0024	0	−0.0012
Led to dose reduction	0	0	0	0	0	0
Led to discontinuation	< 1	0.0012	0	0	0.1	0.0012
Death	0	0	0	0	0	0
Non−skin cancer (malignant)	2	0.0168	1	0.0204	0.4	−0.0036
Grade 3/4	1	0.0132	1	0.0096	0.8	0.0036
SAE	2	0.0168	1	0.1068	1.1	−0.09
Led to dose reduction	0	0	0	0	0	0
Led to discontinuation	1	0.006	1	0.0072	0.2	−0.0012
Death	1	0.0048	< 1	0.0024	0.1	0.0024
Hepatobiliary disorders	4	0.0384	3	0.0384	1.4	0
Grade 3/4	1	0.0132	1	0.0108	0.7	0.0024
SAE	1	0.0048	1	0.0168	−0.7	−0.012
Led to dose reduction	0	0	< 1	0.0012	−0.1	−0.0012
Led to discontinuation	0	0	< 1	0.0036	−0.3	−0.0036
Death	0	0	< 1	0.0036	−0.3	−0.0036

Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib; SAE = serious adverse event.
[a]Negative numbers indicate greater rates with comparator.

Supplemental Table 8 Additional Infection Types of Interest (High-level Group Terms and High-level Terms) in Pooled Analysis: Cumulative and Exposure-adjusted Incidence Rates

Infection Types of Interest	Ibr (n = 756)		Comp (n = 749)		Δ, %[a]	Δ, EAIR[a]
	%	EAIR	%	EAIR		
Mycobacterial infectious disorders	1	0.006	0	0	0.7	0.006
Mycoplasma infectious disorders	0	0	< 1	0.0024	−0.1	−0.0024
Bacterial infectious disorders	12	0.1152	8	0.12	3.5	−0.0048
Infection, pathogen unspecified	63	1.0716	54	1.2144	9.3	−0.1428
Skin structures and soft tissue infections	9	0.084	5	0.0636	4.4	0.0204
Central nervous system and spinal infections	< 1	0.0012	0	0	0.1	0.0012
Sepsis, bacteremia, viremia, and fungemia NEC	4	0.036	3	0.042	0.9	−0.006
Urinary tract infections	9	0.0876	7	0.1008	2.2	−0.0132
Lower respiratory tract and lung infections	20	0.2076	17	0.2616	3.3	−0.054
Fungal infectious disorders	7	0.0684	6	0.0876	1.1	−0.0192
Aspergillus infections	1	0.0048	< 1	0.006	0.1	−0.0012
Pneumocystis infections	1	0.0048	< 1	0.006	0.1	−0.0012
Viral infectious disorders	17	0.1668	18	0.2832	−1.5	−0.1164
Polyomavirus infections	< 1	0.0012	0	0	0.1	0.0012
Epstein-Barr viral infections	< 1	0.0012	0	0	0.1	0.0012
Cytomegalovirus infections	< 1	0.0024	< 1	0.006	−0.1	−0.0036
Hepatitis viral infections	< 1	0.0024	1	0.0072	−0.2	−0.0048

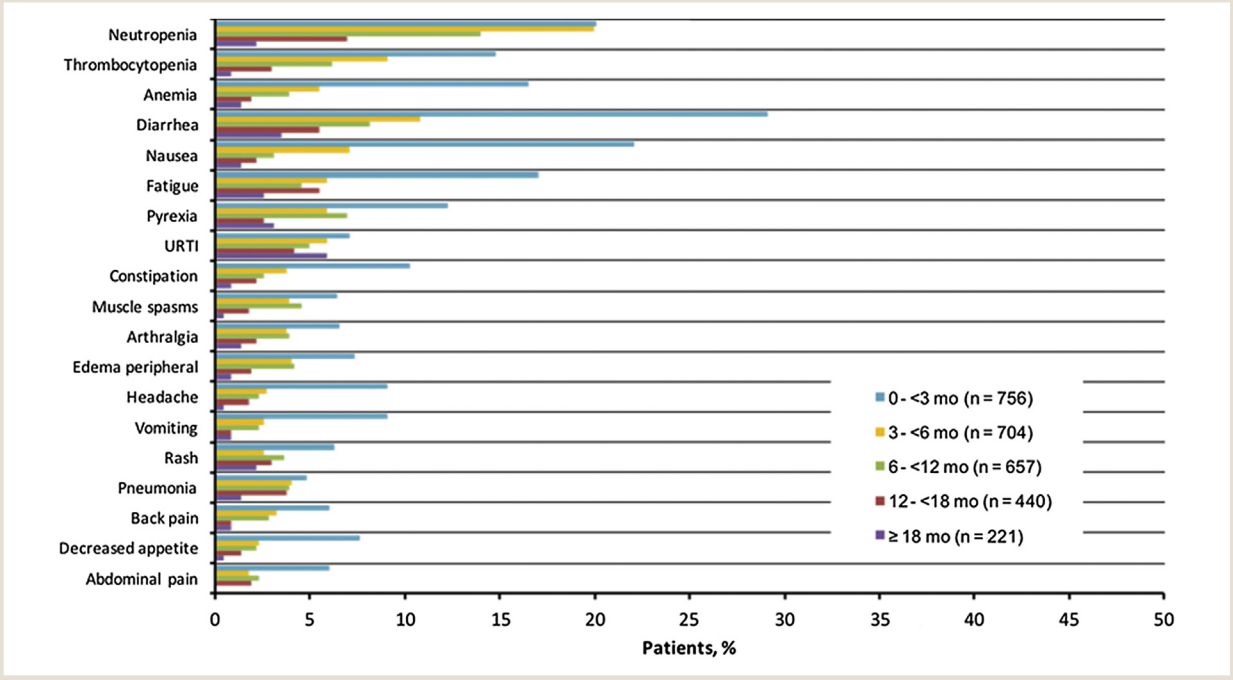
Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib; NEC = not elsewhere classified.
[a]Negative numbers indicate higher rates with comparator.

Supplemental Table 9 Cardiac Events Stratified by High-level Terms in Pooled Analysis: Cumulative and Exposure-adjusted Incidence Rates

Variable	Ibr (n = 756)		Comp (n = 749)		Δ, %[a]	Δ, EAIR[a]
	%	EAIR	%	EAIR		
Supraventricular arrhythmia	8	0.0753	3	0.0440	5	0.0312
Arrhythmia supraventricular	< 1	0.0012	0	0	0.1	0.0012
Atrial fibrillation	6	0.0547	2	0.0219	4	0.0329
Atrial flutter	< 1	0.0059	0	0	0.7	0.0059
Atrial tachycardia	< 1	0.0024	0	0	0.3	0.0024
Sinus arrhythmia	< 1	0.0012	0	0	0.1	0.0012
Sinus bradycardia	< 1	0.0024	0	0	0.3	0.0024
Sinus node dysfunction	< 1	0.0012	0	0	0.1	0.0012
Sinus tachycardia	< 1	0.0059	1	0.0145	−0.4	−0.0086
Supraventricular tachycardia	< 1	0.0047	< 1	0.0072	−0.005	−0.0025
Ventricular arrhythmias and cardiac arrest	2	0.0154	< 1	0.0054	1.3	0.0100
Cardiac arrest	< 1	0.0035	< 1	0.0018	0.3	0.0017
Cardiorespiratory arrest	< 1	0.0012	0	0	0.1	0.0012
Sudden death	< 1	0.0012	0	0	0.1	0.0012
Ventricular arrhythmia	< 1	0.0024	0	0	0.3	0.0024
Ventricular extrasystoles	1	0.0047	< 1	0.0036	0.27	0.0011
Ventricular fibrillation	< 1	0.0012	0	0	0.1	0.0012
Ventricular flutter	< 1	0.0012	0	0	0.1	0.0012
Ventricular tachycardia	< 1	0.0012	0	0	0.1	0.0012

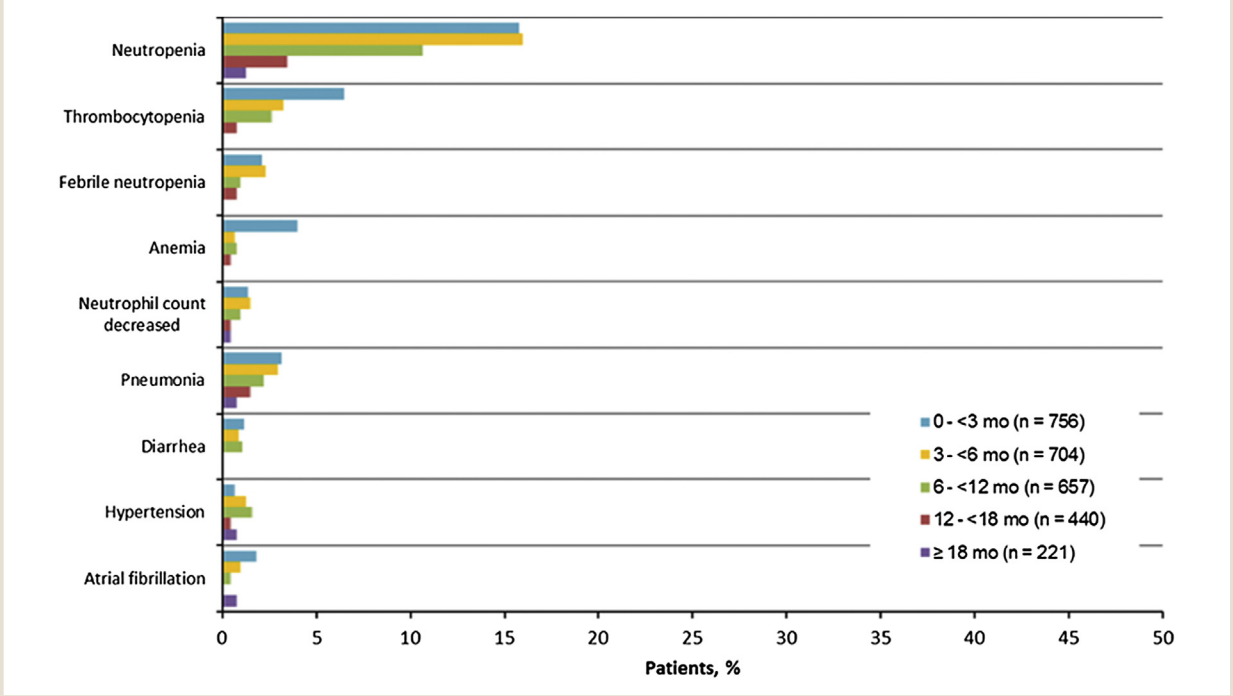
Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib.
[a]Negative numbers indicate greater rates with comparator.

Supplemental Figure 1 Prevalence of Most Common (≥ 10%) All-grade Adverse Events With Ibrutinib Over Time

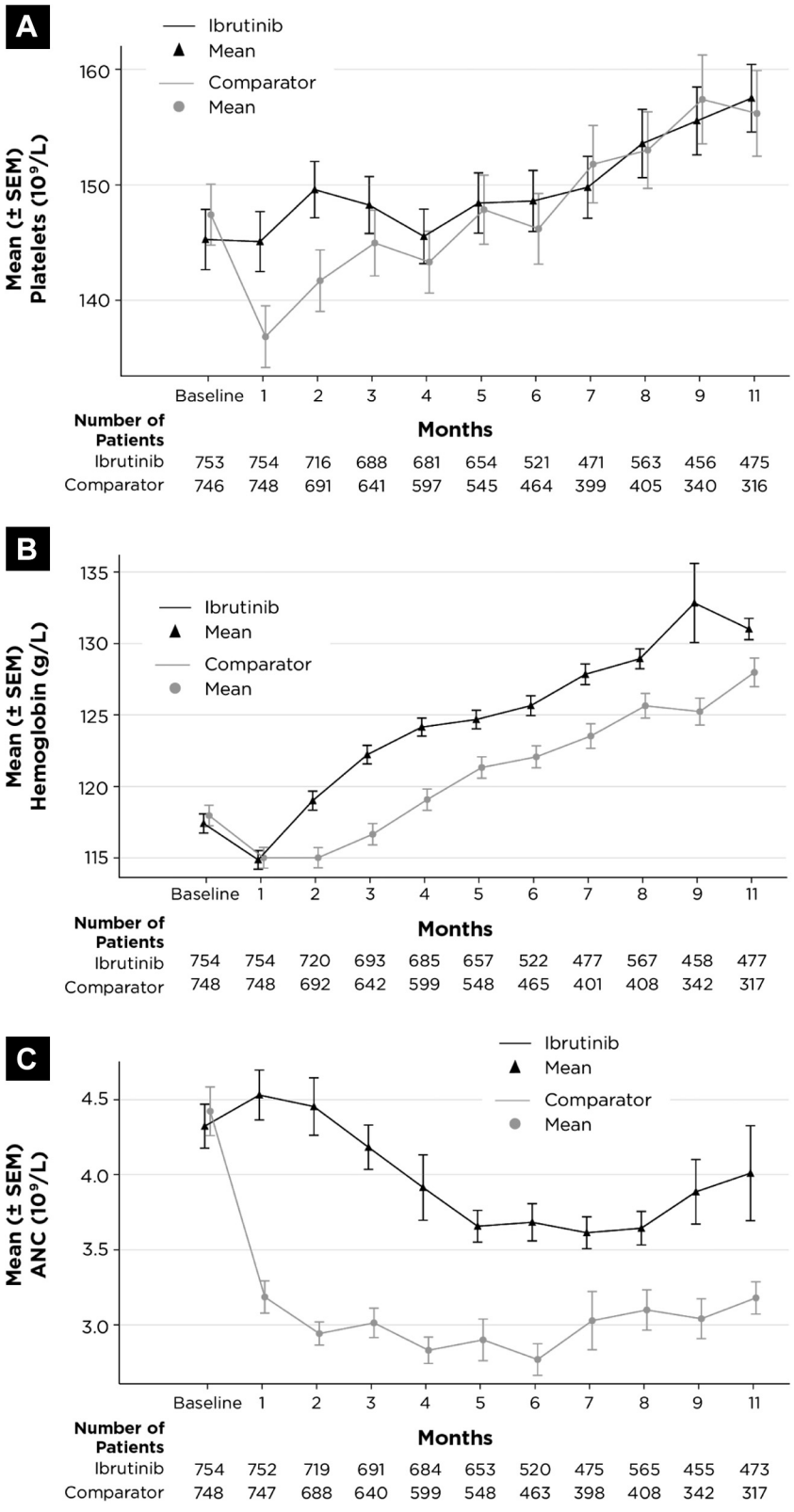


Abbreviation: URTI = upper respiratory tract infection.

Supplemental Figure 2 Prevalence of Most Common (≥ 3%) Grade 3/4 Adverse Events With Ibrutinib Over Time

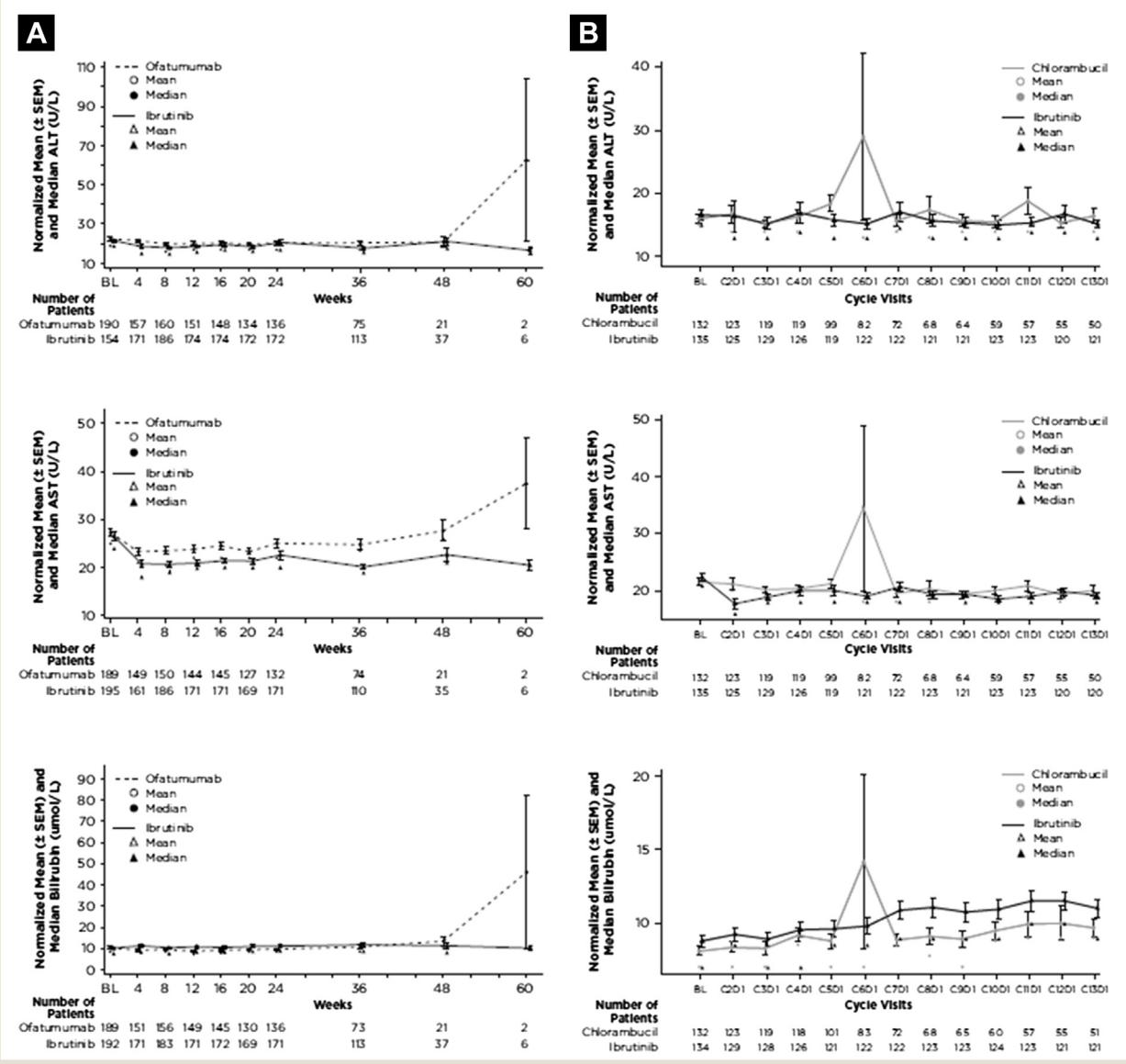


Supplemental Figure 3 (A) Mean Platelet, (B) Hemoglobin, and (C) Neutrophil Counts Over Time



Abbreviations: ANC = absolute neutrophil count; SEM = standard error of the mean.

Supplemental Figure 4 Liver Values Over Time in Studies (A) 1112, (B) 1115, (C) CLL3001, and (D) MCL3001



Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; SEM = standard error of the mean.

Supplemental Figure 4 continued