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Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies

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Key Points

- In 424 patients with CLL on long-term ibrutinib, AEs were primarily grade 1/2 and manageable; the majority of patients continued therapy.
- AE management requiring dose modification most commonly occurs in the first year of ibrutinib and does not preclude extended therapy.

Ibrutinib, a first-in-class once-daily oral Bruton tyrosine kinase inhibitor indicated for chronic lymphocytic leukemia (CLL), is continued until progressive disease or unacceptable toxicity. We conducted an integrated safety analysis of single-agent ibrutinib from randomized phase 3 studies PCYC-1112 (RESONATE, n = 195) and PCYC-1115/1116 (RESONATE-2, n = 135), and examined longer-term safety separately in the phase 1b/2 PCYC-1102/1103 study (n = 94, 420 mg/d). In the integrated analysis (ibrutinib treatment up to 43 months), the most common adverse events (AEs) were primarily grade 1/2; diarrhea (n = 173, 52% any-grade; n = 15, 5% grade 3) and fatigue (n = 119, 36% any-grade; n = 10, 3% grade 3). The most common grade 3/4 AEs were neutropenia (n = 60, 18%) and pneumonia (n = 38, 12%). Over time, prevalence of AEs of interest (diarrhea, fatigue, grade ≥3 infection, bleeding, and neutropenia) trended down; prevalence of hypertension increased, but incidence decreased after year 1. AEs led to dose reductions in 42 (13%) patients and permanent discontinuations in 37 (11%); dose modifications due to AEs were most common during year 1 and decreased in frequency thereafter. The most common AEs (preferred term) contributing to discontinuation included pneumonia (n = 4), anemia (n = 3), and atrial fibrillation (n = 3). With long-term follow-up on PCYC-1102/1103 (ibrutinib treatment up to 67 months), grade 3/4 AEs were generally similar to those in the integrated analysis. Overall, AEs were primarily grade 1/2 and manageable during prolonged ibrutinib treatment in patients with CLL. These trials were registered at www.clinicaltrials.gov as #NCT01578707, #NCT01722487, #NCT01724346, #NCT01105247, and #NCT01109069.

Introduction

Ibrutinib, a first-in-class oral once-daily inhibitor of Bruton tyrosine kinase, is approved for the treatment of patients with chronic lymphocytic leukemia (CLL) and allows for treatment without chemotherapy. The initial efficacy and tolerability of ibrutinib were shown in a phase 1b/2 study, PCYC-1102/1103, in patients with previously untreated or relapsed/refractory CLL or small lymphocytic lymphoma (SLL).[1,2] In

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Individual participant data from this clinical study are not available; Pharmacyclics LLC, an AbbVie Company, is currently developing a data-sharing plan.

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The full-text version of this article contains a data supplement.

this study, single-agent ibrutinib resulted in high response rates and durable remissions with manageable toxicity, leading to subsequent randomized phase 3 trials, including PCYC-1112 (RESONATE)[3] and PCYC-1115/1116 (RESONATE-2).[4] In RESONATE, ibrutinib significantly prolonged progression-free survival (PFS) and overall survival (OS) compared with ofatumumab in patients with relapsed/refractory CLL/SLL.[3] In RESONATE-2, ibrutinib significantly prolonged PFS and OS compared with chlorambucil in patients with previously untreated CLL/SLL who were 65 years of age or older.[4]

Unlike other treatment options for CLL that are given for finite numbers of cycles,[5-7] ibrutinib is continued until the occurrence of progressive disease (PD) or unacceptable toxicity, leading to extended treatment with clinical benefit in most patients.[8,9] We conducted an integrated safety analysis to evaluate the safety and tolerability of single-agent ibrutinib in a large group of patients with previously untreated or relapsed/refractory CLL/SLL from RESONATE and RESONATE-2. We also analyzed separately the long-term safety of single-agent ibrutinib in patients from PCYC-1102/1103.

Methods

Data sources

For the integrated safety analysis, data for all patients treated with ibrutinib (420 mg daily) in 2 international randomized phase 3 clinical trials and an open-label extension (RESONATE [NCT01578707] and RESONATE-2 [NCT01722487, NCT01724346])[3,4] were pooled (N = 330). In RESONATE, 391 patients with CLL/SLL who had received ≥1 prior therapy and were inappropriate for treatment or retreatment with purine analogs (supplemental Table 1) were randomly assigned (1:1) to receive ibrutinib 420 mg once daily until the occurrence of PD or unacceptable toxicity (n = 195) or to receive ofatumumab according to a standard 24-week treatment schedule (n = 196).[3] Following PD, patients in the ofatumumab arm were eligible to cross over to ibrutinib therapy. In RESONATE-2, 269 previously untreated patients with CLL/SLL (aged ≥65 years), without 17p deletion, requiring treatment were randomly assigned (1:1) to receive ibrutinib 420 mg once daily until PD or unacceptable toxicity occurred (n = 136) or to receive chlorambucil 0.5 mg/kg (with allowable dose increase to a maximum of 0.8 mg/kg as tolerated) on days 1 and 15 of a 28-day cycle for 12 cycles (n = 133).[4] Inclusion of patients aged 65 to 69 years required a comorbidity precluding chemoimmunotherapy (supplemental Table 1). All patients dosed in the PCYC-1115 study could enroll in an extension study (PCYC-1116) at the time of disease progression or at the time of PCYC-1115 study closure, where second-line ibrutinib was available for crossover for patients who progressed on the chlorambucil arm.[9]

For evaluation of longer-term safety, data were also analyzed from patients treated in the phase 1b/2 study (PCYC-1102; NCT01105247).[1] Briefly, this study enrolled 132 patients requiring treatment, of whom 101 had relapsed/refractory CLL/SLL and 31 patients aged ≥65 years had previously untreated CLL/SLL. Ninety-four of the 132 patients enrolled, including 67 relapsed/refractory patients and 27 previously untreated patients, received ibrutinib 420 mg once daily until PD or unacceptable toxicity occurred. The remaining 38 patients, including 34 relapsed/refractory patients and 4 previously untreated patients, received ibrutinib 840 mg as initially planned as part of the clinical trial. In this analysis, only data for all of the patients treated with ibrutinib 420 mg were examined (n = 94), for a homogenously treated population. Patients were eligible to continue receiving ibrutinib in a long-term extension study (PCYC-1103, NCT01109069),[10] in which collection of treatment-emergent adverse events (AEs) was limited to grade ≥3 AEs, serious AEs, major hemorrhage, or AEs leading to ibrutinib dose modification or discontinuation.

Details of the study designs have been published previously.[1,2,4,8,10] The studies were approved by the independent ethics committee or institutional review board at each participating institution and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent. Data analyses were performed by Pharmacyclics LLC, and all authors had full access to study data.

Assessments

Safety was assessed by the frequency and severity of treatment-emergent AEs, including evaluation of AEs that required dose modifications or treatment discontinuations. Severity of nonhematologic AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0,[11] with the exception of RESONATE-2, which used version 4.03[12]). In addition to examining the most commonly reported AEs, we assessed select AEs of clinical interest, including diarrhea, arthralgia, hypertension, rash, bleeding/bruising, fatigue, atrial fibrillation, and infections. Among these AEs of interest, hypertension, rash, and bleeding/bruising constituted pooled AE terms that included multiple preferred terms relevant to the AE of interest. Infections represented pooled AE preferred terms categorized under the "infections and infestations" system organ class. Diarrhea, rash, musculoskeletal pain/arthralgia, bruising, and fatigue are each noted as common adverse reactions to ibrutinib in the prescribing information; the "warnings and precautions" of the prescribing information also address infections, bleeding (hemorrhage), and atrial fibrillation.[13] Hematologic toxicities were graded according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (2008).[14] The protocol-specified criteria for treatment discontinuations are shown in supplemental Table 2.

Safety data were summarized using descriptive statistics, including medians for continuous variables and proportions for discrete variables. Kaplan-Meier methods were used for the landmark analysis of OS for each patient cohort in the studies evaluated.

Results

Integrated safety analysis

The integrated safety analysis of RESONATE and RESONATE-2 included 330 patients with CLL/SLL (Table 1). The majority of patients (66%) were male and had an Eastern Cooperative Oncology Group performance status of 1 (55%). The pooled cohort included 135 previously untreated patients (41%) and 195 relapsed/refractory patients, as published previously[3,4] (35/195 [11%] had been treated with 1 prior regimen, and 160/195 [48%] had been treated with ≥2 prior regimens). One patient randomized to ibrutinib treatment in RESONATE-2 did not receive a dose of study drug and was excluded from the safety analysis. High-risk

Table 1. Demographics and baseline disease characteristics in integrated safety analysis

Characteristic	Ibrutinib (N = 330)
Age, median (range), y	70 (30-89)
Male sex	217 (66)
ECOG performance status	
0	139 (42)
1	181 (55)
2	10 (3)
Baseline Rai stage III/IV	169 (51)
Bulky disease ≥5 cm, n/N (%)	178/329 (54)
Del(11q), n/N (%)	92/319 (29)
Del(17p)*, n/N (%)	60/328 (18)
Unmutated *IGHV*, n/N (%)	156/235 (66)
Complex karyotype, n/N (%)	45/245 (18)
β2-microglobulin >3.5 mg/L, n/N (%)	238/309 (77)
Creatinine clearance <60 mL/min, n/N (%)	121/329 (37)
CIRS score, median (range)	5 (0-20)
Cytopenia at baseline	
Any cytopenia	196 (59)
Absolute neutrophil count ≤1.5 × 10^9/L	51 (15)
Platelets ≤100 × 10^9/L	109 (33)
Hemoglobin ≤11 g/dL	140 (42)
No. of prior regimens	
0	135 (41)
1	35 (11)
≥2	160 (48)

Unless otherwise indicated, data are n (%).
CIRS, Cumulative Illness Rating Scale; ECOG, Eastern Cooperative Oncology Group; *IGHV*, immunoglobulin heavy chain variable.
*RESONATE enrolled patients with del(17p); RESONATE-2 excluded patients with del(17p).

Table 2. Treatment exposure and reasons for discontinuation in integrated safety analysis

	Ibrutinib (N = 330)
Treatment exposure	
Exposure, median (range), mo	29.0 (0.2-42.9)
Duration of treatment, mo	
≤6	32 (10)
>6 to 12	18 (5)
>12 to 24	34 (10)
>24 to 36	193 (58)
>36	53 (16)
Treatment discontinuation	124 (38)
PD	52 (16)
AE	37 (11)
Death	18 (5)
Physician decision	9 (3)
Withdrawal by patient	8 (2)

Unless otherwise noted, all data are n (%).

disease features were common (eg, unmutated *IGHV*, bulky disease) (Table 1). Patients often were of advanced age: 52% (173/330) were aged ≥70 years, and 24% (80/330) had a Cumulative Illness Rating Scale score > 6.

Patients received ibrutinib for a median of 29.0 months (range, 0.2-42.9) (Table 2). The median relative dose intensity of ibrutinib was 98% (range, 35-101). Concomitant treatments of interest for this safety analysis included CYP3 inhibitors (n = 176, 53%), antiplatelet agents (n = 164, 50%), anticoagulants (n = 92, 28%), packed red blood cell transfusions (n = 20, 6%), granulocyte growth factors (n = 9, 3%), and IV immunoglobulin (n = 6, 2%). Overall, 206 of 330 patients (62%) remained on ibrutinib treatment at the time of analysis, including 51% (99/195) of relapsed/refractory patients and 79% (107/135) of previously untreated patients. The most common primary reasons for discontinuation were PD (n = 52, 16%) and AEs (n = 37, 11%) (Table 2; supplemental Table 3). Discontinuations due to PD occurred more frequently among relapsed/refractory patients (25% [48/195]) than among previously untreated patients (3% [4/135]), whereas discontinuations due to AEs occurred at a similar rate between these patient populations (11% [21/195] and 12% [16/135], respectively). PD with Richter's transformation occurred in 14 relapsed/refractory patients but only in 1 previously untreated patient.

All 330 patients in the integrated analysis experienced AEs during the long-term follow-up. Diarrhea (n = 173, 52% any-grade; n = 15, 5% grade 3) and fatigue (n = 119, 36% any-grade; n = 10, 3% grade 3) were the most common all-grade AEs. The most common grade 3/4 AEs were neutropenia (n = 22, 7% grade 3; n = 38, 12% grade 4), pneumonia (n = 33, 10% grade 3; n = 5, 2% grade 4), hypertension (n = 21, 6% grade 3), and anemia (n = 21, 6% grade 3; n = 2, 1% grade 4) (Figure 1).

AEs contributing to dose discontinuations occurred in 10% (33/330) of patients in year 1, 5% (15/282) of patients in year 1 to 2, and 6% (15/249) of patients in year 2 to 3 (supplemental Table 4). AEs contributing to dose discontinuation in >1 patient included pneumonia (n = 4, 1%), anemia (n = 3, 1%), atrial fibrillation (n = 3, 1%), diarrhea (n = 2, 1%), subdural hematoma (n = 2, 1%), and thrombocytopenia (n = 2, 1%). Dose reductions due to AEs were reported in 13% (n = 42) of patients in the integrated analysis. AEs leading to dose reduction in >2 of 330 patients were diarrhea (n = 5, 2%), neutropenia (n = 4, 1%), atrial fibrillation (n = 4, 1%), anemia (n = 3, 1%), thrombocytopenia (n = 3, 1%), and arthralgia (n = 3, 1%). Twenty-eight patients (8%) died, most frequently due to PD (n = 9, 3%) or pneumonia/lung infection (n = 7, 2%) (supplemental Table 5). Seven of the 9 deaths due to PD occurred in relapsed/refractory patients, including 1 patient who died of progression with Richter's transformation. The remaining 2 deaths due to PD occurred in previously untreated patients.

We further analyzed the frequency and outcomes of select AEs of clinical interest (Table 3). These select AEs were primarily grade 1/2 and infrequently led to ibrutinib dose adjustments or discontinuations. Grade ≥3 infections occurred in 31% (101/330) of all patients and occurred more frequently among relapsed/refractory patients (36% [70/195]) than among previously untreated patients

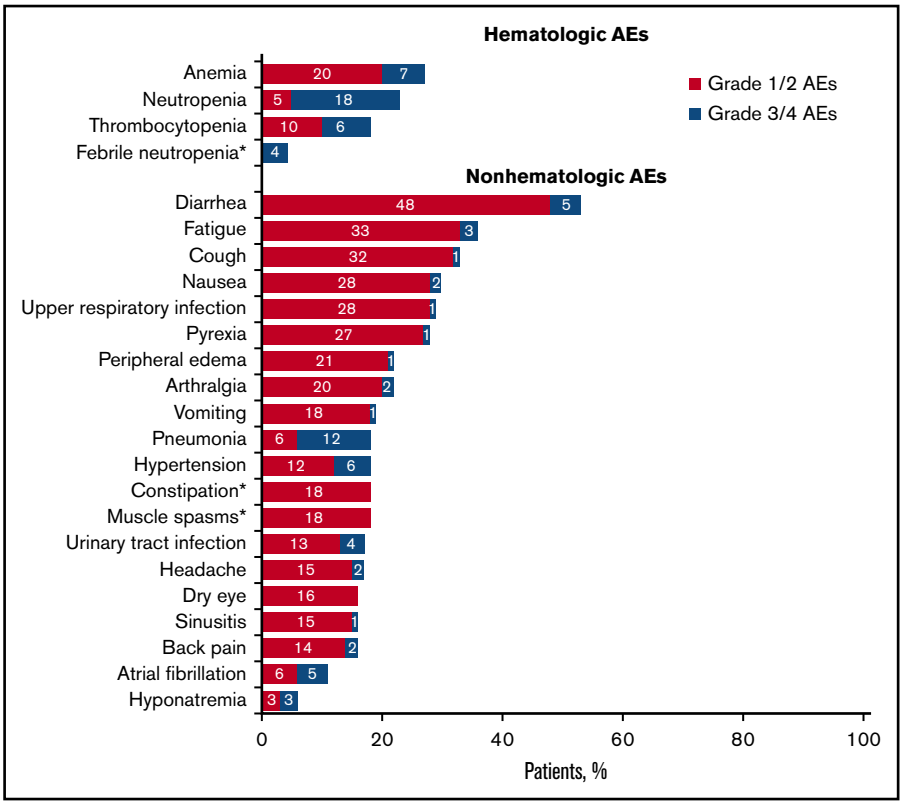

Figure 1. Most common treatment-emergent AEs in the integrated safety analysis (N = 330). AEs of any grade occurring in >15% of patients or grade 3/4 AEs occurring in >3% of patients are shown. *Muscle spasm and constipation included 1 (<1%) grade 3/4 AE each, and febrile neutropenia included 1 (<1%) grade 1/2 (AEs not shown).

(23% [31/135]). Opportunistic infections[15] of any grade occurred in 16% (54/330) of all patients, with the most common being herpes zoster (5% [15/330]) and oral herpes (4% [14/330]). A higher rate of opportunistic infection was observed among relapsed/refractory patients compared with those previously untreated (21% [41/196] vs 10% [13/135], respectively). Any-grade infections leading to dose reductions (1% [3/274] of all infections) or treatment discontinuations (6% [16/274] of all infections) were infrequent. The occurrence of any-grade atrial fibrillation was similar between relapsed/refractory and previously untreated patients (11% [22/195] and 10% [14/135], respectively). Any-grade bleeding events were frequent (n = 182, 55% any-grade combining multiple AE preferred terms for bleeding); however, grade ≥3 bleeding events were less common (n = 17, 5%) and occurred similarly among relapsed/refractory patients (5% [9/195]) and previously untreated patients (6% [8/135]). The majority of AEs of interest resolved during follow-up, per investigator assessment, with the exception of hypertension (resolution in 36% [25/69] of cases with standard medical management) (Table 3).

For diarrhea, fatigue, bleeding, rash, and grade ≥3 infections, prevalence rates were highest during the first year of treatment and decreased in frequency thereafter (Table 4). The prevalence of major hemorrhage events was low and consistent across time periods (year 1, 2% [8/330]; year 2, 3% [9/280]; year 3, 2% [5/246]). For arthralgia and atrial fibrillation, rates were relatively consistent over time. Among patients with atrial fibrillation, a substantial portion of events after the first-year interval were ongoing in nature; 50% of patients (6/12) with atrial fibrillation during year 2 and 37% of patients (7/19) with atrial fibrillation during year 3 also had events during earlier years. The incidence of atrial fibrillation across time was 6% (20/330) in year 1, 2% (6/280) in year 2, and 5% (12/246) in year 3. Although the prevalence of hypertension increased over time (year 1, 11% [36/330]; year 2, 15% [41/280]; year 3, 20% [48/246]), the incidence decreased after the first year (year 1, 11% [36/330]; year 2, 7% [19/280]; year 3, 7% [17/246]).

A similar analysis of hematologic AEs (Table 5) and their prevalence over time (Table 4) was also conducted. Febrile neutropenia was reported during the first 2 years of treatment but was uncommon overall (n = 14, 4%). Cytopenias occurred more frequently among relapsed/refractory patients (49% [95/195]) than in previously untreated patients (36% [49/135]). Cytopenias were reported most frequently during the first year of ibrutinib (anemia n = 68, 21%; neutropenia n = 64, 19%; thrombocytopenia n = 42, 13%) and decreased or remained stable during subsequent years of treatment.

Long-term safety analysis

The updated long-term safety analysis of PCYC-1102/1103 included 94 patients who received ibrutinib 420 mg daily for a median of 47.9 months (range, 0.3-67.4), ~19 months longer than the median for the integrated analysis. For the entire long-term cohort, the median relative dose intensity of ibrutinib was 98% (range, 35-101). Included in this cohort were 25 patients (27%) who were treated for >5 years with ibrutinib.

Overall, 78 patients (83%) had grade 3/4 AEs, most commonly hypertension (30% [28/94] grade 3), pneumonia (17% [16/94] grade 3), neutropenia (9% [8/94] grade 3; 6% [6/94] grade 4), and atrial fibrillation (11% [10/94] grade 3) (Figure 2). Grade 3/4 infections were reported in 41% (n = 39) of all patients (36% [34/94] grade 3; 5% [5/94] grade 4). The most frequently reported grade 3/4 AEs in PCYC-1102/1103 were generally similar to those

Table 3. Integrated safety analysis: frequency (by severity) of and outcomes with select AEs of clinical interest

	Diarrhea	Arthralgia	Fatigue	Atrial fibrillation	HTN*	Infection†	Rash*	Bleeding/bruising*
Any-grade AE, n (% of all patients)	173 (52)	74 (22)	119 (36)	36 (11)‡	69 (21)	274 (83)	117 (35)	182 (55)§
Grade 1	116 (35)	45 (14)	65 (20)	5 (2)	11 (3)	24 (7)	74 (22)	130 (39)
Grade 2	42 (13)	22 (7)	44 (13)	14 (4)	34 (10)	149 (45)	32 (10)	35 (11)
Grade 3	15 (5)	7 (2)	10 (3)	16 (5)	24 (7)	81 (25)	11 (3)	14 (4)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	12 (4)	0 (0)	2 (1)
Grade 5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (2)	0 (0)	1 (<1)
AE management and resolution, n (% of patients with the AE)								
AE(s) resolved¶	157 (91)	41 (55)	67 (56)	20 (56)	25 (36)	195 (71)	89 (76)	124 (68)
Received concomitant medication for management	64 (37)	45 (61)	3 (3)	30 (83)	45 (65)	257 (94)	65 (56)	41 (23)
Ibrutinib dose held for >7 d‖	14 (8)	3 (4)	7 (6)	7 (19)	2 (3)	50 (18)	9 (8)	20 (11)
Ibrutinib dose reduction	5 (3)	3 (4)	2 (2)	4 (11)	0 (0)	3 (1)	3 (3)	4 (2)
Ibrutinib discontinuation#	2 (1)	0 (0)	1 (1)	3 (8)	1 (1)	16 (6)	2 (2)	6 (3)
Median duration until resolution of AE(s),** d	7	33	57	3	34	13	31	23

HTN, hypertension.
*Pooled AE terms include multiple preferred terms relevant to the AE of interest.
†System organ class.
‡AE severity grade was not reported for 1 patient with atrial fibrillation.
§Twenty-one patients reported 25 major hemorrhage events, including grade 1 subdural hematoma (n = 1); grade 2 hyphema, subdural hematoma, and vitreous hemorrhage (n = 1 each); grade 3 hematuria (n = 3), postprocedural hemorrhage (n = 2), spontaneous hematoma (n = 2), subdural hematoma (n = 2), traumatic hematoma (n = 2), and ecchymosis, epistaxis, gastrointestinal hemorrhage, rectal hemorrhage, subarachnoid hematoma, subarachnoid hemorrhage, and vitreous hemorrhage (n = 1 each); grade 4 cerebral hemorrhage and subdural hematoma (n = 1 each); and grade 5 subdural hematoma (n = 1).
¶Resolved or resolved with sequelae, as assessed by the investigator. If patient had multiple AEs, then all AEs must have been deemed by the investigator to be resolved to be counted as resolved.
‖The onset of the missing dose event must have occurred on or ≤7 d after the related AE onset date.
#Includes patients with any AEs contributing to treatment discontinuation.
**Median event duration based on all resolved AEs.

found in the integrated safety analysis. In this study, 8 patients developed Richter's transformation.

Second malignancies of any grade were identified in 15 patients, most commonly basal cell carcinoma (n = 4), squamous cell carcinoma of the skin (n = 4), and myelodysplastic syndrome (n = 2). In 7 of these 15 patients, the second malignancy was diagnosed during the first year of ibrutinib therapy. The other cases occurred over time through the latest follow-up conducted after >5 years of treatment.

Table 4. Prevalence of select AEs of clinical interest over time with ibrutinib treatment in the integrated safety analysis (N = 330)

AE, n (%)	0-1 y (N = 330)	>1 to 2 y (n = 280)	>2 to 3 y (n = 246)
Hematologic AEs			
Anemia	68 (21)	24 (9)	21 (9)
Neutropenia	64 (19)	26 (9)	15 (6)
Thrombocytopenia	42 (13)	26 (9)	25 (10)
Febrile neutropenia	8 (2)	6 (2)	0
Nonhematologic AEs			
Diarrhea	155 (47)	56 (20)	38 (15)
Fatigue	97 (29)	65 (23)	53 (22)
Arthralgia	53 (16)	35 (13)	33 (13)
Atrial fibrillation	20 (6)	12 (4)	19 (8)
Pooled AE terms* or system organ class			
Hypertension	36 (11)	41 (15)	48 (20)
Bleeding	147 (45)	100 (36)	68 (28)
Rash	88 (27)	58 (21)	38 (15)
Grade ≥3 infections†	77 (23)	38 (14)	24 (10)

*Pooled AE terms include multiple preferred terms relevant to the AE of interest.
†AEs reported under "infections and infestations" system organ class category.

Table 5. Integrated safety analysis: frequency (by severity) of and outcomes with hematologic AEs

	Neutropenia	Anemia	Thrombocytopenia	Febrile neutropenia
Any-grade AE, n (% of all patients)	78 (24)	88 (27)	53 (16)	14 (4)
Grade 1	6 (2)	24 (7)	18 (5)	0 (0)
Grade 2	12 (4)	41 (12)	15 (5)	1 (< 1)
Grade 3	22 (7)	21 (6)	12 (4)	13 (4)
Grade 4	38 (12)	2 (1)	8 (2)	0 (0)
Grade 5	0 (0)	0 (0)	0 (0)	0 (0)
AE management and resolution, n (% of patients with the AE)				
AE(s) resolved*	66 (85)	64 (73)	26 (49)	14 (100)
Received concomitant medication for management	16 (21)	28 (32)	2 (4)	7 (50)
Ibrutinib dose held for >7 d†	18 (23)	9 (10)	7 (13)	3 (21)
Ibrutinib dose reduction	4 (5)	3 (3)	3 (6)	0 (0)
Ibrutinib discontinuation‡	1 (1)	3 (3)	3 (6)	0 (0)
Median duration until resolution of AE(s),§ d	14	17	15	5

*Resolved or resolved with sequelae, as assessed by the investigator. If patient had multiple AEs, then all AEs must have been deemed by the investigator to be resolved to be counted as resolved.

†The onset of the missing dose event must have occurred on or ≤7 d after the related AE onset date.

‡Includes patients with any AEs contributing to treatment discontinuation.

§Median event duration based on all resolved AEs.

Survival

Landmark survival rates were estimated separately for previously untreated and relapsed/refractory patients across the 3 clinical studies evaluated (supplemental Table 6). For previously untreated patients, the OS rate was 95% at 2 years in RESONATE-2 and 91% at 5 years in PCYC-1102/1103. For patients with relapsed/refractory disease, the OS rate was 74% at 3 years in RESONATE and 62% at 5 years in PCYC-1102/1103.

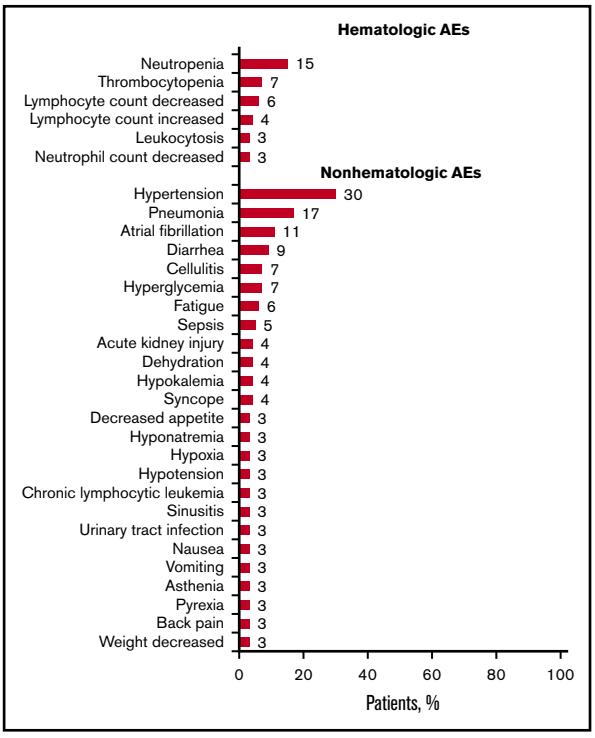

Figure 2. Most common grade 3/4 AEs in the PCYC-1102/1103 long-term cohort (n = 94). Grade 3/4 AEs occurring in >3% of patients are shown.

Discussion

This article characterizes the long-term safety of single-agent ibrutinib for the treatment of previously untreated and relapsed/refractory CLL/SLL. It includes safety information for the largest number of ibrutinib-treated patients with CLL/SLL described to date, who have received continuous treatment with ibrutinib for the longest period of time (in some cases >5 years).

Toxicities observed with prolonged continuous dosing of ibrutinib remain unchanged when compared with earlier reports with shorter treatment durations.[1-4,8] No new treatment-emergent events have been observed, and the prevalence rates of previously described events fall within the same range, with the exception of hypertension, for which prevalence increased over time. Additional analysis of the integrated safety data over time found that rates of many early-onset toxicities, including rash, fatigue, and diarrhea, declined over time, despite ongoing drug dosing, and few resulted in treatment discontinuations. In contrast, atrial fibrillation rates were persistent over time. Previous analyses have shown that atrial fibrillation typically occurs early after ibrutinib initiation and remains constant or declines over time.[8,16] Patients treated with ibrutinib should be periodically monitored clinically for atrial fibrillation.[17] For hypertension, although the incidence decreased over time, the increase in prevalence across the study underscores the need for vigilant monitoring and management. Bleeding events, which were primarily low-grade (grade 1/2) events, were most common during the first year (45%) and decreased in prevalence over time, although these events remained relatively frequent at 28% during the third year of ibrutinib treatment. Importantly, major hemorrhage

events were less common over the course of treatment. Effective monitoring and management of these complications likely led to infrequent dose reductions or discontinuation due to these AEs. Furthermore, ibrutinib was associated with relatively low rates of hematologic toxicities with continued dosing; cases of febrile neutropenia were particularly uncommon.

The significant ongoing disease control observed with continuous ibrutinib treatment likely contributes to its overall favorable safety profile. For example, heavily pretreated relapsed/refractory CLL/SLL patients often experience treatment-related cytopenias,[6,18] and the incidence of infection and mortality due to infection rises dramatically in these patients.[19-21] Infection is common in patients with CLL owing to the underlying disease, especially in patients whose disease is at an advanced stage and in patients who are exposed to immunosuppressive therapies.[10,22,23] This study demonstrates progressive declines in infection and neutropenia rates over time during ibrutinib treatment, consistent with previous analyses.[10,16,24] Following the approval of ibrutinib in CLL, there have been specific reports of opportunistic infections in patients treated with ibrutinib.[23,25] In the current report, the rate of opportunistic infections observed with ibrutinib was higher among patients who had received $\geq$1 prior therapy compared with previously untreated patients. Patients should be monitored for infection during ibrutinib therapy, with standard-of-care prophylaxis for opportunistic infections in patients at risk and anti-infective therapy administered as indicated.

This safety analysis, together with a median ibrutinib dose intensity of 98%, demonstrates that continuous treatment with ibrutinib is possible without significant AEs limiting its ongoing use in most patients. This finding is noteworthy in the context of previous reports that have shown that the quality and depth of the clinical response increase over time with continued ibrutinib treatment.[10,26-28] A recent network meta-analysis of randomized clinical trials showed superior benefit in survival and safety with ibrutinib compared with other first-line treatments for CLL.[29] According to the network meta-analysis of safety outcomes, ibrutinib was associated with the lowest risk of treatment discontinuations and discontinuations due to AEs vs comparators in the overall first-line population and the fludarabine-ineligible population.[29] Of note, higher discontinuation due to toxicity has been reported with ibrutinib outside of the clinical study setting.[30] Such variations in discontinuation rates between "real-world" and clinical studies are likely due to differences in patient and study characteristics. Long-term disease control with a well-tolerated therapy is an important goal of CLL/SLL treatment. It is especially important given that the average CLL/SLL patient is >70 years old when treatment is first required, and many of these patients will have comorbidities limiting the use of traditional chemoimmunotherapy.[31] Further follow-up of patients treated in clinical trials with ibrutinib will provide additional data to clinicians regarding the tolerability and safety of long-term treatment with ibrutinib in relapsed/refractory and first-line settings.

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