CLL-418

Characteristics and Clinical Outcomes of Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Receiving Long-Term Ibrutinib Treatment in the RESONATE-2 Study

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KEY TAKEAWAYS

- Across patient subgroups, more than half (58%) of ibrutinib-randomized patients continued to benefit from long-term ibrutinib treatment for ≥5 years.
- Dose modification was effective in resolving AEs for the majority of patients, thereby allowing patients to remain on treatment.

OBJECTIVE

- To describe characteristics and outcomes of patients on long-term ibrutinib treatment for ≥5 years in the RESONATE-2 study.

CONCLUSIONS

- Across patient subgroups, more than half (58%) of ibrutinib-randomized patients continued to benefit from long-term ibrutinib treatment for ≥5 years.
- Efficacy and safety results in patients on long-term ibrutinib treatment for ≥5 years were consistent with those seen in the overall population of ibrutinib-treated patients.[1]
- Among patients who were on long-term ibrutinib treatment, complete response rates improved over time through 5 years.
- The safety profile of long-term ibrutinib treatment was consistent with previous reports and no new safety signals were identified.
- Active management of AEs with dose reductions or dose holds resulted in AE resolution in the majority (>85%) of patients. Additionally, dose reductions prevented recurrence or worsening for most patients (75%), allowing many patients to continue to benefit from ibrutinib treatment.

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Poster presented at the Tenth Annual Meeting of the Society of Hematologic Oncology (SOHO 2022); September 28–October 1, 2022; Houston, TX

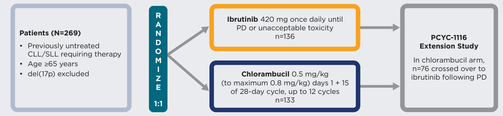
INTRODUCTION

- Ibrutinib, a once-daily oral Bruton tyrosine kinase inhibitor, is the only targeted therapy to demonstrate significant OS benefit in randomized phase 3 studies in first-line CLL/SLL.[1,2]
- Primary results from the phase 3 RESONATE-2 study demonstrated superior efficacy and tolerability with ibrutinib versus chlorambucil and supported approval of ibrutinib as first-line treatment for patients with CLL/SLL in the United States and Europe.[3]
- Real-world evidence suggests that dose management (dose reduction or modification) results in improvement in or resolution of AEs without impacting disease outcomes.[4-7]
  - Active management of AEs by dose modification might enable patients to remain on treatment and maximize clinical outcomes.
- Data on long-term treatment, outcomes, and safety are essential to inform clinical decision making.

METHODS

- RESONATE-2 (PCYC-1115/PCYC-1116; NCT01722487/NCT01724346) is an open-label, multicenter, international, randomized, phase 3 study (**Figure 1**).
- Eligible patients aged ≥65 years with previously untreated CLL/SLL and without del(17p) were randomly assigned 1:1 to receive once-daily single-agent ibrutinib until disease progression or unacceptable toxicity (n=136) or chlorambucil for up to 12 cycles (n=133).
- With up to 8 years of follow-up (median, 82.7 months; range, 0.1–96.6), median PFS was not yet reached for ibrutinib-randomized patients at the latest data cut.[8]
- This analysis included ibrutinib-randomized patients who were on long-term ibrutinib treatment, defined as on treatment for ≥5 years (n=79).
- Outcomes for this analysis were baseline demographics and clinical characteristics, cumulative best overall response rates, prevalence of AEs, and AEs leading to dose modifications among ibrutinib-randomized patients who were on long-term ibrutinib treatment for ≥5 years.
- Per protocol, ibrutinib was held for any unmanageable, potentially study drug-related toxicity that was grade ≥3 in severity. Other AEs, including grade 2 AEs, that were deemed by the investigator to be potentially manageable by dose reduction, were managed with a one dose level dose reduction.

Figure 1. Study Design.



RESULTS

Baseline Characteristics

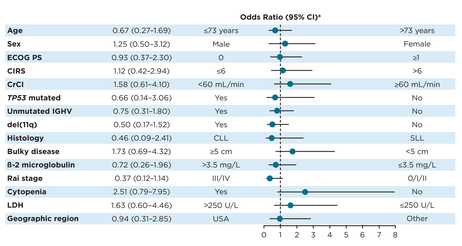
- Baseline characteristics within ibrutinib-randomized patients in the intention-to-treat population (N=136) were generally similar between patients who were on long-term ibrutinib treatment for ≥5 years (n=79) and those who were not (n=57) (**Table 1**).

Table 1. Baseline Characteristics.

Characteristic	Long-term ibrutinib treatment (≥5 years) n=79	Off treatment in first 5 years n=57	All ibrutinib-randomized patients N=136
Median age, years (range)	71 (65–84)	74 (65–89)	73 (65–89)
Age group, n (%)			
65–69 years	29 (37)	11 (19)	40 (29)
70–74 years	29 (37)	21 (37)	50 (37)
75–79 years	13 (16)	11 (19)	24 (18)
≥80 years	8 (10)	14 (25)	22 (16)
Male, n (%)	49 (62)	39 (68)	88 (65)
ECOG PS, n (%)			
0	33 (42)	27 (47)	60 (44)
1	41 (52)	24 (42)	65 (48)
2	5 (6)	6 (11)	11 (8)
Diagnosis, n (%)			
CLL	75 (95)	48 (84)	123 (90)
SLL	4 (5)	9 (16)	13 (10)
Rai stage III/IV disease, n (%)	37 (47)	23 (40)	60 (44)
CIRS score >6, n (%)	26 (33)	16 (28)	42 (31)
CrCl <60 mL/min, n (%)	32 (41)	28 (49)	60 (44)
Bulky disease ≥5 cm, n (%)	29 (37)	25 (44)	54 (40)
Any cytopenia, n (%)	42 (53)	30 (53)	72 (53)
Hemoglobin ≤11 g/dL	28 (35)	23 (40)	51 (38)
Platelets ≤100 × 10^9/L	20 (25)	15 (26)	35 (26)
ANC ≤1.5 × 10^9/L	5 (6)	5 (9)	10 (7)
LDH			
Median, U/L (range)	196 (52–514)	215 (65–1188)	199 (52–1188)
>250 U/L, n (%)	18 (23)	21 (37)	39 (29)
Median ß-2 microglobulin, mg/L (range)	4 (2–20)	5 (2–20)	4 (2–20)
Median time from initial diagnosis, months (range)	35 (1–241)	26 (1–162)	30 (1–241)
High-risk features, n (%)	45 (57)	28 (49)	73 (54)
TP53 mutation	7 (9)	4 (7)	11 (8)
del(11q)	18 (23)	11 (19)	29 (21)
Unmutated IGHV	36 (46)	22 (39)	58 (43)
Geographic region, n (%)			
United States	19 (24)	12 (21)	31 (23)
Europe	39 (49)	32 (56)	71 (52)
Rest of world	21 (27)	13 (23)	34 (25)

- Several baseline characteristics favored achievement of long-term ibrutinib treatment for ≥5 years (for example, female sex, age ≤73 years, absence of cytopenia, absence of bulky disease [<5 cm]), but none reached statistical significance (**Figure 2**).

Figure 2. Long-Term Ibrutinib Treatment (≥5 Years) Was Achieved Irrespective of Baseline Characteristics.

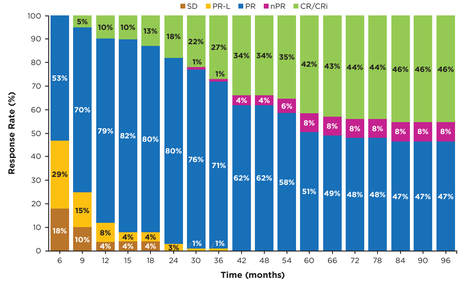


*Odds ratios for the probability of long-term treatment (≥5 years) were obtained using a multivariate logistic regression model; odds ratios <1 favor achievement of long-term ibrutinib treatment for the subgroup to the left of the plot, while odds ratios >1 favor achievement of long-term ibrutinib treatment for the subgroup to the right of the plot.

Response

- Median follow-up duration for patients who were on long-term ibrutinib treatment for ≥5 years (n=79) was 89.2 months (range, 61.3–96.6).
- Complete response rates improved over time, from 10% (8/79 patients) at 1 year to 42% (33/79) by 5 years (**Figure 3**).
- Of 44 patients with complete response in the overall population of all ibrutinib-randomized patients, 36 received long-term ibrutinib treatment for ≥5 years.

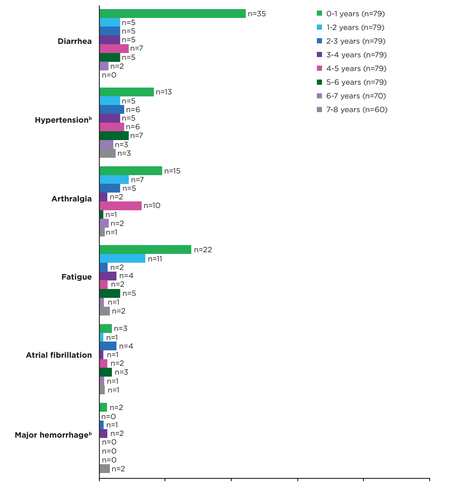
Figure 3. Cumulative Best Response Deepened Over Time in Patients on Long-Term Ibrutinib Treatment (≥5 Years).



Safety

- In patients who were on long-term ibrutinib treatment for ≥5 years, the median duration of treatment was 89.2 months (range, 60.4–96.6).
  - Median relative dose intensity of ibrutinib was 98% (range, 47–100).
- Prevalence of AEs of clinical interest were generally highest in years 0–1 and decreased over time thereafter (**Figure 4**).

Figure 4. Prevalence[a] of AEs of Clinical Interest (Any Grade) Decreased Over Time in Patients on Long-Term Ibrutinib Treatment (≥5 Years).



*Prevalence was determined by the proportion of patients with a given AE (existing event or new onset of an event) during each yearly interval; multiple onsets of the same AE term within a specific yearly interval were counted once, and the same AE term continuing across several yearly intervals was counted in each of the intervals. †Combined terms.

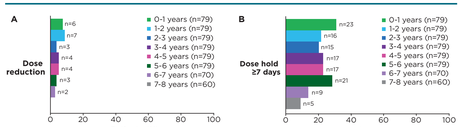
- Dose reductions were used for AE management in 16/79 patients (20%) who were on long-term ibrutinib treatment for ≥5 years (**Table 2**) and were similar to those seen in all ibrutinib-treated patients (**Supplemental Information**).
  - At data cutoff, 3/16 were on 420 mg once daily, 10/16 were on 280 mg once daily, and 3/16 were on 140 mg once daily.
  - The median duration of treatment with ibrutinib at a reduced dose was not estimable (range, 8.4–84+).
  - Following dose reduction, 14/16 patients (88%) had resolution of the initial AE; 2 patients had AEs that were not resolved at data cutoff (grade 3 malignant lung neoplasm and grade 2 fatigue in 1 patient each).
    - AEs did not recur or recurred at a lower grade for 12/16 patients (75%).
    - For AEs with recommended dose reductions per USPI, AEs did not recur or recurred at a lower grade in 3/4 patients (75%); 1 patient had recurrence at the same grade after 3 years (grade 3 atrial fibrillation) that resolved without further dose reduction.
  - The frequency of AEs leading to dose reductions was highest in years 0–2 and lower in subsequent years (**Figure 5A**).
- Dose holds of ≥7 days were used for AE management in 45/79 patients (57%) who were on long-term ibrutinib treatment for ≥5 years, 25 of whom had 2 or more dose holds (**Supplemental Information**).
  - The frequency of AEs leading to dose holds of ≥7 days remained relatively consistent across the first 6 years of treatment (**Figure 5B**).

Table 2. AEs Leading to Dose Reductions in Patients on Long-Term Ibrutinib Treatment (≥5 Years).

AEs leading to dose reduction	Long-term ibrutinib treatment (≥5 years) n=79
Any AEs	
Any AE leading to dose reduction, n (%)	16 (20)
Number of dose reductions, n (%)	
1	12 (15)
2	3 (4)
3	1 (1)
AEs leading to dose reduction by SOC, n (%)*	
Infection	4 (5)
Hematologic	3 (4)
Dermatologic	2 (3)
Gastrointestinal	1 (1)
Cardiac	1 (1)
Injuries	1 (1)
Musculoskeletal	1 (1)
Neoplasms	1 (1)
Other	4 (5)
AEs leading to dose reduction by grade, n (%)*	
Grade 1	6 (8)
Grade 2	7 (9)
Grade 3	5 (6)
Grade 4	1 (1)
Outcome of first AE leading to dose reduction, n/N (%)[b]	
Initial AE resolved	14/16 (88)
No recurrence or recurred at lower grade	12/16 (75)
Recurred at same or higher grade	4/16 (25)
AEs with recommended dose reductions per USPI[c]	
Any AE leading to dose reduction, n (%)	4 (5)
Lowest dose reduced to, n (%)	
280 mg	2 (3)
140 mg	1 (1)
140 mg (from 280 mg)	1 (1)
Outcome of first AE leading to dose reduction, n/N (%)[d]	
Initial AE resolved	3/4 (75)
No recurrence or recurred at lower grade	3/4 (75)
Recurred at same or higher grade	1/4 (25)

*The same patient may be counted in more than one category due to multiple events. †Denominator is patients with any AE leading to dose reduction. ‡AEs for which dose reductions are recommended in the ibrutinib USPI (grade 2 cardiac failure, grade 3 cardiac arrhythmia, grade 3 or 4 nonhematologic AEs [excluding cardiac failure and cardiac arrhythmia], grade 3 or 4 neutropenia with infection or fever, and grade 4 hematologic AEs)". §Denominator is patients with AEs for which dose reductions are recommended in the ibrutinib USPI.

Figure 5. AEs Leading to (A) Dose Reductions[a] or (B) Dose Holds ≥7 Days[a] Were Stable Over Time in Patients on Long-Term Ibrutinib Treatment (≥5 Years).



*The same patient may appear in more than one year.

ABBREVIATIONS

AE, adverse event; ANC, absolute neutrophil count; CI, confidence interval; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete bone marrow recovery; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain; LDH, lactate dehydrogenase; nPR, nodular partial response; OS, overall survival; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma; SOC, system organ class; USPI, US prescribing information.

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DISCLOSURES

JAW: consulting/advisory role with AbbVie, AstraZeneca, ArQule, BeiGene, Genentech, Janssen, Loxo, Newave, and Pharmacyclics LLC, an AbbVie Company; research funding from AbbVie, Loxo, Karyopharm, MorphoSys, Schrodinger, and Verastem; **PMB:** consulting/advisory role with AbbVie, AstraZeneca, Bristol Myers Squibb, Celgene, Genentech, Gilead, Janssen, MEI Pharma, Merck, Morphosys, Pharmacyclics LLC, an AbbVie Company, Seattle Genetics, and TG Therapeutics; research funding from AstraZeneca and TG Therapeutics; **TJK:** consulting/advisory role with AbbVie, Celgene, Genentech-Roche, Gilead, and Pharmacyclics LLC, an AbbVie Company; research funding from AbbVie, Genentech-Roche, Oncternal Therapeutics, and Pharmacyclics LLC, an AbbVie Company; **JCB:** honoraria from Janssen; consulting/advisory role for BeiGene, AbbVie, MEI, and AstraZeneca; research funding from Oncternal Therapeutics, Velosbio/Merck, and Pharmacyclics LLC, an AbbVie Company; **IEA:** no conflicts of interest; **PG:** honoraria from and consulting/advisory role with AbbVie, AstraZeneca, ArQule/Merck Sharp & Dohme, Celgene/Juno/Bristol Myers Squibb, Janssen, Loxo/Lilly, MEI Pharma and Roche; research funding from AbbVie, AstraZeneca, Janssen, and Sunesis; **VG:** employment with Everest Clinical Research; other relationship with AbbVie; EH: employment with Pharmacyclics LLC, an AbbVie Company; stock or other ownership with AbbVie; **MJ:** employment and stock or other ownership with Pharmacyclics LLC, an AbbVie Company (self) and Gilead Sciences (family member); **JAB:** honoraria from Gilead, Janssen, Novartis, TG Therapeutics, and Pharmacyclics LLC, an AbbVie Company; consulting/advisory role and speakers bureau for BeiGene, Gilead, Janssen, TG Therapeutics, and Pharmacyclics LLC, an AbbVie Company; research funding from AstraZeneca, BeiGene, and Pharmacyclics LLC, an AbbVie Company; travel/accommodations/expenses from Gilead, Janssen, Novartis, TG Therapeutics, and Pharmacyclics LLC, an AbbVie Company.

ACKNOWLEDGMENTS

We thank the patients who participated in the study and their supportive families, as well as the investigators and clinical research staff from the study centers. This study was sponsored by Pharmacyclics LLC, an AbbVie Company. Editorial support was provided by Melanie Sweetlove, MSc, and funded by Pharmacyclics LLC, an AbbVie Company.