Ibrutinib Treatment for First-Line and Relapsed/Refractory Chronic Lymphocytic Leukemia: Final Analysis of the Pivotal Phase Ib/II PCYC-1102 Study

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ABSTRACT

Purpose: The safety and efficacy of ibrutinib, a once-daily Bruton's tyrosine kinase (BTK) inhibitor, in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) was demonstrated in this phase Ib/II study. Extended follow-up up to 8 years is described, representing the longest follow-up for single-agent ibrutinib, or any BTK inhibitor, to date.

Patients and Methods: Phase Ib/II PCYC-1102 (NCT01105247) and extension study PCYC-1103 (NCT01109069) included patients receiving single-agent ibrutinib in first-line or relapsed/refractory CLL/SLL.

Results: Overall response rate was 89%, with similar rates in first-line (87%; complete response, 35%) and relapsed/refractory settings (89%; 10%). Estimated 7-year progression-free survival (PFS) rates were 83% in first-line and 34% in relapsed/refractory settings. Forty-one patients had CLL progression ($n = 11$ with Richter's transformation). Median PFS was not reached with first-line ibrutinib. In relapsed/refractory CLL/SLL, median PFS was 52 months overall, 26 months in patients with chromosome 17p deletion, 51 months with 11q deletion, not reached with trisomy 12 or 13q deletion, and 88 months in patients without these cytogenetic abnormalities. Estimated 7-year overall survival rates were 84% in first-line and 55% in relapsed/refractory settings. Grade ≥3 adverse events (AE) in >15% of patients were hypertension (28%), pneumonia (24%), and neutropenia (18%). These grade ≥3 AEs generally declined over time, except hypertension. AEs leading to discontinuation in ≥2 patients were observed only in the relapsed/refractory setting (sepsis, diarrhea, subdural hematoma, and Richter's transformation).

Conclusions: With up to 8 years of follow-up, sustained responses and long-term tolerability of single-agent ibrutinib were observed with treatment of first-line or relapsed/refractory CLL/SLL, including high-risk CLL/SLL.

Introduction

Treatment for chronic lymphocytic leukemia (CLL) and other low-grade B-cell malignancies has changed significantly over the past decade, in great part as a consequence of identifying B-cell receptor signaling as a critical contributor to the initiation, progression, and maintenance of these diseases (1–4). The most vulnerable B-cell receptor kinase exploited therapeutically has been Bruton's tyrosine kinase (BTK); its congenital absence results in a predominantly B-cell–deficient phenotype with predisposition to select bacterial and viral infection (5–7). Genetic knockout or pharmacologic inhibition of BTK prevents or effectively controls the disease in preclinical murine models of CLL (2, 8). These observations prompted development of small molecules that inhibit BTK as a potential therapeutic option for CLL.

Ibrutinib, a once-daily, orally bioavailable inhibitor of BTK, was first introduced to clinical trials in February 2009 and represented a novel compound for treating B-cell malignancies and drug development. By virtue of the cysteine 481 residue on BTK, ibrutinib binds covalently, thereby inhibiting kinase activity. Restoration of cellular BTK activity requires the generation of new BTK protein (9, 10). Before this, application of irreversible kinase inhibitors had generally been avoided because of concern about potential toxicity and because adjunct formation between the BTK protein and irreversible inhibitor could theoretically promote a potentially life-threatening immune response. Covalent binding of ibrutinib allowed for monitoring target occupancy in surrogate and tumor cells via a labeled ibrutinib analogue (9). Great caution was employed within the first phase I study of ibrutinib, including intermittent dosing, but it became readily apparent that continuous administration was safe and more efficacious with significant, durable clinical activity noted at doses producing ≥90% BTK occupancy (11). Ibrutinib has demonstrated the most impact in CLL, extending both progression-free survival (PFS) and overall survival (OS) in the symptomatic, first-line, and relapsed/refractory treatment settings (12, 13). Clinically meaningful and durable responses to ibrutinib are observed regardless of high-risk genomic features, such as complex karyotype; chromosome 17p deletion [del(17)(13.1)],

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Clin Cancer Res 2020;26:3918–27

doi: 10.1158/1078-0432.CCR-19-2856

Translational Relevance

This report describes the longest follow-up to date for single-agent ibrutinib in the first-line and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) settings, providing valuable clinical data on durability of the efficacy and safety profile of ibrutinib. Sustained efficacy of single-agent ibrutinib was observed in first-line treatment and for relapsed/refractory CLL/SLL, including for patients with high-risk genomic factors. Of interest, the progression-free survival and overall survival benefits of ibrutinib were minimally impacted by complex karyotype in the absence of concurrent chromosome 17p deletion. With up to 8 years of follow-up, the safety profile shows continued tolerability and therapeutic benefit of long-term ibrutinib. Taken together, the sustained disease control and acceptable tolerability observed with prolonged single-agent ibrutinib treatment provide strong evidence for use in patients with CLL/SLL, even those with unfavorable disease characteristics.

referred to hereafter as del(17p); and mutated *TP53* (14, 15). Remissions with ibrutinib are durable overall, with decrements seen in patients with high-risk features (14, 15). However, single-agent ibrutinib therapy is associated with low frequency of complete response (CR) with undetectable minimal residual disease, and continuous therapy is believed to be required to maintain remission (12–14, 16–18). Such continuous therapy makes it important to understand the long-term effects of ibrutinib for patients with CLL. While side effects of ibrutinib in the short-term have been well characterized and include gastrointestinal symptoms, rash, ecchymosis/bruising, infection, ocular symptoms, atrial fibrillation, and hypertension, the impact of long-term treatment continues to be investigated (19–21).

PCYC-1102, a CLL/small lymphocytic lymphoma (SLL)-specific study initiated in 2010, examined the efficacy of single-agent ibrutinib in patients with CLL in both the first-line and relapsed/refractory settings and provided data for accelerated approval in patients with relapsed/refractory CLL (22, 23). Patients continuing to receive clinical benefit were allowed to enroll in PCYC-1103, a long-term extension study that prospectively assessed the persistence of therapeutic efficacy, toxicity, and long-term disease status (14, 15). PCYC-1103 was completed in November 2018. Herein is the final assessment of the long-term safety and efficacy in patients receiving single-agent ibrutinib with up to 8 years of follow-up, the longest follow-up to date for single-agent ibrutinib or any BTK inhibitor.

Patients and Methods

Study design and patients

Study design details have been published previously (22, 23). In brief, PCYC-1102 (NCT01105247) was a phase Ib/II, open-label, nonrandomized study of single-agent ibrutinib in the first-line (patients ≥65 years old) and relapsed/refractory (one or more prior therapies, including a purine analogue, in patients ≥18 years old) CLL/SLL treatment settings. After the primary analysis, patients who completed ≥6 treatment cycles without disease progression could participate in PCYC-1103 (NCT01109069), an open-label, extension study.

In PCYC-1102, ibrutinib 420 or 840 mg/day was administered in 28-day cycles until disease progression or unacceptable toxicity. Comparable safety and efficacy were observed during ongoing review between patients receiving ibrutinib 420 and 840 mg/day; the results were reported in the primary analysis for patients treated for relapsed/refractory CLL/SLL (420 mg/day, $n = 51$; 840 mg/day, $n = 34$) (22). Four patients receiving first-line ibrutinib also received 840 mg/day dosing, but the cohort was closed before full accrual after comparable efficacy of the doses was shown in the relapsed/refractory setting (22, 23). In PCYC-1103, patients continued ibrutinib at the same dose they received in PCYC-1102. The study was not designed to examine the two different dose levels in a comparative fashion and outcomes were not separated by dosage in long-term follow-up.

The study was conducted in accordance with principles of the Declaration of Helsinki, International Conference on Harmonisation, and Good Clinical Practice guidelines. Institutional review boards at each respective institution approved the study protocols and patients provided written informed consent.

Data sharing

Requests for access to individual participant data from clinical studies conducted by Pharmacyclics LLC, an AbbVie Company, can be submitted through Yale Open Data Access Project site at http://yoda.yale.edu.

Endpoints

The primary endpoint was frequency, severity, and relatedness of adverse events (AE). AEs were monitored from the first dose of ibrutinib until 30 days after the last dose, and grading was according to the NCI Common Terminology Criteria for Adverse Events v4.0. All-grade AEs were collected in PCYC-1102 (22, 23); in PCYC-1103, grade ≥3 AEs, grade ≥2 eye-related AEs, or any grade serious AEs, AEs leading to dose reduction, AEs leading to treatment discontinuation, other malignancies, and major hemorrhage were collected. AEs described herein are across the full study period combined for PCYC-1102 and PCYC-1103, unless otherwise specified. AEs of particular clinical interest identified during early ibrutinib clinical development are reported and include grade ≥3 bleeding, hypertension, atrial fibrillation, infection, thrombocytopenia, anemia, and arthralgia. Long-term efficacy was based on investigator assessment and included overall response rate [ORR, included partial response (PR) with lymphocytosis (PR-L)] (24, 25), duration of response (PR-L or better), PFS, and OS.

Subgroup and exploratory assessments

Baseline genomic testing was performed in a central laboratory; it included but was not limited to FISH, CpG-stimulated metaphase cytogenetics, and immunoglobulin heavy chain variable region (*IGHV*) mutational status (22, 23). Complex karyotype was defined as ≥3 unrelated chromosomal abnormalities. PFS and OS were assessed in patient subgroups with and without lymphocytosis at 1- and 2-year time points. Lymphocytosis at 1 year was defined as an absolute lymphocyte count $\geq 5 \times 10^9$/L between the first day of month 11 and the last day of month 13, and lymphocytosis at 2 years was defined as an absolute lymphocyte count $\geq 5 \times 10^9$/L between the first day of month 23 and the last day of month 25. Other exploratory analyses based on long-term follow-up data of single-agent ibrutinib included treatment-induced lymphocytosis (defined as absolute lymphocyte count $\geq 5 \times 10^9$/L), sustained hematologic improvement, and dose intensity. Sustained hematologic improvement in all treated patients with cytopenia at baseline was assessed; cytopenia was defined as platelet counts $\leq 100 \times 10^9$/L, hemoglobin levels ≤11 g/dL, and absolute neutrophil counts $\leq 1.5 \times 10^9$/L. Sustained hematologic improvement was defined as ≥56 days without blood transfusion or growth factors: platelets $>100 \times 10^9$/L if baseline $\leq 100 \times 10^9$/L or

>50% increase over baseline or hemoglobin >11 g/dL if baseline ≤11 g/dL or ≥2 g/dL increase over baseline; and absolute neutrophil count, >1.5 × 10^9/L if baseline ≤1.5 × 10^9/L or ≥50% increase over baseline. Evaluation of potential factors associated with achieving CR was done using logistic regression analyses. Variables tested included age (<65 vs. ≥65 years), sex (male vs. female), Eastern Cooperative Oncology Group performance status (ECOG PS, 0 vs. ≥1), del(11q) mutation status (no vs. yes), del(17p) mutation status (no vs. yes), *IGHV* mutation status (mutated vs. unmutated), Rai stage (0–II vs. III–IV), bulky disease (none vs. ≥5 cm), number of prior therapies (0 vs. ≥1 vs. 0–1 vs. ≥2), and β-2 microglobulin level (≤3.5 mg/L vs. >3.5 mg/L). Variables identified as significant at the $P < 0.1$ level based on univariate regression modeling were tested using stepwise multivariate regression to evaluate independent factors associated with achieving CR.

Statistical analysis

Analyses are reported for patients who received ≥1 dose of ibrutinib and represent outcomes for the 420 and 840 mg/day dose groups combined. Descriptive statistics were used to summarize findings. ORRs with 95% confidence intervals (CI) are reported, and the Kaplan–Meier method was used for time-to-event analysis. To explore the effects of subgroup analyses for PFS or OS, HRs and their 95% CIs are provided and were determined using Cox regression modeling. In the *post hoc* hypothesis testing subgroup analyses, *P* values were calculated for reference purposes only.

Results

Patients

In total, 132 patients were treated, including 31 treated with first-line ibrutinib and 101 treated for relapsed/refractory CLL/SLL. The median (range) age for patients in the first-line and relapsed/refractory settings was 71 years (65–84) and 64 years (37–82), respectively (**Table 1**). Baseline genomic characteristics in the first-line and relapsed/refractory settings, respectively, included many high-risk features particularly in patients with relapsed/refractory disease, with 4 (13%) and 37 (37%) patients with complex karyotype, 15 (48%) and 79 (78%) patients with unmutated *IGHV*, and 2 (6%) and 34 (34%) with del(17p). For patients with relapsed/refractory CLL/SLL, 22 (22%) and 15 (15%) patients had complex karyotype with and without del(17p), respectively. The median (range) number of prior therapies in the relapsed/refractory setting was 4 (1–12).

Patient disposition

The median (range) follow-up was 87 months (1–98) in the first-line and 82 months (0.7+ to 98) in relapsed/refractory settings. Median (range) average daily dose in the first-line ($n = 27$) and relapsed/refractory settings ($n = 67$) for patients who received 420 mg/day initially in PCYC-1102 was 420 mg/day (317–420) and 420 mg/day (175–422), respectively (Supplementary Table S1). The median (range) treatment duration was 75 months (0.3–98) in the first-line and 39 months (0.3–98) in relapsed/refractory treatment settings (Supplementary Table S1). At the time of study closure, 12 patients (39%) and 16 patients (16%) in the first-line and relapsed/refractory settings, respectively, remained on ibrutinib treatment, and subsequent to study closure continued ibrutinib treatment (either in a rollover study or per investigator reporting of commercial ibrutinib use). Most frequent primary reasons for treatment discontinuation were disease progression [first-line, 6% (2/31); relapsed/refractory, 38% (38/101)] and AEs [first-line, 26% (8/31); relapsed/refractory, 23% (23/101)]. Among the 38 patients who received 840 mg/day dosing, 3 patients remained on ibrutinib at the time of study closure (1 patient was receiving 840 mg/day and 2 patients were receiving 420 mg/day at end of the study), and subsequent to study closure continued ibrutinib treatment (either in a rollover study or commercial ibrutinib). The most frequent primary reasons for treatment discontinuation among those receiving 840 mg/day dosing were disease progression [37% (14/38)] and AEs [24% (9/38)].

In 41 patients with disease progression, 30 progressed without Richter's transformation (first-line, $n = 1$; relapsed/refractory, $n = 29$). The median (range) time to CLL progression without Richter's transformation was 38 months [1–88; first-line, 75 (75–75); relapsed/refractory, 38 (1–88)], with these CLL progression events occurring most frequently beyond 3 years of treatment [≤1 year, 2/132 (2%); >1–2 years, 4/103 (4%); >2–3 years, 6/89 (7%); >3–4 years, 7/79 (9%); >4–5 years, 5/63 (8%); >5–6 years, 2/50 (4%); and years >6, 4/37 (11%)]. Richter's transformation was reported for 11 patients (first-line, $n = 1$; relapsed/refractory, $n = 10$). Richter's transformation was primarily an early event with a median time to

Table 1. Baseline demographics and clinical characteristics of patients receiving ibrutinib in the first-line and relapsed/refractory treatment settings.

	First-line ≥65 years $n = 31$	Relapsed/refractory $n = 101$
Median age, years (range)	71 (65–84)	64 (37–82)
≥70 years, *n* (%)	23 (74)	34 (34)
Male, *n* (%)	19 (61)	79 (78)
ECOG PS, *n* (%)		
0	23 (74)	43 (43)
1	8 (26)	54 (53)
2	0	4 (4)
Bulky disease ≥5 cm, *n* (%)	6 (19)	55 (54)
Baseline Rai stage III–IV, *n* (%)	17 (55)	58 (57)
Cytogenetics[a], *n* (%)		
Del(17p)	2 (6)	34 (34)
Del(11q)	1 (3)	28 (28)
Trisomy 12	8 (26)	5 (5)
Del(13q)	13 (42)	13 (13)
No abnormality detected	6 (19)	16 (16)
β-2 microglobulin level >3 mg/L, *n* (%)	8 (26)	49 (49)
Unmutated *IGHV, n* (%)	15 (48)	79 (78)
Complex karyotype[b], *n* (%)	4 (13)	37 (37)
Complex karyotype with del(17p), *n* (%)	0	22 (22)
Complex karyotype without del(17p), *n* (%)	4 (13)	15 (15)
ANC ≤1.5 × 10^9/L	1 (3)	34 (34)
Hemoglobin ≤11 g/dL, *n* (%)	11 (35)	42 (42)
Platelets ≤100 × 10^9/L, *n* (%)	12 (39)	49 (49)
Median prior therapy, *n* (range)	—	4 (1–12)
Number of prior therapies, *n* (%)		
1–2	—	27 (27)
3	—	14 (14)
≥4	—	60 (59)

Abbreviation: ANC, absolute neutrophil count.
[a]FISH cytogenetic subgroups are presented in a hierarchy of CLL chromosomal abnormalities based on Döhner classification (26). A total of 1 patient receiving first-line ibrutinib and 5 patients receiving ibrutinib for relapsed/refractory CLL/SLL had missing FISH cytogenetic data.
[b]Complex karyotype was performed at a central laboratory and was defined as ≥3 unrelated chromosomal abnormalities by CpG stimulated metaphase cytogenetics.

Table 2. Investigator-assessed best responses in patients receiving ibrutinib in the first-line and relapsed/refractory treatment settings.

	First-line ≥65 years *n* = 31	Relapsed/refractory[a] *n* = 101
ORR (CR+CRi+nPR+PR+PR-L), *n* (%)	27 (87)	90 (89)
Best response, *n* (%)		
CR	11 (35)	10 (10)
CRi	0	0
nPR	0	0
PR	14 (45)	77 (76)
PR-L	2 (6)	3 (3)
SD, *n* (%)	2 (6)	4 (4)
PD, *n* (%)	0	2 (2)
No assessment, *n* (%)[b]	2 (6)	4 (4)

Abbreviations: CRi, complete response with incomplete marrow recovery; nPR, nodular partial response; SD, stable disease.
[a]One patient treated for relapsed/refractory CLL/SLL was not evaluable.
[b]Patients without any postbaseline response assessment.

Richter's transformation of 11 months (range, 1–26) for all patients, 10 months for the 1 patient receiving first-line treatment, and 11 months (range, 1–26) for patients treated for relapsed/refractory CLL/SLL. Most transformations occurred during the first year of treatment (≤1 year, $n = 8$; >1–2 years, $n = 2$; >2–3 years, $n = 1$; and years >3, no cases).

Long-term response

ORR was 89% (117/132), with similar rates observed in the first-line (87%; 27/31) and relapsed/refractory (89%; 90/101) settings (**Table 2**). The CR rate overall was 16% (21/132) and was substantially higher in the first-line setting (35%; 11/31) than relapsed/refractory setting (10%; 10/101). The median (range) duration of response was not reached (NR, 0+–96+) with first-line treatment and was 57 months (0+–96+) with treatment for relapsed/refractory CLL/SLL. Median (range) time to initial response of PR-L or better was similar in the first-line and relapsed/refractory settings [2 (2–51) vs. 2 (1–12) months]. The median (range) time to CR was 38 months (7–76) and 28 months (5–46) in the first-line and relapsed/refractory settings, respectively. Depth of response improved over time in the 77 (58%) patients with initial PR-L; 72/77 (94%) patients with PR-L achieved a PR or better [first-line, 12/14 (86%); relapsed/refractory, 60/63 (95%)]. In the relapsed/refractory setting, ORR was high (≥79%) across all tested chromosomal abnormalities, including patients with del(17p) (**Table 3**).

Table 3. Best responses by Döhner hierarchy (26) for chromosomal abnormality in patients receiving ibrutinib for relapsed/refractory CLL/SLL.

	Relapsed/refractory *n* = 101	
	ORR (CR+CRi+nPR+PR+PR-L), *n/N* (%)	CR, *n/N* (%)
Del(17p)	27/34 (79)	2/34 (6)
Del(11q)	27/28 (96)	2/28 (7)
Trisomy 12	4/5 (80)	0/5
Del(13q)	12/13 (92)	2/13 (15)
No abnormality	15/16 (94)	2/16 (13)
Missing	5/5 (100)	2/5 (40)

Abbreviations: CRi, complete response with incomplete marrow recovery; nPR, nodular partial response.

Possible associations between baseline factors and CR were evaluated in univariate then multivariate analyses. Factors identified as significant in univariate modeling were ECOG PS (0 vs. ≥1), Rai stage (0–II vs. III–IV), bulky disease (none vs. ≥5 cm), and number of previous lines of therapy (0 vs. ≥1 and 0 vs. ≥2). Of these factors, multivariate analysis showed lower Rai stage (0–II vs. III–IV; OR, 0.120; $P = 0.0032$) and fewer number of previous lines of therapy (0–1 vs. ≥3; OR, 0.103; $P = 0.0160$) were significantly associated with the odds of achieving a CR.

Long-term survival outcomes

Median PFS was NR [95% CI, not estimable (NE)–NE] with first-line treatment and was 52 months (38–70) with treatment for relapsed/refractory CLL/SLL (**Fig. 1A**); estimated 7-year PFS rates were 83% and 34%, respectively. For patients with relapsed/refractory CLL/SLL, median PFS trended longer in patients with 1–2 prior lines of therapy [66 months (95% CI, 37–NE); one prior line, $n = 3$; two prior lines, $n = 24$] and patients with three prior lines of therapy [59 months (22–NE); $n = 14$] versus patients with ≥4 prior lines of therapy [39 months (26–51); $n = 60$; Supplementary Fig. S1A]. Median PFS varied by chromosomal abnormality for patients treated for relapsed/refractory CLL/SLL, although the CIs for the subgroups were wide and overlapping (**Fig. 1B**). Median PFS for relapsed/refractory patients without ($n = 49$) and with ($n = 37$) complex karyotype was 73 months (95% CI, 40–NE) and 31 months (95% CI, 20–43), respectively. Interestingly, median PFS for patients treated for relapsed/refractory CLL/SLL with both complex karyotype and del(17p) ($n = 22$) was 25 months (95% CI, 12–33), while median PFS for those with complex karyotype without concurrent del(17p) ($n = 15$) was 88 months (95% CI, 14–NE; Supplementary Fig. S1B).

Median PFS was substantially longer in patients with versus without lymphocytosis at the 1-year (92 vs. 52 months) or 2-year (92 vs. 62 months) time points (Supplementary Fig. S1C and S1D). Estimated 7-year PFS rates in patients with lymphocytosis at 1 and 2 years were 54% and 56%, respectively, and were 39% and 43% in patients without lymphocytosis at those time points, respectively. PFS was similar for patients who achieved PR-L or CR/PR within the first year of treatment (Supplementary Fig. S1E). Median PFS appeared best in patients aged >60–≤80 years (Supplementary Fig. S1F).

With a median (range) follow-up of 87 months (1–98) for first-line treatment, median OS was NR (95% CI, NE–NE) and the estimated 7-year OS rate was 84% (**Fig. 2A**). With a median (range) follow-up of 82 months (0.7+–98) for treatment for relapsed/refractory CLL/SLL, median OS was 92 months (95% CI, 66–NE) and the estimated 7-year OS rate was 55% (**Fig. 2A**). As seen with PFS, median OS trended longer for patients treated for relapsed/refractory CLL/SLL with fewer prior lines of therapy: 1–2 (NR; 95% CI, 63–NE) and three prior lines of therapy (NR; 95% CI, NE–NE) versus those with four or more prior lines of therapy (70 months; 95% CI, 41–NE; Supplementary Fig. S2A). Median OS varied by chromosomal abnormality for patients treated for relapsed/refractory CLL/SLL, although the CIs for the subgroups were wide and overlapping (**Fig. 2B**). Median OS for patients treated for relapsed/refractory CLL/SLL without and with complex karyotype was NR (95% CI, 82–NE) and 54 months (95% CI, 25–NE), respectively. Median OS was 32 months (95% CI, 17–NE) for patients treated for relapsed/refractory CLL/SLL with both complex karyotype and

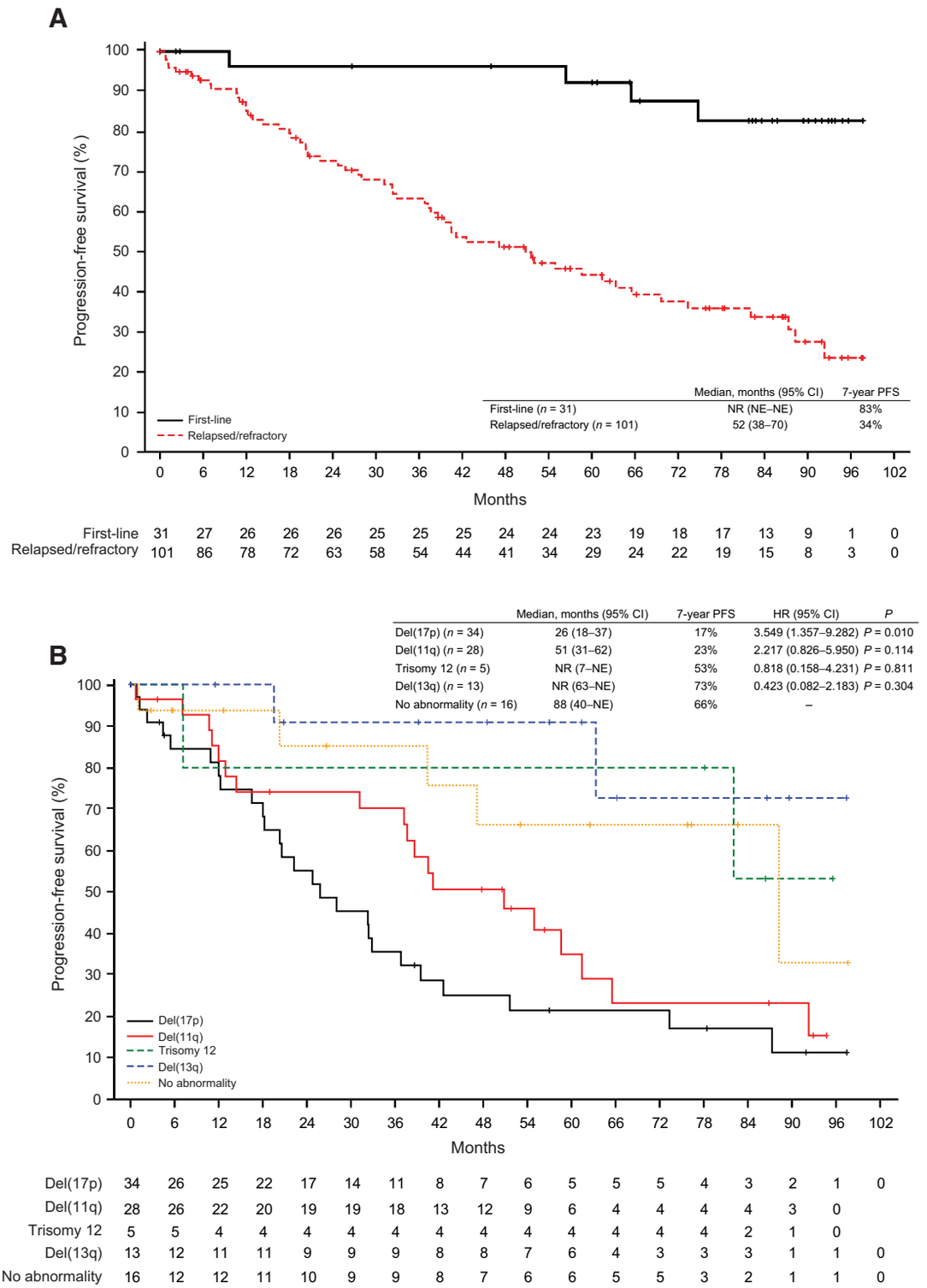

Figure 1.

PFS in patients receiving ibrutinib in the first-line and relapsed/refractory treatment settings (**A**) and by chromosomal abnormality in the relapsed/refractory setting (**B**). Cytogenetic subgroups presented in a hierarchy of CLL chromosomal abnormalities based on Döhner classification (26). Progression-free time is calculated as the number of months from first dose date of study treatment to disease progression or death or date of censoring. Patients were censored if they were not assessed as having disease progression by investigators or died at the time of analysis. Tick marks represent censored patients. In panel **B**, HR, 95% CI, and *P* value are for cytogenetic subgroups versus no abnormality subgroup.

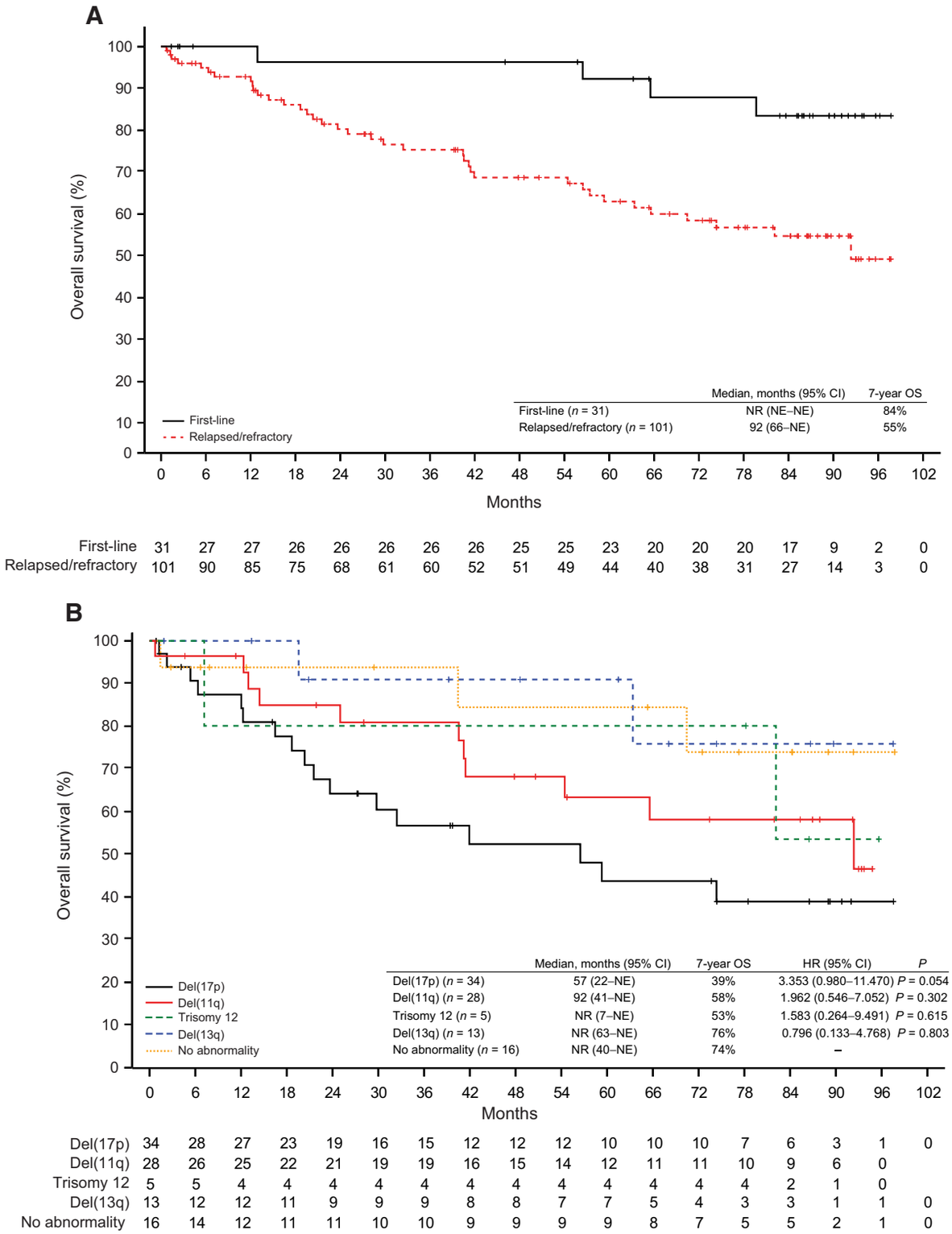

Figure 2.

OS in patients receiving single-agent ibrutinib in the first-line and relapsed/refractory treatment settings (**A**) and by chromosomal abnormality for patients treated for relapsed/refractory CLL/SLL (**B**). Cytogenetic subgroups presented in a hierarchy of CLL chromosomal abnormalities based on Döhner classification (26). OS time is calculated as the number of months from first dose date of study treatment to death or date of censoring. Tick marks represent censored patients. In panel **B**, HR, 95% CI, and *P* value are for cytogenetic subgroups versus no abnormality subgroup.

del(17p) compared with 92 months (95% CI, 25–NE) in patients with complex karyotype without del(17p) (Supplementary Fig. S2B).

Lymphocytosis upon treatment was observed in 29 patients receiving first-line treatment and 86 patients treated for relapsed/refractory CLL/SLL. Median OS for patients with versus without lymphocytosis at the 1 year or 2 year time points was NR (Supplementary Fig. S2C and S2D). Estimated 7-year OS rates in patients with lymphocytosis at 1 year and 2 years were 71% at both time points, and 54% and 60% in patients without lymphocytosis, respectively. The median (range) time to lymphocytosis was 0.26 months in both the first-line (range, 0.1–0.3) and relapsed/refractory settings (range, 0.1–3.7). Among patients treated for relapsed/refractory CLL/SLL with chromosomal abnormalities (by Döhner hierarchy) (26), lymphocytosis was observed in 31 of 34 (91%) patients with del(17p), 23 of 28 (82%) patients with del(11q), 4 of 5 (80%) patients with trisomy 12, 13 of 13 (100%) patients with del(13q), and 11 of 16 (69%) patients with no above mentioned abnormality. The median (95% CI) time to lymphocytosis resolution was 15 months (8–35) in first-line and 10 months (6–13) in the relapsed/refractory setting.

OS was similar regardless of whether patients achieved a PR-L or CR/PR within the first year of treatment (Supplementary Fig. S2E). With up to 98 months of follow-up overall, patients with disease progression within 1 ($n = 10$), >1–3 ($n = 13$), or >3–5 ($n = 12$) years of treatment initiation had a median OS after disease progression of 5 months (95% CI, 0.4–13), 14 months (95% CI, 3–50), and NR (95% CI, 5–NE), respectively. Median OS after disease progression was shorter for patients who had progressive disease (PD) with Richter's transformation ($n = 11$; median 4 months; 95% CI, 0.9–5) than for those who had PD without Richter's transformation ($n = 27$; median 50 months; 95% CI, 14–56). Patients who discontinued treatment due to an AE within 1 ($n = 11$), >1–3 ($n = 6$), >3–5 ($n = 7$), or >5 ($n = 7$) years had a median OS after discontinuation of 6 months (95% CI, 0.2–10), 1 month (95% CI, 0.1–NE), 6 months (95% CI, 1–NE), and 20 months (95% CI, 0–20), respectively. Median OS trended better in patients >50 years old compared with ≤50 years old (Supplementary Fig. S2F).

Sustained hematologic improvement

In patients with baseline cytopenias, sustained hematologic improvement in platelet counts, hemoglobin levels, and absolute neutrophil counts were observed in both the first-line [8/12 (67%), 9/11 (82%), and 1/1 (100%), respectively] and relapsed/refractory [40/49 (82%), 35/42 (83%), and 28/34 (82%)] settings.

Safety

All-grade AEs collected in PCYC-1102 have been described previously (22, 23). The most frequent grade ≥3 AEs (>15% of all patients) were hypertension ($n = 37$; 28%), pneumonia ($n = 32$; 24%), and neutropenia ($n = 24$; 18%). Onset of grade ≥3 AEs from time of first dose generally decreased over time, with variation observed for different AEs. Hypertension was a notable exception, with rates that did not decrease over time. Similar trends in onset over time were seen for all grade AEs collected in PCYC-1102 and PCYC-1103 (combined) up to June 2012, after which only grade ≥3 AEs with exceptions (as noted in the Patients and Methods) were collected per protocol (**Fig. 3**; Supplementary Fig. S3).

In general, grade ≥3 AEs were less frequent with first-line treatment than treatment for relapsed/refractory CLL/SLL [$n = 25$ (81%) vs. $n = 91$ (90%)], despite longer median time on first-line ibrutinib (75 vs. 39 months). Grade ≥3 AEs occurring >5% more frequently with first-line treatment than treatment for relapsed/refractory CLL/SLL were hypertension [$n = 11$ (35%) vs. $n = 26$ (26%)], diarrhea [$n = 5$ (16%) vs. $n = 4$ (4%)], and hyponatremia [$n = 3$ (10%) vs. $n = 0$; Supplementary Table S2]. Grade ≥3 AEs occurring >5% more frequently with treatment for relapsed/refractory CLL/SLL than with first-line treatment were pneumonia [$n = 28$ (28%) vs. $n = 4$ (13%)], neutropenia [$n = 22$ (22%) vs. $n = 2$ (6%)], thrombocytopenia [$n = 11$ (11%) vs. $n = 1$ (3%)], sepsis [$n = 9$ (9%) vs. $n = 1$ (3%)], and cellulitis [$n = 9$ (9%) vs. $n = 0$; Supplementary Table S2].

Treatment-related grade ≥3 AEs occurred in 10 (32%) patients receiving first-line treatment and 40 (40%) patients treated for relapsed/refractory CLL/SLL. Onset of treatment-related grade ≥3 AEs from time of first dose was most frequent in year 1 ($n = 5$, 16%) and less frequent in years 2 ($n = 2$, 8%), 3 ($n = 1$, 4%), 4 ($n = 0$), 5 ($n = 3$, 13%), 6 ($n = 2$, 9%), and 7 ($n = 0$) for patients receiving first-line treatment. Similarly, for patients treated for relapsed/refractory CLL/SLL, onset of treatment-related grade ≥3 AEs from time of first dose was most frequent in year 1 ($n = 27$, 27%) and less frequent in years 2 ($n = 5$, 6%), 3 ($n = 6$, 10%), 4 ($n = 4$, 7%), 5 ($n = 0$), 6 ($n = 3$, 11%), and 7 ($n = 1$, 5%).

The frequency and pattern of onset for AEs identified during early ibrutinib clinical development as being of clinical interest for ibrutinib are reported in Supplementary Fig. S4. The rate of grade ≥3 atrial fibrillation [first-line: $n = 2$ (6%); relapsed/refractory: $n = 10$ (10%)], thrombocytopenia [$n = 1$ (3%); $n = 11$ (11%)], anemia [$n = 0$; $n = 3$ (3%)], and arthralgia [$n = 0$; $n = 1$ (1%)] was ≤11% in all patients. The rate of grade ≥3 bleeding was similar in the first-line [$n = 3$ (10%)] and relapsed/refractory settings [$n = 9$ (9%)]. Although limited by small numbers of patients with events, the onset of grade ≥3 bleeding from first dose was highest in years 1–3 in the first-line and year 1 in relapsed/refractory settings. No other events of major hemorrhage were reported. The rate of grade ≥3 hypertension, as noted, was more frequent with first-line treatment than treatment for relapsed/refractory CLL/SLL and the onset from time of first dose was gradual and highest in later years (3–6) for both treatment settings. The rate of grade ≥3 infections was lower with first-line treatment than treatment for relapsed/refractory CLL/SLL [$n = 8$ (26%) vs. $n = 56$ (55%)]. The onset of grade ≥3 infections from time of first dose fluctuated over time with first-line treatment (yearly onset range, 0%–14%), whereas it was most frequent in year 1 and declined over time with treatment for relapsed/refractory CLL/SLL. Pneumonia was the most frequent infection in the first-line ($n = 4$, 13%) and relapsed/refractory settings ($n = 28$, 28%; Supplementary Table S3). Grade 4 infections were infrequent [first-line: $n = 1$ (3%); relapsed/refractory: $n = 6$ (6%)]; no fatal infections occurred with first-line treatment and six occurred in patients treated for relapsed/refractory CLL/SLL (pneumonia, $n = 3$; sepsis, pneumonia cryptococcal, and pneumonia influenza, $n = 1$ each). Cataract ($n = 8$; 6%) was the most common grade ≥2 eye-related condition [first-line: $n = 3$ (10%); relapsed/refractory: $n = 5$ (5%)]. Second malignancies were reported in 6 patients (19%) receiving first-line treatment, and 27 (27%) of those treated for relapsed/refractory CLL/SLL. Nonmelanoma skin cancers were noted in 2 (6%) patients receiving first-line treatment and 20 (20%) treated for relapsed/refractory CLL/SLL. Nonskin cancers occurred in 6 (19%) patients receiving first-line treatment and 15 (15%) treated for relapsed/refractory CLL/SLL (Supplementary Table S4).

Serious AEs occurred in 21 (68%) patients receiving first-line treatment and 79 (78%) treated for relapsed/refractory CLL/SLL. The most frequently occurring serious AEs (≥5% of patients) with first-line treatment were pneumonia ($n = 4$, 13%), atrial fibrillation ($n = 3$, 10%), hypertension ($n = 2$, 6%), pyrexia ($n = 2$, 6%) and pneumonia ($n = 27$, 27%), atrial fibrillation ($n = 10$, 10%), cellulitis

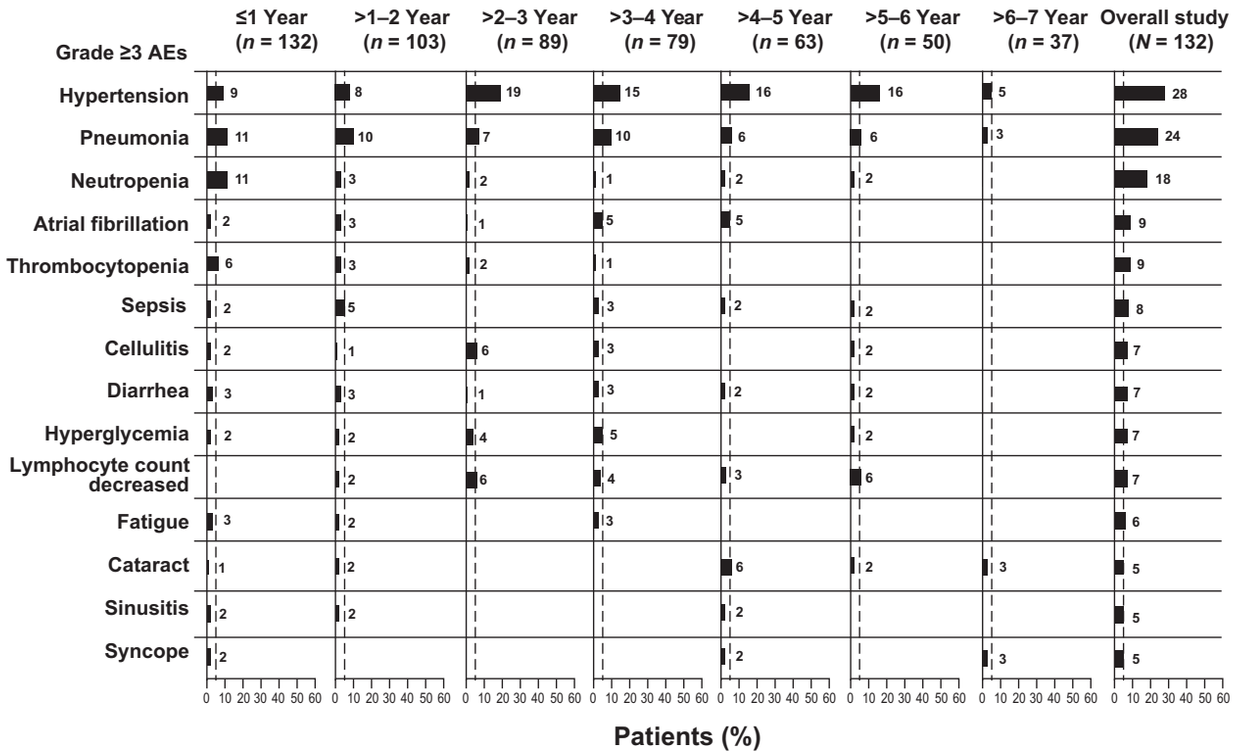

Figure 3.
Grade ≥3 AEs by time to onset from first dose occurring in ≥5% of patients receiving ibrutinib. The dashed lines represent a 5% rate. Numbers at the end of each bar represent the percentage of patients with AE onset during that time interval.

($n = 9$, 9%), sepsis ($n = 9$, 9%), bacteremia ($n = 5$, 5%), and febrile neutropenia ($n = 5$, 5%) with treatment for relapsed/refractory CLL/SLL. For first-line treatment, onset of serious AEs from time of first dose was most frequent in year 1 ($n = 8$, 26%) and generally occurred less frequently in years 2 ($n = 6$, 23%), 3 ($n = 1$, 4%), 4 ($n = 4$, 16%), 5 ($n = 6$, 25%), 6 ($n = 3$, 14%), and 7 ($n = 1$, 6%). Similarly for treatment for relapsed/refractory CLL/SLL, the onset of serious AEs from time of first dose was most frequent in year 1 ($n = 53$, 53%) and was less frequent in years 2 ($n = 34$, 44%), 3 ($n = 21$, 33%), 4 ($n = 19$, 35%), 5 ($n = 12$, 31%), 6 ($n = 5$, 18%), and 7 ($n = 3$, 14%). Treatment-related serious AEs occurred in 5 (16%) patients receiving first-line treatment and 12 (12%) patients treated for relapsed/refractory CLL/SLL. The onset of treatment-related serious AEs from time of first dose was most frequent in year 1 in both the first-line ($n = 3$, 10%) and relapsed/refractory ($n = 9$, 9%) settings, with no patients experiencing treatment-related serious AEs in subsequent years except for 2 (8%) patients in year 5 in the first-line setting and 2 (3%) patients in year 3 and 1 (2%) patient in year 4 in the relapsed/refractory setting. Fatal AEs occurred in 1 patient receiving first-line treatment (secondary malignancy, $n = 1$) and 13 patients treated for relapsed/refractory CLL/SLL [pneumonia, $n = 5$; secondary malignancy, $n = 3$; sepsis/multiorgan dysfunction, $n = 3$; respiratory failure (secondary to chronic obstructive pulmonary disorder), $n = 1$; or cardiac disorders, $n = 1$]. Events of disease progression captured as fatal AEs occurred in 1 patient receiving first-line treatment (Richter's transformation, $n = 1$) and 5 treated for relapsed/refractory CLL/SLL (CLL progression without transformation, $n = 3$; Richter's transformation, $n = 2$).

AEs led to dose reduction in 4 (13%) patients receiving first-line treatment and 19 (19%) treated for relapsed/refractory CLL/SLL and were more common in year 6 with first-line treatment and year 7 for treatment for relapsed/refractory CLL/SLL (Supplementary Table S1). The most frequently reported AEs (≥2 of all patients) leading to dose reduction were diarrhea [first-line: $n = 1$ (3%); relapsed/refractory: $n = 2$ (2%)], fatigue [relapsed/refractory: $n = 2$ (2%)], hypertension [relapsed/refractory: $n = 2$; (2%)], nausea [first-line: $n = 1$ (3%); relapsed/refractory: $n = 1$ (1%)], and neutropenia [relapsed/refractory: $n = 2$ (2%)]. AEs led to treatment discontinuation in 8 (26%) patients receiving first-line treatment and 29 (29%) patients treated for relapsed/refractory CLL/SLL, with most treatment discontinuations for AEs generally occurring in year 1 (Supplementary Table S1). AEs leading to discontinuation in ≥2 of all patients were sepsis ($n = 3$), diarrhea, and subdural hematoma ($n = 2$ each) and occurred in the relapsed/refractory setting. Richter's transformation was captured as an AE leading to discontinuation for 2 patients treated for relapsed/refractory CLL/SLL.

Discussion

The long-term safety and efficacy data described herein for single-agent ibrutinib in patients with CLL/SLL demonstrate that ibrutinib is a very effective long-term therapy in both the first-line and relapsed/refractory settings. Sustained responses were observed, with improved quality of response over time from the initial reports (22, 23). For patients who received first-line ibrutinib, remissions were durable with only a small subset of patients progressing. In contrast, patients with

prior CLL/SLL therapy before ibrutinib, in particular those who received four or more prior therapies and those with del(17p), more frequently progressed. Of particular interest, the benefit of ibrutinib (PFS and OS) was minimally impacted by complex karyotype in the absence of concurrent del(17p). Lymphocytosis at 1 and 2 years was associated with longer PFS in this patient population; however, this observation should be interpreted with caution, given that many patients were highly pretreated, with other baseline clinical and/or biological factors potentially contributing to this observation. Notably, PFS was similar in patients with any response within the first year, including even those with PR-L.

At a median follow-up of 85 months, no new serious AEs have been noted, and the most frequently occurring grade ≥3 AEs are as reported previously (15). The onset of grade ≥3 hypertension from time of first dose was gradual and most frequent in years 3–6 with both first-line treatment and treatment for relapsed/refractory CLL/SLL. In contrast, the yearly onset of grade ≥3 infection from time of first dose fluctuated over time for patients receiving first-line treatment. Grade ≥3 infection was most frequent in the first year for patients receiving treatment for relapsed/refractory CLL/SLL and gradually declined over time. These patterns likely reflect cellular and innate immune recovery previously described with ibrutinib over more than 4 years of treatment; longer-term effects of ibrutinib on immune function remain to be elucidated (14, 22, 27). High rates of grade ≥3 infection are expected in this study given the patients' baseline demographic and disease characteristics, which were indicative of a heavily pretreated population with advanced disease. Exposure to immunosuppressive therapy and advanced disease stage has been established as factors that increase susceptibility to infection in patients with CLL (28, 29). Ibrutinib was generally well-tolerated with prolonged treatment; discontinuations due to AEs were similar in the first-line and relapsed/refractory settings. No fatal cardiac or unknown events were observed among the 31 patients ≥65 years old receiving first-line treatment. Extended follow-up allowed for more complete understanding of the frequencies of relapse and AEs occurring on therapy over time. It is notable that Richter's transformation developed at a median (range) of 11 months (1–26) after starting ibrutinib in the 11 patients who experienced Richter's transformation. In contrast, CLL progression without transformation occurred at a median (range) of 38 months (1–88) from starting ibrutinib. Patients relapsing with CLL early (≤3 years) had shorter survival compared with those with relapse >3 years, suggesting that patients relapsing after extended periods (>3 years) may have a different natural history. Similarly, we examined the outcome of patients who had to discontinue ibrutinib due to AEs versus disease progression using a landmark survival analysis. This analysis demonstrated shorter survival in those who ceased therapy early regardless of causality (AE or disease progression), whereas those who discontinued later had improved outcomes. This is likely reflective of control of the disease and preponderance of early infectious morbidity in the enrolled populations.

This report describes the longest follow-up to date for single-agent ibrutinib in the first-line and relapsed/refractory settings, providing valuable clinical data on the efficacy, durability, and safety profile. Sustained efficacy of single-agent ibrutinib was observed as first-line treatment and treatment for relapsed/refractory CLL/SLL, including for patients with high-risk genomic factors. In addition, in patients treated for relapsed/refractory CLL/SLL, ibrutinib administration in earlier lines of therapy resulted in improved PFS outcomes, providing evidence for earlier introduction of ibrutinib treatment. With up to 8 years of follow-up, single-agent ibrutinib was associated with acceptable tolerability. Taken together, the sustained disease control and acceptable tolerability observed with prolonged single-agent ibrutinib provides strong evidence for the use of ibrutinib in patients with CLL/SLL, even those with unfavorable disease characteristics.

Disclosure of Potential Conflicts of Interest

J.C. Byrd is a paid consultant for AstraZeneca and Acerta, and an unpaid advisor to Kartos and Telios. R.R. Furman is an employee/paid consultant for Pharmacyclics LLC, an AbbVie Company, Janssen, and AbbVie; reports receiving speakers bureau honoraria from Janssen; and reports receiving other remuneration from AbbVie. S.E. Coutre reports receiving commercial research grants from AbbVie, Acerta, Janssen, Pharmacyclics LLC, an AbbVie Company, and Takeda, and reports receiving other remuneration from BeiGene, Genentech, AbbVie, Janssen, Pharmacyclics LLC, an AbbVie Company, Astellas, AstraZeneca, and Adaptive. I.W. Flinn reports receiving other commercial research support from AbbVie, Acerta Pharma (to institution), Agios, ArQule, AstraZeneca, BeiGene, Calithera Biosciences, Celgene, Constellation Pharmaceuticals, Curis, F. Hoffmann-La Roche Ltd, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Juno Therapeutics, Karyopharm Therapeutics, KITE Pharma, Loxo, Merck, MorphoSys, Novartis, Pfizer, Pharmacyclics LLC, an AbbVie Company, Portola Pharmaceuticals, Roche, Seattle Genetics, Takeda, Teva, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp., Unum Therapeutics, and Verastem; ownership interest (including patents) in Johnson & Johnson; and unpaid consultant/advisory board relationships with AbbVie, AstraZeneca, BeiGene (to institution), Curio Science, Gilead Sciences, Janssen, Juno Therapeutics, Kite Pharma, MorphoSys, Nurix Therapeutics, Pharmacyclics LLC, an AbbVie Company, Roche, Seattle Genetics, Takeda, TG Therapeutics, Unum Therapeutics, Verastem, and Yingli Pharmaceuticals. J.A. Burger reports receiving other commercial research support from Gilead, TG Therapeutics, Pharmacyclics LLC, an AbbVie Company, and BeiGene; speakers bureau honoraria from Gilead, TG Therapeutics, Pharmacyclics LLC, an AbbVie Company, Novartis, and Janssen; an unpaid consultant/advisory board relationship with Janssen; and other remuneration for travel/accommodations from Gilead, TG Therapeutics, Pharmacyclics LLC, an AbbVie Company, Novartis, and Janssen. K. Blum reports receiving other commercial research support from Pharmacyclics LLC, an AbbVie Company, and Janssen. J.P. Sharman is an employee/paid consultant for Pharmacyclics LLC, an AbbVie Company. W. Wierda reports receiving commercial research grants from GlaxoSmithKline/Novartis, AbbVie, Genentech, Pharmacyclics LLC, an AbbVie Company, Acerta Pharma, Gilead Sciences, Juno Therapeutics, KITE Pharma, Sunesis, Miragen, Oncternal Therapeutics, Cyclacel, Loxo Oncology, Janssen, and Xencor; reports receiving speakers bureau honoraria from Janssen Scientific Affairs, Mayo Clinic, PER Physician Education Resource, and Froedtert Medical College; and is an advisory board member/unpaid consultant for NCCN. Y. Luan is an employee/paid consultant for Pharmacyclics LLC, an AbbVie Company, and reports receiving commercial research grants from AbbVie. E. A. Liu is an employee/paid consultant for Pharmacyclics LLC, an AbbVie Company. J.P. Dean is an employee/paid consultant for Pharmacyclics LLC, an AbbVie Company, and holds ownership interest (including patents) in AbbVie. S. O'Brien is an employee/paid consultant for Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen Oncology, Aptose Biosciences, Vaniam Group, AbbVie, Alexion, Verastem, Eisai, and Juno Therapeutics, and reports receiving other commercial research support from Kite, Regeneron, and Acerta. No potential conflicts of interest were disclosed by the other authors.

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Development of methodology: J.C. Byrd, R.R. Furman, S. O'Brien

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Acknowledgments

The authors thank all the patients who participated in this trial and their supportive families. This study was sponsored by Pharmacyclics LLC, an AbbVie Company, and Janssen. Medical writing support was provided by Lauren D'Angelo, PhD, and funded by Pharmacyclics LLC, an AbbVie Company. J.C. Byrd was supported by NIH grants R01-CA197870 and R35-CA197734.

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Received August 30, 2019; revised December 20, 2019; accepted March 20, 2020; published first March 24, 2020.

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