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Original Article

Efficacy and safety of ibrutinib in relapsed/refractory CLL and SLL in Japan: a post-marketing surveillance

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Ibrutinib is approved in Japan for the treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) based on the results of global and domestic clinical studies. Following approval, we conducted an all-case post-marketing surveillance in Japanese patients with relapsed/refractory CLL/SLL newly initiated on ibrutinib treatment between May 2016−September 2017. Of the 323 patients enrolled, the safety and efficacy analysis sets comprised 289 and 205 patients, respectively. The overall response rate with ibrutinib treatment was 64.4%, and the estimated 52-week progression-free survival (PFS) and overall survival (OS) rates were 71.7 and 79.1%, respectively. No significant difference in the PFS rate was observed among patients with and without del(17p) (P = 0.160); however, PFS was significantly longer in patients who received 1 prior line of therapy versus >1 prior lines of therapy (P = 0.007). Adverse events occurred in 74.0% of patients, and typically occurred early (≤12 weeks) after ibrutinib initiation, followed by a decline in incidence thereafter. The overall rates of infection, bleeding, and arrhythmia were 22.5, 12.8, and 4.8%, respectively. Grade ≥3 bleeding events and atrial fibrillation occurred in 2.4% of patients each. The efficacy and safety profile of ibrutinib treatment in routine clinical practice was consistent with clinical trials and previously reported domestic data.

UMIN-CTR Clinical Trials Register ID: UMIN000021963.

Keywords: Chronic lymphocytic leukemia, ibrutinib, Japanese patients, small lymphocytic lymphoma, tyrosine kinase inhibitor

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is an incurable malignant disease of B-lymphocytes, characterized by the clonal expansion of mature CD5- and CD23-positive B-cells in the blood, bone marrow, and lymphoid tissue.[1] Small lymphocytic lymphoma (SLL) is a distinct expression of the same disease, with the differentiating feature being the malignant cells primarily reside in the lymph nodes rather than the blood and bone marrow.[2] The clinical course of CLL is extremely heterogeneous, with many patients experiencing a relatively indolent course for decades in the absence of treatment;[3] however, marked variations in the prognosis exist, and approximately 3−10% of patients experience early aggressive disease (Richter's transformation) with rapid progressive disease (PD) and early death.[4,5] Reasons for these variations are based on the presence of several background clinical features and genetic aberrations. For example, patients with unmutated immunoglobulin heavy chain (IGHV) gene or deletions in chromosome 17p13.1 (del[17p])/TP53 mutation are considered high-risk phenotypes, with these CLL subtypes shown to experience rapid PD with symptomatic disease, frequent relapses, or refractoriness to conventional chemoimmunotherapy (CIT), and drastically reduced survival.[6-8]

Although CLL is the most common form of leukemia in Western countries,[9] it has historically been relatively rare in Asian countries, including Japan, with an incidence of 0.05−0.12 per 100,000 person-years in 1993.[10] However, the incidence of CLL has increased substantially in Japan in recent years to 0.12−0.27 in 2008.[10] CIT with fludarabine plus cyclophosphamide, and rituximab has historically been the standard of care for patients with CLL/SLL in Japan.[11] For elderly/frail patients with CLL, bendamustine plus rituximab or CIT/CD20 monoclonal antibody monotherapy is an alternative option.[11] However, these regimens are less efficacious in patients with high-risk CLL, and CIT regimens (excluding CD20 monoclonal antibody therapy) are associated with significant toxicities, including infection due to hematotoxicity,[12,13] and secondary malignancies.[14]

Recently, the introduction of a number of targeted therapies has resulted in a shift in the treatment paradigm for CLL

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and dramatically changed the natural course of the disease.[9,15] Ibrutinib is a first-in-class, once daily oral Bruton's tyrosine kinase (BTK) inhibitor approved in multiple countries, including the United States, Europe, and Asian countries for the treatment of CLL/SLL. It is the only targeted therapy to demonstrate both a significant progression-free survival (PFS) and overall survival (OS) benefit in multiple randomized phase 3 studies, including both the first-line[16-19] and relapsed/refractory (R/R)[20,21] setting.

In Japan, ibrutinib was approved for the treatment of R/R CLL/SLL in March 2016,[22] with the indication expanded to include treatment-naïve patients in July 2018.[23] In a domestic Phase 1 dose-escalation study, ibrutinib demonstrated acceptable safety in 15 Japanese patients with R/R B-cell malignancies, including 11 patients with CLL/SLL.[24] An all-case post-marketing surveillance study (PMS) was conducted from May 2016 with a 12-month observation period in patients with R/R CLL/SLL. Here we present the final results of the PMS, which represents the first large-scale real-world efficacy and safety evaluation of ibrutinib in Japanese patients with R/R CLL/SLL.

MATERIALS AND METHODS

Study Design, Patients, and Data Collection

This all-case surveillance was conducted in Japanese patients with R/R CLL/SLL (by physician assessment) initiated on ibrutinib during the registration period (May 2016−September 2017) (UMIN ID: UMIN000021963). Patients who had received ibrutinib in a clinical trial or off-label were excluded. The enrolled patients were prospectively observed for 52 weeks from ibrutinib initiation or until the date of discontinuation/lost-to-follow-up (Figure 1). Patient data were collected via electronic case report forms from May 2016−November 2019 (data lock) at baseline and at routine clinic visits during the observation period. This study was conducted in compliance with the Japanese Good Post-marketing Study Practice regulations. Anonymized patient data were collected via survey forms utilizing an Electronic Data Capture system. The protocol was reviewed and approved by the Pharmaceuticals and Medical Devices Agency.

Assessments

Baseline data were collected on demographics (sex, age, height, body weight), disease-related characteristics (disease type [CLL/SLL], time of disease onset and recurrence/s, Eastern Cooperative Oncology Group Performance Status [ECOG PS], del[17p] and del[11q] status, presence of splenomegaly, diameter of largest lymph node, Rai classification [R/R CLL], Binet classification [R/R CLL], Ann Arbor classification [R/R SLL]), medical history, ibrutinib treatment (indication, dose, treatment duration, and reason/s for dose modification, interruption or discontinuation), and prior and concomitant therapies (e.g., blood transfusion, stem cell transplantation, infection prophylaxis, and antiplatelet/anticoagulant drug use).

Safety assessment included the frequency and severity of adverse events (AEs), including evaluation of AEs that required dose modification or treatment discontinuation. AEs were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1, and graded according to the National Cancer Institute Common Terminology criteria for Adverse Events, version 4.0. The time to onset, relationship with the study drug, and outcome of the AEs were also recorded. The following AEs were defined as priority survey items: hemorrhage (hereafter termed 'bleeding'), bone marrow depression (hereafter termed 'hematotoxicity'), infections, arrhythmia, hypersensitivity, tumor lysis syndrome, eye disorders, hepatic failure/hepatic function disorder, interstitial lung disease, secondary cancers, leukocyte disorders, and oculomucocutaneous syndrome (Stevens-Johnson syndrome). Progression of CLL/SLL was reported as AEs. Evaluation of efficacy was based on the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines for the diagnosis and treatment of CLL (2018),[25] and included the best overall response (including complete response [CR], complete remission with incomplete hematologic recovery [CRi], nodular partial remission, partial response [PR], stable disease [SD], or PD) during the period from baseline to weeks 12 and 52 (or date of last ibrutinib dose), PFS (defined as the time from ibrutinib initiation to the first documentation of PD or death from

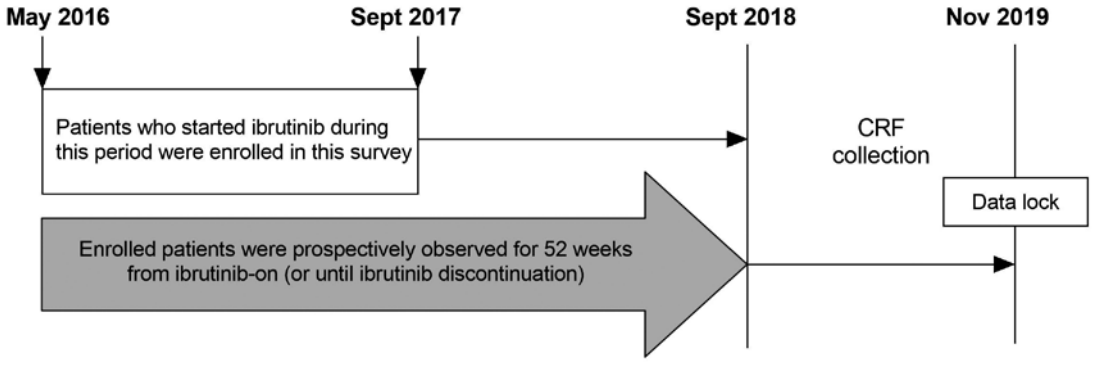


Fig. 1. Study design
CRF, case report form

any cause), was measured from study enrolment to Weeks 12 and 52 (or date of last ibrutinib dose), and OS was measured from study enrolment to the date of the visit immediately after the completion of the observation period or the last visit. Patients who did not experience an event were censored at the data cut-off date (November 2019).

Statistical Analysis

A sample size of 200 patients was planned for this study. This assumption was based on the results of the ibrutinib global phase 1b/2 and phase 3 studies,[20,26] in which the least common events were lung-related events, including interstitial cystitis, occurring with an incidence of 1.5%. Accordingly, on the assumption that the incidence of adverse drug reactions (ADRs) in the current study will be 1.5%, approximately 200 patients are required to detect ≥1 ADR event with ≥95% probability. The safety analysis set was defined as all patients who had case report forms collected, excluding those meeting the predefined exclusion criteria, and was used for the baseline, demographics, exposure, and safety analyses. The efficacy-evaluable population was defined as all patients in the safety analysis set who had an efficacy evaluation available based on the iwCLL criteria during the observation period.[25] The overall response rate (ORR) with 95% CI was calculated.

The Kaplan-Meier method was used to evaluate the PFS (overall and according to specific subgroups [e.g., del(17p) status and number of prior therapies [prior lines of treatment; 1 or >1]) and OS rates. The survival data were compared using the log-rank test.

The average dose intensity was calculated as follows: best adherence (%), with the average weekly dose prescribed as per the package insert for each patient ([mg])÷(420[mg/day]×7[days])×100. Real case (%): (Average actual weekly dose prescribed for each patient [mg])÷(420[mg/day]×7[days])×100.

Univariate and multivariate logistic regression analyses were used to evaluate trends for prophylaxis for fungal/*Pneumocystis jiroveci* infection and risk factors for the development of bleeding events, with the odds ratio (95% CI) and *P* value reported. For the prophylaxis trend, potential predictors evaluated included the number of prior lines of treatment, age, neutrophil count at ibrutinib initiation, ECOG PS, and history of prior steroid usage. For the bleeding risk trend, potential predictors evaluated included AEs of thrombocytopenia, platelet count at ibrutinib initiation, arrhythmia history, and concomitant use of anticoagulant/antiplatelet agents. All other data were summarized using descriptive statistics, including the mean, standard deviation, and median for continuous variables and proportions for discrete variables.

In both the safety and efficacy analyses, the Fisher's exact test was employed for 2-level factorials and the chi-square test was employed for 3- or more level factorials. Differences were considered significant at $P < 0.05$.

All statistical analyses were performed using SAS® version 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

From May 2016 to September 2017, a total of 323 patients were enrolled (Figure 2). Of these, 34 patients were excluded: 16 patients had uncollected case report forms and 18 patients were excluded due to protocol violations, a lack of ibrutinib prescription, re-treatment with ibrutinib, off-label use (not treated for R/R CLL), or unavailable safety evalua-

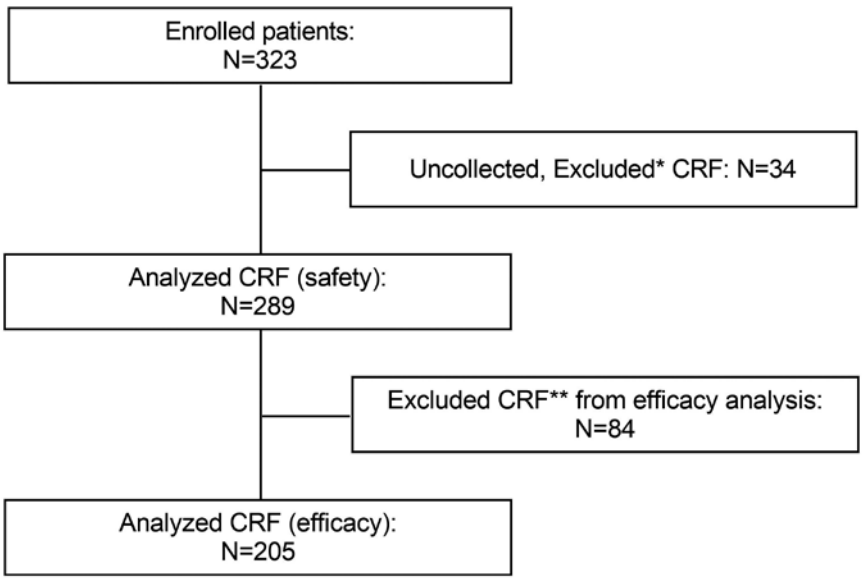


Fig. 2. Study population
*Protocol violations, no ibrutinib prescription, re-treatment case, off-label use (not treated for R/R CLL), or safety evaluation unavailable.
**No report of efficacy evaluation based on iwCLL criteria during the observation period.
CRF, case report form

tions. Although no history of prior treatment was recorded in three patients, they were included in this study because the physician had determined that they had refractory/recurrent disease. Therefore, the data for 289 patients were assessed for the safety analysis. For the efficacy analysis set, the efficacy evaluation based on the iwCLL criteria was not reported in 84 patients, resulting in 205 patients being assessed.

Baseline demographics and clinical characteristics

The baseline demographic and characteristics of patients included in the safety analysis set are summarized in Table 1. The median (range) age was 72.0 (33−92) years, and 65.4% of the patients were male. Approximately half of the patients had Rai stage III−IV (50.5%) or Binet stage C (52.6%) disease. The patients had received a median (range) of 2.0 (0−12) therapies prior to ibrutinib initiation. The mean (SD) and median (min, max) duration from the last day of pretreatment to the first day of ibrutinib treatment was 331.6 (481.6) days and 108.0 (2, 2501) days, respectively. Del17p and del11p were observed in 23.7 (49/207 patients) and 13.7% (23/168 patients) of patients with results available, respectively.

Table 1. Demographic and baseline clinical characteristics (safety analysis set)

	Patients
Safety analysis set, n (%)	289 (100.0)
Age, years, median (range)	72.0 (33−92)
Age category, years, n (%)	
<70	121 (41.9)
≥70	168 (58.1)
Sex, male, n (%)	189 (65.4)
Rai stage, n (%)	
0−II	56 (19.4)
III−IV	146 (50.5)
Unknown	87 (30.1)
Binet stage, n (%)	
A	13 (4.5)
B	48 (16.6)
C	152 (52.6)
Unknown	76 (26.3)
ECOG PS, n (%)	
0	139 (48.1)
1	90 (31.1)
2	32 (11.1)
3−4	23 (8.0)
Unknown	5 (1.7)
Number of prior therapies, median (range)	2.0 (0−12)
Number of prior therapies, n (%)	
0	3 (1.0)
1	106 (36.7)
2	43 (14.9)
3	46 (15.9)
≥4	91 (31.5)
Del(17p), n (%)	
Yes	49 (17.0)
No	158 (54.7)
Unknown	82 (28.4)
Del(11q), n (%)	
Yes	23 (8.0)
No	145 (50.2)
Unknown	121 (41.9)
Time from diagnosis, years, median (range)	5.6 (0.1−24.0)

Del, deletion; ECOG PS, Eastern Cooperative Oncology Group Performance Status

Patient disposition

Details of the patient disposition are listed in Table 2. Among all the 289 patients, the median (range) duration of ibrutinib treatment was 11.3 (0.1−31.8) months. A total of 128 (44.3%) patients discontinued treatment with ibrutinib. Reasons for discontinuation included insufficient effect (n=28, 9.7%), AEs excluding death (n=58; 20.1%), death (n=17, 5.9%), and other reasons, including financial burden, physician decision, hospital transfer, or other reasons not specified (n=25, 8.7%). Among the 205 patients with an efficacy evaluation, 81 (39.5%) patients discontinued treatment due to PD (n=19, 9.3%), AEs excluding PD or death (n=36, 17.6%), death (n=5, 2.4%), and other reasons (n=21, 10.2%).

Dose intensity

The average ibrutinib weekly dose-intensity was assessed in patients on therapy, and compared to the recommended dose in the package insert.[27] The adherence was 92.3% at ibrutinib initiation and the ibrutinib dose intensity was approximately 80% (76.6−83.3%) throughout the study.

Efficacy

In the 205 patients with an efficacy evaluation, the ORR with ibrutinib treatment was 64.4%, and the estimated 52-week PFS and OS rates with ibrutinib were 71.7 and 79.1%, respectively. Kaplan-Meier curves for PFS and OS during ibrutinib treatment are presented in Figure 3A−B. When analyzed by del(17p) status, no significant difference

Table 2. Ibrutinib management of adverse events of interest (safety analysis set)

Patient Disposition (N=289)	
Median follow-up, months (range)	11.3 (0.1−31.8)
Dose reduction or dose-hold, n (%)	108 (37.4)
Adverse event[a]	93 (32.2)
Other[a]	25 (8.7)
Unknown	1 (0.4)
Discontinuation, n (%)	128 (44.3)
Insufficient effect[b]	28 (9.7)
Adverse event except for death[b]	58 (20.1)
Death[b]	17 (5.9)
Other	25 (8.7)

PD, progressive disease
[a]Allowing for overlapped patients; [b]Including PD patients who were analyzed in the efficacy analysis set

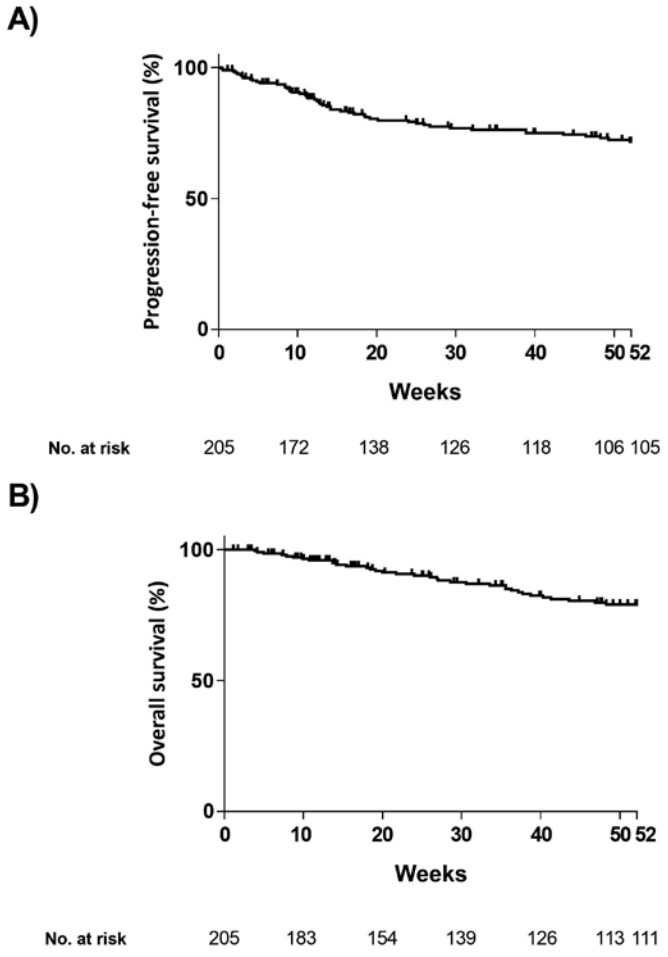


Fig. 3. Rates of progression-free survival (***A***) and overall survival (***B***)

in PFS was observed among patients with and without del(17p) (log-rank $P = 0.160$; Figure 4A). The 52-week PFS rate was significantly higher in patients who had received 1 prior line of treatment versus those who had received >1 prior line of treatment (85.6 vs 78.4%, respectively; log-rank $P = 0.007$; Figure 4B).

Safety

The incidence of AEs according to the number of prior lines of treatment and age, as well as AEs with a total incidence of ≥5% are presented in Figure 5. With respect to AE incidence, 74.0% of patients experienced AEs of any grade during the survey, with no significant difference in the AE frequency or distribution observed according to age ($P = 0.752$) or number of prior lines of treatment (1 or >1; $P = 0.096$) (Figure 5A). The most common (≥5% incidence) AEs over the 52-week study period were a decreased platelet count (10.4% of patients), followed by an increased lymphocyte count (8.0% of patients), most of which were grade 3 in severity (5.5% of patients) (Figure 5B). Grade 5 AEs (not due to PD) occurred in 10 patients. The AE profile at ibrutinib discontinuation is shown in Figure S1.

The timing of onset of all grades and grade ≥3 AEs of interest over the 52-week study period are presented in Figure 6. Any grade and grade ≥3 AEs tended to occur within the first 12 weeks after ibrutinib initiation, followed by a general decline in AE incidence, although late events did occur infrequently.

Adverse Events of Interest

The incidence of AEs of interest (infection, bleeding, and arrhythmia) and their outcome, including ibrutinib dose modifications, are presented in Table 3.

Infections

Of the 289 patients analyzed, 22.5% (n=65) of patients experienced an episode of infection (median of 1 episode of infection). Of these, 80.0% resolved by the end of the survey periods (Table 3). Grade 5 infections occurred in 5 patients during the study, including bronchopulmonary aspergillosis (n=1), sepsis/infectious enteritis (n=1), sepsis (n=1), and pneumonia (n=2). These patients were predominantly older (median age, 81 years), had a high ECOG PS score (median, 3.0), and had received multiple prior lines of treatment (median, 3.0).

A total of 39.8% (n=115) of patients were prescribed prophylactic treatment for fungal infection, including *Pneumocystis jiroveci*. Fungal infection occurred in 10 patients, including 2 patients with *Pneumocystis jiroveci*. Of these, 5 were receiving prophylaxis and 5 were not receiving prophylaxis. Patients aged ≤80 years or those who had received ≥3 prior lines of treatment or had a neutrophil count $<0.5 \times 10^3/\mu L$ at ibrutinib initiation were more likely to receive prophylactic treatment for fungal infection (Figure S2).

Bleeding

Bleeding events occurred in 37 (12.8%) patients, most of which (n=30, 10.4%) were grade 1/2 in severity. The median number of bleeding episodes was 1, and 89.2% of bleeding events resolved by the end of the survey period. The most common (>3 patients) bleeding events were petechiae (n=7), purpura (n=5), and subdural hematoma, hematuria, and subcutaneous hemorrhage (n=4 each). Among the 37 patients who experienced bleeding events, 70.3% (n=27) continued ibrutinib treatment with or without dose modification. Bleeding, infection, arrhythmia, and other events typically occurred within 12 weeks of ibrutinib initiation (Figure 6).

Of the 289 patients analyzed, 46 (15.9%) patients were receiving concomitant antiplatelet or anticoagulant medication, including aspirin (n=10), heparin (n=2), vitamin K antagonists (n=4), direct oral anticoagulants/direct thrombin and factor Xa inhibitors (n=8), and other medications (n=27) alone or in combination (Table S1).

The median exposure to antiplatelet and anticoagulant treatment was 36 days. Bleeding events considered causally related to ibrutinib treatment occurred in 8 (17.4%) patients receiving concomitant anticoagulant or antiplatelet treatment, including 4 (8.7%) patients receiving aspirin, 1 (2.2%) patient receiving direct oral anticoagulants, and 3 (6.5%)

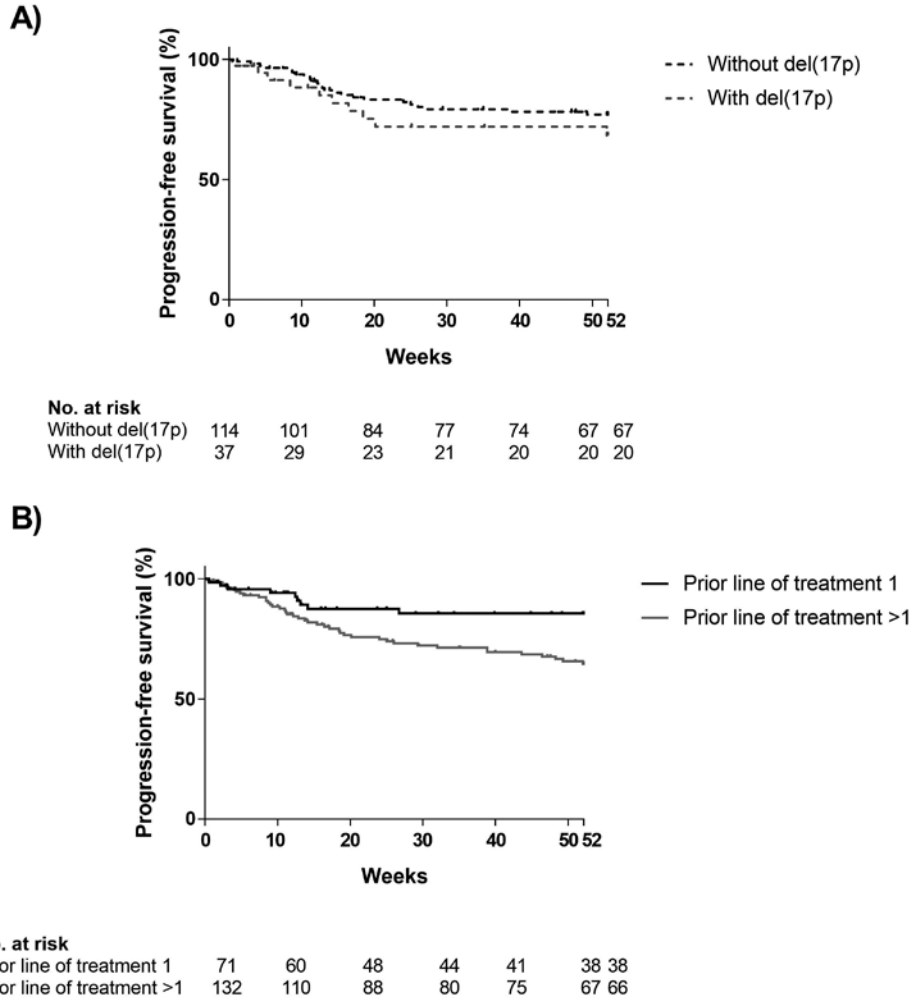


Fig. 4. Rates of progression-free survival by del(17p) status (***A***) and by number of prior therapies (***B***)

patients receiving other antiplatelet or anticoagulant treatment. Conversely, bleeding events not considered causally related to ibrutinib occurred in 1 (2.2%) patient receiving concomitant heparin and another anticoagulant or antiplatelet treatment (Table S1). Eight (17.4%) patients were receiving anticoagulant treatment with direct thrombin and factor Xa inhibitors, including dabigatran (n=2), apixaban (n=2), rivaroxaban (n=2), and edoxaban (n=2), for a median of approximately 3-8 months (Table S2). Of these patients, 1 bleeding event was observed in 1 (12.5%) patient being treated with rivaroxaban, which was considered causally related to ibrutinib treatment.

Arrhythmia

A total of 15 events of arrhythmia occurred in 14 patients (4.8%) (Figure 7), 78.6% of which resolved by the end of the survey period (Table 3). Among the patients who experienced arrhythmia, 57.1 and 60.0% of patients with all grade and grade ≥3 events continued ibrutinib treatment, respectively, with dose modification in 55.5 and 100.0% of these patients, respectively. Atrial fibrillation (AF) occurred in 7 patients (2.4%). One patient experienced ventricular tachycardia during the survey, which resolved within the observation period. No grade 5 event was observed in patients with cardiac arrhythmia or arrhythmia-related events (Figure S1). Of the 14 patients who developed arrhythmia, 7 (50.0%) patients were administered concomitant antiplatelet/anticoagulant medication, including aspirin (n=1), direct oral anticoagulants (n=2), and other antiplatelet/anticoagulant medication (n=4).

Of the 289 patients analyzed, 26 (9.0%) patients had a prior history of arrhythmia. In the 26 patients with a prior history of arrhythmia (median initial ibrutinib dose, 420 mg), arrhythmia events occurred in 4 (15.4%) patients. However, most (84.6%) patients with a prior history of arrhythmia did not experience a new episode of arrhythmia on ibrutinib therapy. Conversely, in 263 patients without a prior history, the incidence of arrhythmia was 3.8% (n=10); therefore, patients with a prior history of arrhythmia were more likely to develop arrhythmia in the observation period than those without (P = 0.028).

The rates of progression-free survival in patients with and without arrhythmia and with and without a history of arrhythmia are presented in Figure S3.

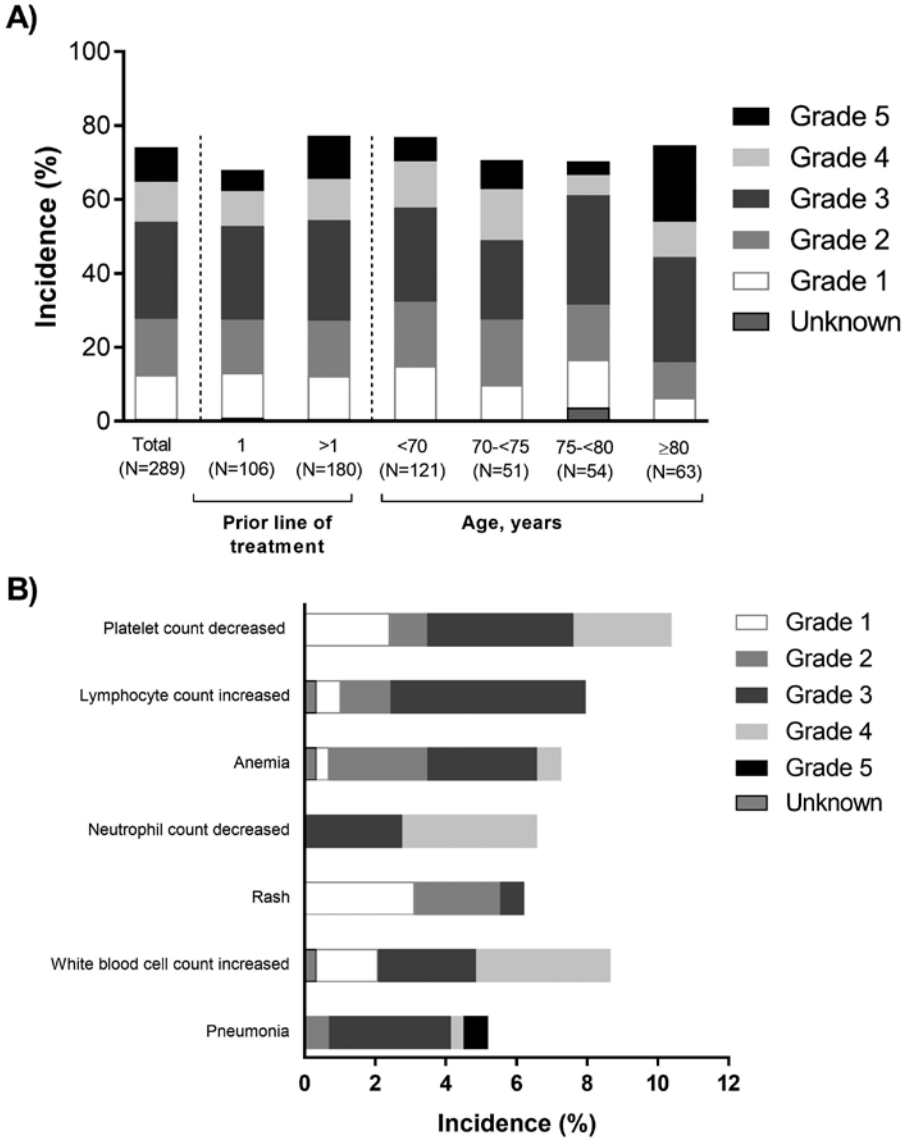


Fig. 5. Incidence of adverse events in the overall safety analysis set and by number of prior therapies and age (***A***) and those with a total incidence ≥5% (***B***)

DISCUSSION

This final analysis of an all-case post-marketing surveillance, which represents the first large-scale evaluation of a BTK inhibitor in Japan, demonstrates the real-world safety and efficacy of ibrutinib in Japanese patients with relapsed/refractory CLL/SLL. The efficacy and safety profile of ibrutinib was consistent with the established profile of this drug at the time of its approval in Japan,[16,18,20,24] as well as the results reported in global clinical trials[20,21,28,29] and real-world studies.[30-33]

With respect to efficacy, an ORR of 64.4%, and estimated 52-week PFS and OS rates of 71.7 and 79.1%, respectively, were achieved in the current study. Although the 52-week PFS and OS rates were slightly lower than those reported with ibrutinib in the RESONATE study (PFS: 84%; OS: 90%),[21,34] this is not unexpected considering the older age (median [range] age: 72.0 [33−92] vs 67.0 [30−86] years, respectively) and worse performance status of the patients in our study (ECOG PS score ≥2: 19 vs 0% [excluded], respectively) compared with RESONATE.[20] Consistent with the results of previously reported global clinical studies,[21,29,35] a trend was observed between earlier use of ibrutinib and significantly longer PFS (52-week PFS, 1 prior line of treatment vs >1 prior lines of treatment: $P = 0.007$). More importantly, the PFS benefits with ibrutinib therapy were similar between patients with and without del17p. The IGHV mutation status is not routinely assessed in clinical practice in Japan and no data were available in this survey. Overall, the magnitude of the efficacy of ibrutinib was also in accordance with that reported in other real-world studies,[30-33] including the Swedish compassionate use and French early access programs, which were well matched with respect to age, gender, performance status, CLL stage, and/or number of prior lines of treatment.

The safety and tolerability profile was consistent with that

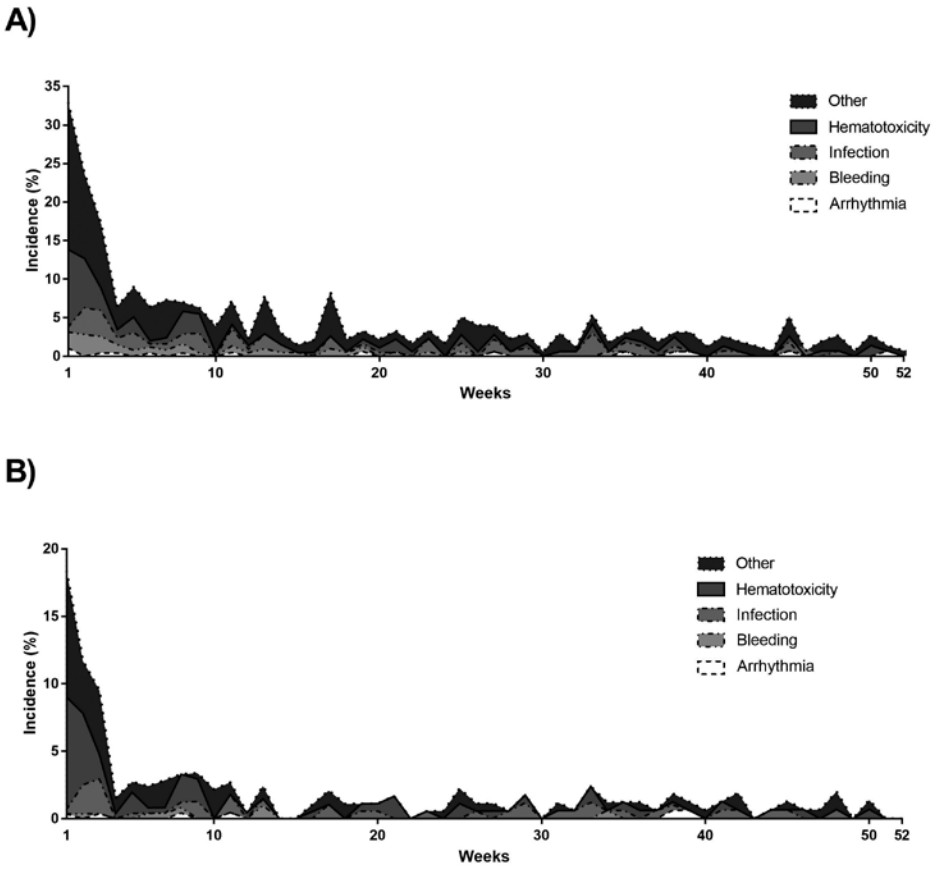


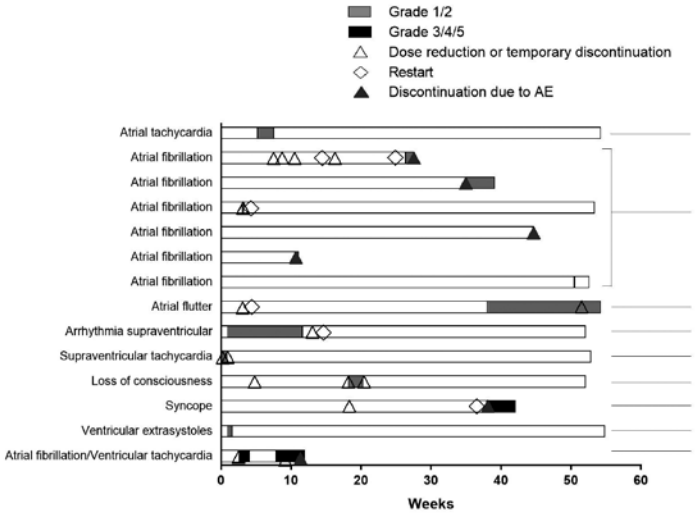
Fig. 6. Timing of onset of all grade (***A***) and grade ≥3 (***B***) adverse events during the study
The incidence of each categorized AE was assessed weekly and presented as a stacked line chart.
AE, adverse event

Table 3. Adverse events of Interest and Outcomes in Patients Treated with Ibrutinib

Total, N=289	Infection		Bleeding		Arrhythmia	
	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
Patients with each AE of interest	65 (22.5)	34 (11.8)	37 (12.8)	7 (2.4)	14 (4.8)	5 (1.7)
Patients with resolved AEs	52 (80.0)	25 (73.5)	33 (89.2)	4 (57.1)	11 (78.6)	4 (80.0)
Patients who continued treatment[a]	50 (76.9)	20 (58.8)	27 (70.3)	2 (28.5)	9 (57.1)	3 (60.0)
Patients with dose modification[b]	22 (44.0)	15 (75.0)	14 (51.9)	2 (100.0)	5 (55.5)	3 (100.0)
Number of episodes of AEs, median (range)	1 (1−7)		1 (1−5)		1 (1−2)	

[a]Patients who did not discontinue ibrutinib from onset to resolution of each AE. [b]Patients with dose reduction or temporary dose-hold during AE periods. The proportion of patients who continued treatment are presented. Indicates the median number of episodes throughout the study.
AE, adverse event. Data are shown as n (%) unless otherwise specified, allowing for overlapping patients.

reported in global clinical studies[16,18,20,28,29] and the established profile of this drug at the time of its approval in Japan,[27] with no new safety concerns identified. A total of 74.0% of patients experienced AEs of any grade in the current study. No notable differences in the frequency or nature of AEs were observed according to the age or number of prior lines of treatment (1 or >1). Consistent with other studies,[17,21,36] AEs tended to occur early after ibrutinib initiation with a gradual decrease thereafter. AEs of interest were successfully managed in the majority of patients via temporary dose modifications and allowed patients who developed AEs to remain on therapy. The overall rates of infection, bleeding, and arrhythmia were 22.5, 12.8, and 4.8%, respectively. Interestingly, the rate of AF was relatively low in our study (2.4%) compared with the rates reported across randomized controlled registration studies (6.5%).[37] This suggests that Japanese patients may have a lower incidence of AF compared with Caucasian patients, although further investigation is warranted. Previous studies have reported an increased incidence of AF in patients with specific risk factors, such as being male, older age, and a history of AF;[37-41] in our study, the incidence of arrhythmia events was elevated in patients



N* (All/Grade ≥3)	Use of AC/AP from onset of arrhythmia	Cerebral stroke	Bleeding
1/0	Others (200 mg)	0	1
6/1	Aspirin (100 mg) / DOAC (220 mg) / Others (120 mg)	0	1
1/1	DOAC (60 mg)	0	0
1/0	-	0	0
1/1	Others (100 mg)	0	0
1/0	-	0	1
1/1	-	0	0
1/0	-	0	1
1/1	Others (200 mg)	0	0
Total 14/4	Aspirin (N=1)	0	1
	DOAC (N=2)	0	0
	Others (N=4)	0	1
	No use (N=7)	0	2

Fig. 7. Incidence and time of onset of arrhythmia events during the study
AC, anticoagulant drugs; AE, adverse event; AP, antiplatelet drugs; DOAC, direct oral anticoagulant drugs

with a prior history of arrhythmia. Nevertheless, similar PFS rates (including the number of patients at risk at 52 weeks) were observed irrespective of a prior history of arrhythmia, as well as the presence or absence of arrhythmia events on ibrutinib therapy. Regarding the management of arrhythmia, anticoagulant and/or antiarrhythmic therapy for AF is generally considered safe to use in patients receiving ibrutinib, with appropriate monitoring for signs of bleeding.[37,42,43]

Ten patients developed fungal infection during ibrutinib therapy over the 52-week observation period, including 2 patients with *Pneumocystis jiroveci*. Although the number of patients was relatively small, antibiotic prophylaxis did not appear to affect the outcome, with 5 of these patients receiving prophylaxis for opportunistic infection. However, because of the small sample size and the fact that fungi and *Pneumocystis jiroveci* were analyzed together, these data should only be used as a reference and require careful interpretation. Further studies are therefore required. Notably, all patients who developed fungal infection had a history of, or concurrent, grade 4 hematotoxicity. Regular monitoring for fever and infection during ibrutinib therapy, particularly when other risk factors for fungal infection are present, is therefore recommended. In accordance with the Proper Use Guidelines, prophylaxic medications may be used under certain conditions.

Although major bleeding events are relatively uncommon with ibrutinib treatment, the risk of these events is reportedly increased in patients receiving antiplatelet or anticoagulant therapies while on ibrutinib therapy.[44] Nine Grade 1-2 bleeding events occurred among the 46 patients taking concomitant anticoagulant or antiplatelet therapy in our study. Concomitant antiplatelet/anticoagulant use was not predictive of bleeding events ($P = 0.851$). Interestingly, of the 8 patients receiving anticoagulant treatment with direct thrombin and factor Xa inhibitors, including dabigatran (n=2), apixaban (n=2), rivaroxaban (n=2), and edoxaban (n=2) alone or in combination for a median of 3−8 months, only 1 low-grade bleeding event in a patient treated with rivaroxaban was considered causally related to ibrutinib. Specific risk factors predisposing patients to the development of major bleeding events could not be explored due to the limited concomitant usage of anticoagulants or antiplatelets and major bleeding events in our study. Although no major bleeding events were observed in patients receiving anticoagulant/antiplatelet in this survey, clinicians should consider the risk-benefit when using these agents and closely monitor patients for signs of bleeding.

Limitations are inherent to post-marketing studies and included the non-interventional, observational nature of the study, including the lack of an independent control arm, and the presence of incomplete or missing data. Further, although this study represents the most comprehensive safety and efficacy data of ibrutinib to date in Japan, the 52-week observation period is relatively short when taking into consideration the long-term nature of the disease and expected duration of ibrutinib therapy. Underreporting of AEs may also be more common in post-marketing studies, due to the potential for investigator bias when reporting. Nevertheless, the study population represented a large and heterogeneous cohort of Japanese patients, including patients who were elderly, had high risk del(17p) and del(11p) deletions, and had received multiple prior lines of treatment, reflecting the population typically seen in clinical practice.

In conclusion, the final results of this large post-marketing surveillance confirm the real-world safety and efficacy of ibrutinib in Japanese patients with R/R CLL/SLL. AEs typically occurred within the first 3 months of treatment and decreased over time, most of which were manageable, with no notable differences in the frequency or nature of AEs according to the age or number of prior lines of treatment (1 or >1). With respect to efficacy, PFS was significantly lon-

ger in the subgroup with 1 prior line of treatment versus >1 prior lines of treatment. Overall, the PFS trends were similar to the known profile reported in the previous global phase 3 study. Importantly, no new safety concerns were identified, and the safety and efficacy profiles of ibrutinib were consistent with the established profiles of this drug at the time of its approval in Japan.[16,18,20,28,29] These findings add to the wealth of data supporting the safety and efficacy of ibrutinib in the treatment of CLL,[16-18,20,28,29] and further support the rationale for initiation of ibrutinib early in the treatment algorithm for optimal outcomes.[23]

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Study conception and design: FN; data acquisition: FN; data analysis and interpretation of results: AO, FN, ST, AF, and RA. All authors participated in the drafting, critical revision, and approval of the final version of the manuscript.

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CONFLICT OF INTEREST

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