Received: 30 November 2023 | Accepted: 8 March 2024

DOI: 10.1002/hem3.74

HemaSphere EHA EUROPEAN HEMATOLOGY ASSOCIATION

LETTER

First-line ibrutinib treatment in patients with chronic lymphocytic leukemia is associated with overall survival rates similar to those of an age-matched general population: A pooled post hoc analysis

Paolo Ghia[1] | Carolyn Owen[2] | John N. Allan[3] | Jacqueline C. Barrientos[4] | Paul M. Barr[5] | Chunxue Shi[6] | Anita Szoke[7] | Christopher Abbazio[7] | Gabriel S. Krigsfeld[7] | Jan A. Burger[8]

Correspondence: Paolo Ghia (ghia.paolo@hsr.it)

Currently, there are no targeted agents that can cure chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), which is the most common leukemia among older adults.[1] In the absence of a curative regimen, the therapeutic goal is to maximize patients' life span while effectively managing disease symptoms.

Ibrutinib, a covalent, once-daily Bruton's tyrosine kinase inhibitor, has been shown to have survival superiority to chemotherapy (CT) and chemoimmunotherapy (CIT) in the first-line setting, including older adults and those with high-risk characteristics, and has demonstrated overall survival (OS) improvements in multiple pivotal trials.[2–4] In a long-term follow-up from RESONATE-2 of up to 8 years, first-line treatment with ibrutinib was associated with superior progression-free survival and OS compared with standard-of-care CT. Based on the results from the same study, adverse events (AEs) associated with ibrutinib can be managed effectively with dose reductions or dose holds, which results in AE resolution in most patients (85% and 90%, respectively), allowing them to remain on treatment and continue benefiting from ibrutinib.[5] The relatively long survival of patients with CLL/SLL treated with ibrutinib raises the question of whether the initiation of first-line ibrutinib could remove the survival hazard associated with CLL/SLL compared with the general population. The aims of this pooled analysis were to compare OS estimates of previously untreated patients with CLL/SLL who received ibrutinib or CT/CIT across three phase 3 studies with the OS estimates for an age-matched general population.

This post hoc analysis included data pooled from three randomized (1:1) controlled studies in patients with previously untreated CLL/SLL: RESONATE-2 (NCT01722487),[2] iLLUMINATE (NCT02264574),[4] and ECOG-ACRIN E1912 (NCT02048813).[3] Patients were separated into two groups: ibrutinib cohort (patients treated with ibrutinib, ibrutinib with rituximab, or ibrutinib with obinutuzumab); and CT/CIT cohort (patients receiving rituximab plus fludarabine plus cyclophosphamide, chlorambucil plus obinutuzumab, or single-agent chlorambucil). Details of the treatments and populations have been previously published for each study, and brief descriptions are included in the Supporting Information.

OS data from the time of initial CLL/SLL diagnosis for the ibrutinib-treated cohort or CT/CIT-treated cohort were compared with survival estimates for an age-matched US population in 2019 published by the Centers for Disease Control and Prevention (CDC).[6] Age-matched (1:1 match) simulated databases were generated based on the age distribution of patients treated with ibrutinib or CT/CIT from the three phase 3 clinical studies. OS probabilities were estimated using the Kaplan–Meier methodology. Safety data were evaluated for ibrutinib-based therapy from a pooled safety population consisting of patients from RESONATE-2 and iLLUMINATE. Participants in the ECOG-ACRIN E1912 study were excluded from safety assessments due to limitations in the details of AE data collection. Additional information about the study design and methods is included in the Supporting Information.

In the pooled sample from the three trials, 603 patients received first-line ibrutinib treatment and 424 received CT/CIT treatment (Table 1). The median age of patients in the ibrutinib-treated cohort at the time of randomization was 63 years. Most patients were men (65%), had an Eastern Cooperative Oncology Group (ECOG) performance status score

[1]Division of Experimental Oncology, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy
[2]Tom Baker Cancer Centre, University of Calgary and Alberta Health Services, Calgary, Alberta, Canada
[3]Weill Cornell Medicine, New York, New York, USA
[4]Columbia University Division of Hematology/Oncology at Mount Sinai Medical Center, Miami, Florida, USA
[5]Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, New York, USA
[6]Biostatistics, Everest Clinical Research, Owings Mills, Maryland, USA
[7]AbbVie Inc, North Chicago, Illinois, USA (Pharmacyclics LLC, an AbbVie Company), South San Francisco, California, USA
[8]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

TABLE 1 Baseline characteristics of ibrutinib and CT/CIT cohorts.

Characteristic	Pooled ibrutinib or ibrutinib- combination treatment[a] *N* = 603	Pooled CT/CIT treatment[a] *N* = 424
Median age at initial diagnosis (range), years	60 (30–87)	63 (28–90)
Median age at randomization (range), years	63 (31–89)	67 (28–90)
Median time from initial diagnosis to randomization (range), months	24 (0–342)	28 (0–480)
Sex, *n* (%)		
Men	391 (65)	280 (66)
Women	212 (35)	144 (34)
Age group at randomization, *n* (%), years		
<65	333 (55)	179 (42)
65–75	191 (32)	156 (37)
≥75	79 (13)	89 (21)
Ibrutinib treatment, *n* (%)		
Ibrutinib + rituximab	354 (59)	NA
Ibrutinib	136 (23)	NA
Ibrutinib + obinutuzumab	113 (19)	NA
CT/CIT treatment drug, *n* (%)		
Rituximab + fludarabine + cyclophosphamide	NA	175 (41)
Chlorambucil	NA	133 (31)
Chlorambucil + obinutuzumab	NA	116 (27)
Baseline ECOG performance status, *n* (%)		
0	344 (57)	213 (50)
1	233 (39)	189 (45)
2	26 (4)	22 (5)
CIRS score category, *n* (%)		
≤6	481 (80)	320 (76)
>6	93 (15)	85 (20)
Rai stage, *n* (%)		
0–II	319 (53)	229 (54)
III/IV	284 (47)	195 (46)
del(11q), *n* (%)		
No	474 (79)	320 (76)
Yes	121 (20)	92 (22)
IGHV, *n* (%)		
Mutated	150 (25)	135 (32)
Unmutated	334 (55)	188 (44)
del(17p) or *TP53* mutation, *n* (%)		
No	482 (80)	308 (73)
Yes	56 (9)	31 (7)

Abbreviations: CIRS, Cumulative Illness Rating Scale; CIT, chemoimmunotherapy; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

[a]Percentage totals more than/less than 100% due to rounding.

of 0 (57%), and had a Cumulative Illness Rating Scale (CIRS) score of ≤6 (80%). In the CT/CIT cohort, baseline characteristics were similar (median age at randomization, 67 years; men, 66%; ECOG performance status score of 0, 50%; CIRS score of ≤6, 76%). Other baseline clinical characteristics, including genetic testing results, are presented in Table 1.

In the ibrutinib-treated cohort, median treatment duration and median follow-up from the time of randomization were 39 months and 41 months, respectively; these times were 5 months and 40 months in the CT/CIT-treated cohort (Table S1). The median follow-up from the initial CLL/SLL diagnosis in the ibrutinib-treated cohort was 5.9 years.

OS for the full ibrutinib-treated cohort, calculated from the time of initial CLL/SLL diagnosis, was comparable to the OS estimate for the age-matched general population (hazard ratio [HR]; 95% confidence interval [CI] = 0.87 [0.63–1.19]). Twelve-year OS estimates (95% CI) were also similar between the full ibrutinib-treated cohort (82% [76–87]) and the age-matched general population (80% [76–83]) (Figure 1A). Similar OS estimates were observed between the ibrutinib cohort and the general population over a 12-year horizon in individuals aged <65 years and ≥65 years (Table S2 and Figure S1).

Conversely, OS was significantly lower ($p = 0.05$) for the CT/CIT cohort than for an aged-matched general population (HR [95% CI] = 1.35 [1.00–1.82]), with 12-year OS (95% CI) estimates of 69% (61–76) and 76% (72–80), respectively (Figure 1B).

Of the 248 evaluable patients from the RESONATE-2 and iLLUMINATE studies, 48 (19%) had dose reductions from a starting dose of 420 mg per day to manage AEs (Table S3). The median duration of ibrutinib treatment at a reduced dose was 31 months (range, 0–84+). Following ibrutinib dose reduction, 44 of 48 patients (92%) had resolution of the initial AE, and for 32 of 48 patients (67%), AEs either did not recur or recurred at a lower grade.

After experiencing AEs for which a dose reduction is recommended in the recently updated US Prescribing Information, 21 of 248 patients (9%) had dose reductions (Table S4).[7] Of those, 20 of 21 patients (95%) had resolution of the initial AE, and for 16 of 21 patients (76%), AEs either did not recur or recurred at a lower grade.

Ibrutinib dose holds of ≥7 days was used for AE management in 143 of 248 patients (58%) (Table S5). Ibrutinib was restarted at 420 mg in 118 of 248 patients (48%), at 280 mg in 35 of 248 patients (14%), and at 140 mg in 15 of 248 patients (6%) after a dose hold of ≥7 days. The occurrence of AEs leading to dose reductions and dose holds of ≥7 days was the highest in the first 2 years following ibrutinib initiation and subsided in subsequent years (Figures S2A and S2B).

Since the introduction of targeted CLL/SLL therapies, ibrutinib has had significantly improved outcomes across a broad range of patients with CLL/SLL compared with the previous standard of care, which has been demonstrated in several randomized clinical trials.[2,3,8–11] Ibrutinib has the longest follow-up data available for Bruton's tyrosine kinase inhibitor therapies, which uniquely allows for the assessment of long-term efficacy and safety.

Maintaining patients on therapy appears to be critical for maximizing clinical outcomes, including prolonged survival, with some patients receiving therapy for up to 8 years. For most patients in the RESONATE-2 study, long-term continuous ibrutinib treatment was possible while managing associated side effects through active dose management.[5] In the same study, survival outcomes were similar between patients treated with ibrutinib with and without dose reduction.[12] Similarly, in this pooled analysis, most patients experienced AE resolution after dose reduction, enabling them to stay on ibrutinib treatment.

Treatment discontinuation due to AEs occurred at similar rates across the phase 3 trials of first-line ibrutinib in this pooled

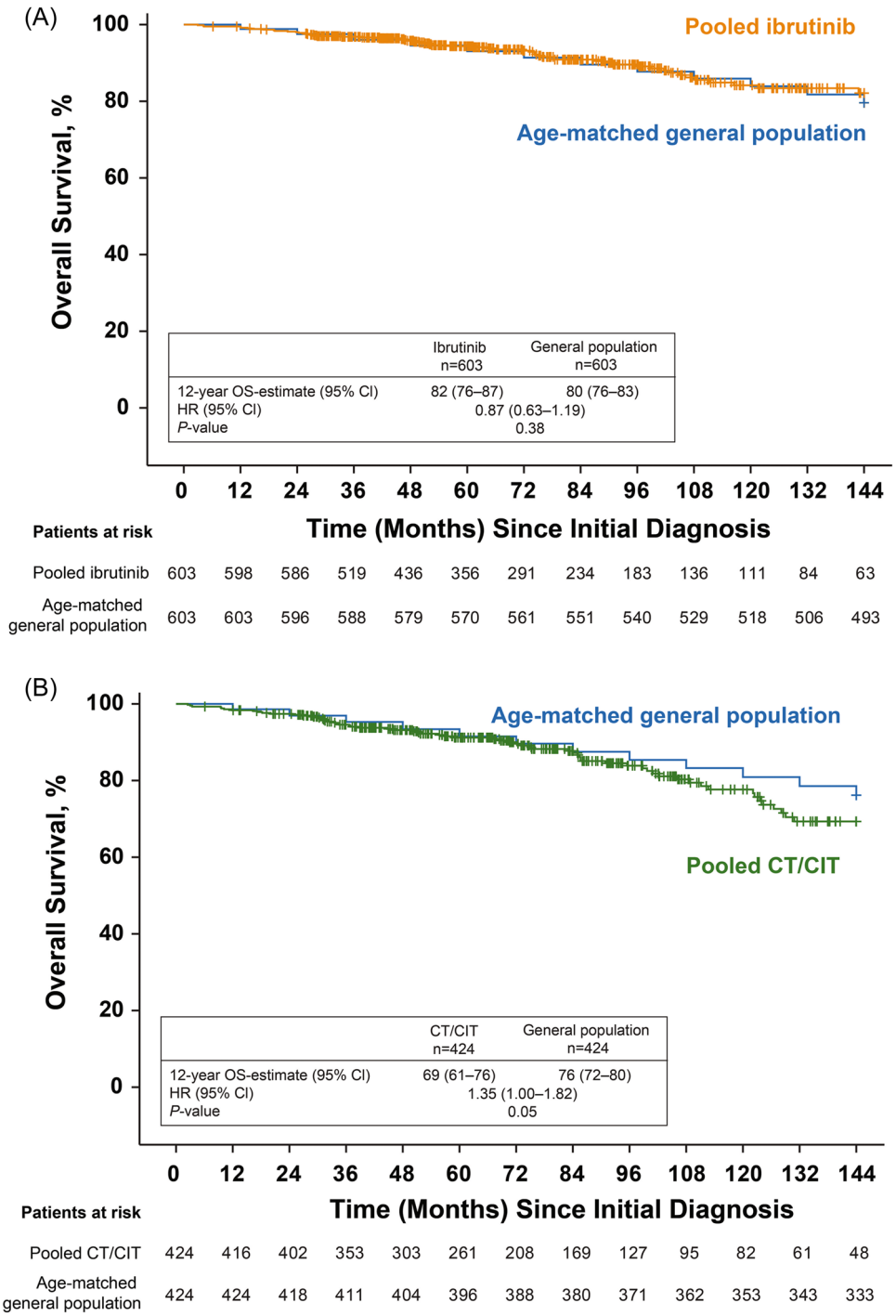

FIGURE 1 OS estimates for pooled patients treated with (A) ibrutinib or (B) CT/CIT versus age-matched general population. Data after 144 months are not represented in the Kaplan-Meier curve. CIT, chemoimmunotherapy; CT, chemotherapy; HR, hazard ratio; OS, overall survival.

analysis: in RESONATE-2, 24%[5] of patients discontinued ibrutinib due to AEs; in iLLUMINATE, 16%[13]; and ECOG1912, 22%.[14]

Overall, the safety findings from this analysis are aligned with the previously described safety profile of first-line ibrutinib and are consistent with the data from individual phase 3 trials.[3,4,15]

The strengths of this study include a relatively large number of patients and the length of follow-up across the three pooled studies. One key limitation was that, because of data availability, pooled ibrutinib data and general population survival estimates were matched only for age and not for other individual patient characteristics. In addition, we did not separate patients treated with CT from those treated with CIT to maintain the original analysis approach from these trials.

In conclusion, this post hoc analysis suggests that unlike first-line CT/CIT treatment, first-line ibrutinib is associated with survival rates that are similar to those seen in the age-matched general population. First-line ibrutinib treatment could eliminate excess mortality risk associated with CLL/SLL diagnosis in both younger and older adult patients.

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. Medical writing support was provided by Agnieszka Looney, PhD, and was funded by Pharmacyclics LLC, an AbbVie Company.

AUTHOR CONTRIBUTIONS

Paolo Ghia, John N. Allan, Christopher Abbazio, and Gabriel S. Krigsfeld conceptualized the study. Christopher Abbazio and Gabriel S. Krigsfeld designed the methodology. Chunxue Shi performed study validation and statistical analysis. Chunxue Shi, Gabriel S. Krigsfeld, and Christopher Abbazio interpreted data. Paolo Ghia, Carolyn Owen, John N. Allan, Jacqueline C. Barrientos, Paul M. Barr, and Jan A. Burger participated in data acquisition/collection. All authors participated in the writing and review of the manuscript.

CONFLICT OF INTEREST STATEMENT

P. G. reports fees for consulting and honoraria from AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Janssen, Loxo@Lilly, Merck Sharp & Dohme Corp., and Roche; and research funding from AbbVie, AstraZeneca, and Janssen; and is an editor for HemaSphere. C. O. reports honoraria from AbbVie, AstraZeneca, BeiGene, Gilead, Incyte, Janssen, Merck, and Roche. J. N. A. reports fees for consulting from AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, Epizyme, Genentech, Janssen, Pharmacyclics LLC, an AbbVie Company, and TG Therapeutics; research funding from BeiGene, Celgene, Genentech, Janssen, and TG Therapeutics; and has served on the speakers' bureau for AbbVie, BeiGene, Janssen, and Pharmacyclics LLC, an AbbVie Company. J. C. B. reports honoraria from Janssen and fees for consulting from AbbVie, AstraZeneca, BeiGene, and MEI Pharma; and research funding from Oncternal Therapeutics, Pharmacyclics LLC, an AbbVie Company, and VelosBio/Merck. P. M. B. reports fees for consulting from AbbVie, AstraZeneca, Bristol Myers Squibb, Celgene, Genentech, Gilead, Janssen, MEI Pharma, Merck, MorphoSys, Seattle Genetics, and TG Therapeutics; and research funding from AstraZeneca and TG Therapeutics. C. S. reports no conflicts of interest. A. S. reports employment and stock ownership with AbbVie. C. A. reports employment with AbbVie and stock ownership with AbbVie and Bristol Myers Squibb. G. S. K. reports employment with AbbVie and Bristol Myers Squibb; stock ownership with AbbVie, Bristol Myers Squibb, Dynavax, Inovio, and Moderna; and travel and accommodation expenses from AbbVie and Bristol Myers Squibb. J. A. B. reports honoraria from Gilead, Janssen, Novartis, Pharmacyclics LLC, an AbbVie Company, and TG Therapeutics; consulting fees from BeiGene, Gilead, Janssen, Pharmacyclics LLC, an AbbVie Company, and TG Therapeutics; research funding from AstraZeneca, BeiGene, and Pharmacyclics LLC, an AbbVie Company; served on the speakers' bureau for BeiGene, Gilead, Janssen, Pharmacyclics LLC, an AbbVie Company, and TG Therapeutics; and received travel and accommodation expenses from Gilead, Janssen, Novartis, Pharmacyclics LLC, an AbbVie Company, and TG Therapeutics.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

FUNDING

This study was sponsored by Pharmacyclics LLC, an AbbVie Company.

ORCID

Paolo Ghia http://orcid.org/0000-0003-3750-7342

SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

REFERENCES

1. National Cancer Insitute. *Cancer Stat Facts: Leukemia—Chronic Lymphocytic Leukemia (CLL)*. National Cancer Insitute. Accessed February 22, 2023. https://seer.cancer.gov/statfacts/html/clyl.html
2. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437. doi:10.1056/NEJMoa1509388
3. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381(5):432-443. doi:10.1056/NEJMoa1817073
4. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(1):43-56. doi:10.1016/s1470-2045(18)30788-5
5. Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv*. 2022;6(11):3440-3450. doi:10.1182/bloodadvances.2021006434
6. Arias E, Xu J. United States life tables, 2019. *Natl Vital Stat Rep*. 2022;70:19.
7. IMBRUVICA® (ibrutinib). *Capsules for Oral Use; IMBRUVICA® (ibrutinib) Tablets, for Oral Use. IMBRUVICA® (ibrutinib) Oral Suspension [prescribing information]*. South San Francisco, CA, USA: Pharmacyclics LLC; 2023.
8. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223. doi:10.1056/NEJMoa1400376
9. Kipps TJ, Fraser G, Coutre SE, et al. Long-term studies assessing outcomes of ibrutinib therapy in patients with del(11q) chronic lymphocytic leukemia. *Clin Lymphoma Myeloma Leuk*. 2019;19(11):715-722. doi:10.1016/j.clml.2019.07.004
10. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379(26):2517-2528. doi:10.1056/NEJMoa1812836
11. Fraser G, Cramer P, Demirkan F, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leukemia*. 2019;33(4):969-980. doi:10.1038/s41375-018-0276-9
12. Woyach JA, Barr PM, Kipps TJ, et al. Characteristics and clinical outcomes of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma receiving ibrutinib for ≥5 years in the RESONATE-2 study. *Cancers*. 2023;15(2):507. doi:10.3390/cancers15020507
13. Moreno C, Greil R, Demirkan F, et al. First-line treatment of chronic lymphocytic leukemia with ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab: final analysis of the randomized, phase III iLLUMINATE trial. *Haematologica*. 2022;107(9):2108-2120. doi:10.3324/haematol.2021.279012
14. Shanafelt TD, Wang XV, Hanson CA, et al. Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. *Blood*. 2022;140(2):112-120. doi:10.1182/blood.2021014960
15. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020;34(3):787-798. doi:10.1038/s41375-019-0602-x