Received: 29 May 2025 | Accepted: 7 October 2025

DOI: 10.1002/hem3.70246

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LETTER

Overall survival outcomes with first-line continuous ibrutinib and fixed-duration ibrutinib-venetoclax treatments in patients with chronic lymphocytic leukemia: Comparison with an age-matched European population

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Overall survival (OS) is widely recognized as the gold standard endpoint in oncology clinical trials, but it can be difficult to assess OS in chronic lymphocytic leukemia (CLL) due to the slow progression of the disease, resulting in extended patient survival following diagnosis.[1,2] Additionally, CLL primarily affects older adults, with a mean age at diagnosis of 70 years,[3] further complicating survival comparisons.[2]

Treatment for CLL has evolved significantly in recent years, shifting from traditional chemotherapy to targeted therapies, subsequently improving life expectancy despite the disease remaining incurable.[4] Consequently, the combination of prolonged survival and potential long-term disease control through multiple lines of therapy can make it challenging to attribute OS benefits to a specific intervention.[1,2]

Ibrutinib, a once-daily Bruton's tyrosine kinase inhibitor (BTKi), has played a pivotal role in this evolution of CLL treatment in either single-agent[5] or combination therapies,[6,7] and more recently, in fixed-duration (time-limited) treatment.[8,9] Long-term follow-up data from the phase 3 RESONATE-2 study demonstrated significant improvement in progression-free survival (PFS) and sustained OS benefit with single-agent ibrutinib in older patients compared with chlorambucil.[10,11] Additionally, the ECOG1912 study, which assessed ibrutinib-rituximab in younger patients, demonstrated superior PFS and OS compared with fludarabine, cyclophosphamide, and rituximab.[12] The iLLUMINATE study evaluated ibrutinib-obinutuzumab in older or comorbid patients and showed sustained PFS benefit compared with chlorambucil-obinutuzumab.[13] Long-term follow-up from the fixed-duration cohort of the phase 2 CAPTIVATE trial, which focused on patients aged 18–70 years,[9] showed clinically meaningful PFS with ibrutinib-venetoclax, including in patients with high-risk genomic features.[14] The phase 3 GLOW study demonstrated the superior efficacy of fixed-duration ibrutinib-venetoclax over chlorambucil-obinutuzumab in older or comorbid patients (≥65 years or 18–64 years with a Cumulative Illness Rating Scale score >6), with the longest reported follow-up for ibrutinib-venetoclax to date.[8,15–17]

A recent pooled analysis revealed that patients receiving first-line continuous ibrutinib-based regimens had OS estimates comparable with an age-matched general US population.[18] Here, we extend that analysis by comparing OS estimates in patients with previously untreated CLL treated with either continuous ibrutinib-based or fixed-duration ibrutinib-venetoclax regimens with those of an age-matched general European population.

Patient-level data for ibrutinib-based treatments were analyzed from five studies in patients with previously untreated CLL/SLL. Three trials were pooled to evaluate continuous ibrutinib-based regimens (RESONATE-2, single-agent ibrutinib; ECOG 1912, ibrutinib-rituximab; iLLUMINATE, ibrutinib-obinutuzumab). Two additional studies (GLOW and CAPTIVATE fixed-duration cohort) were pooled to assess fixed-duration ibrutinib-venetoclax. For the GLOW study, a post hoc analysis for IGHV reclassification was used for baseline status.[16] OS was defined as the time from randomization to death from any cause. If patients were alive or had unknown vital status at the end of follow-up, the duration of their survival was censored at the date last known to be alive. The follow-up, patient numbers, and patient age range for these studies are shown in Table S1.

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OS estimates for ibrutinib-treated patients were compared with their respective age-matched general European population, derived using 2019 World Health Organization (WHO) life tables,[19] thereby providing an accurate representation of survival as the most recent pre-COVID-19 era data. Subpopulation analyses by age (≥65 and <65 years) and IGHV mutation status were also performed; analyses by other prognostic factors, such as del(17p) or *TP53* mutations, were not done due to small sample sizes. For continuous ibrutinib-based regimens, OS estimates were analyzed by treatment type (single-agent ibrutinib or ibrutinib in combination with anti-CD20 monoclonal antibodies [mAbs]).

OS for ibrutinib-treated patients was compared with expected survival of a simulated age-matched general European population where age matching was done separately for each of the comparisons using age at randomization. Available survival probabilities for 5-year age intervals were converted to a daily scale to avoid immortal time bias. OS was analyzed using Kaplan-Meier methodology. Hazard ratios (HRs) with 95% confidence intervals (CIs) were derived from a Cox proportional hazards model using trial and simulated data.

A total of 865 patients were analyzed: 600 treated with continuous ibrutinib-based regimens and 265 with fixed-duration ibrutinib-venetoclax. In the pooled continuous ibrutinib-based regimen groups, 45% were aged ≥65 years (median, 63 years), 9.3% had del(17p) or *TP53* mutations and 55.2% had unmutated IGHV genes (Table S2). Median follow-up was 49.7 months. Treatment distribution varied by age, reflecting enrollment and inclusion/exclusion criteria in each trial: ibrutinib-rituximab was most common overall (58.7%), with single-agent ibrutinib being the primary treatment for patients aged ≥65 years (50.2%) and ibrutinib-rituximab for patients aged <65 years (93.4%) (Figure S1).

In the fixed-duration ibrutinib-venetoclax group, patients had a median age of 65 years at randomization. IGHV genes were unmutated in 58.9% patients, mutated in 37.0% patients, and missing in 4.2% patients; 8.7% had del(17p) or *TP53* mutations (Table S2). Median follow-up was 55.7 months.

Continuous ibrutinib-based regimens showed OS estimates comparable with the age-matched general European population (HR: 1.23; 95% CI: 0.88–1.73; $p = 0.228$) (Figures 1 and 2). Similarly, fixed-duration ibrutinib-venetoclax also showed comparable OS estimates with the age-matched general European population (HR: 1.00; 95% CI: 0.57–1.76; $p = 0.998$) (Figures 1 and 2).

Subgroup analyses of patients treated with continuous ibrutinib-based regimens showed similar OS to the age-matched population for both single-agent ibrutinib and ibrutinib with anti-CD20 mAb (Figures 2 and S2). The differences observed in the OS rates were likely due to the variation in age of the patients treated with either treatment.

OS estimates for patients treated with continuous ibrutinib-based regimens and fixed-duration ibrutinib-venetoclax were comparable with the age-matched general European population for both age groups (≥65 and <65 years) (Figures 2 and S3), and both unmutated and mutated IGHV status groups (Figures 2 and S4).

This comprehensive pooled analysis shows that, within a diverse patient population, continuous ibrutinib-based regimens and fixed-duration ibrutinib-venetoclax provide OS estimates in patients

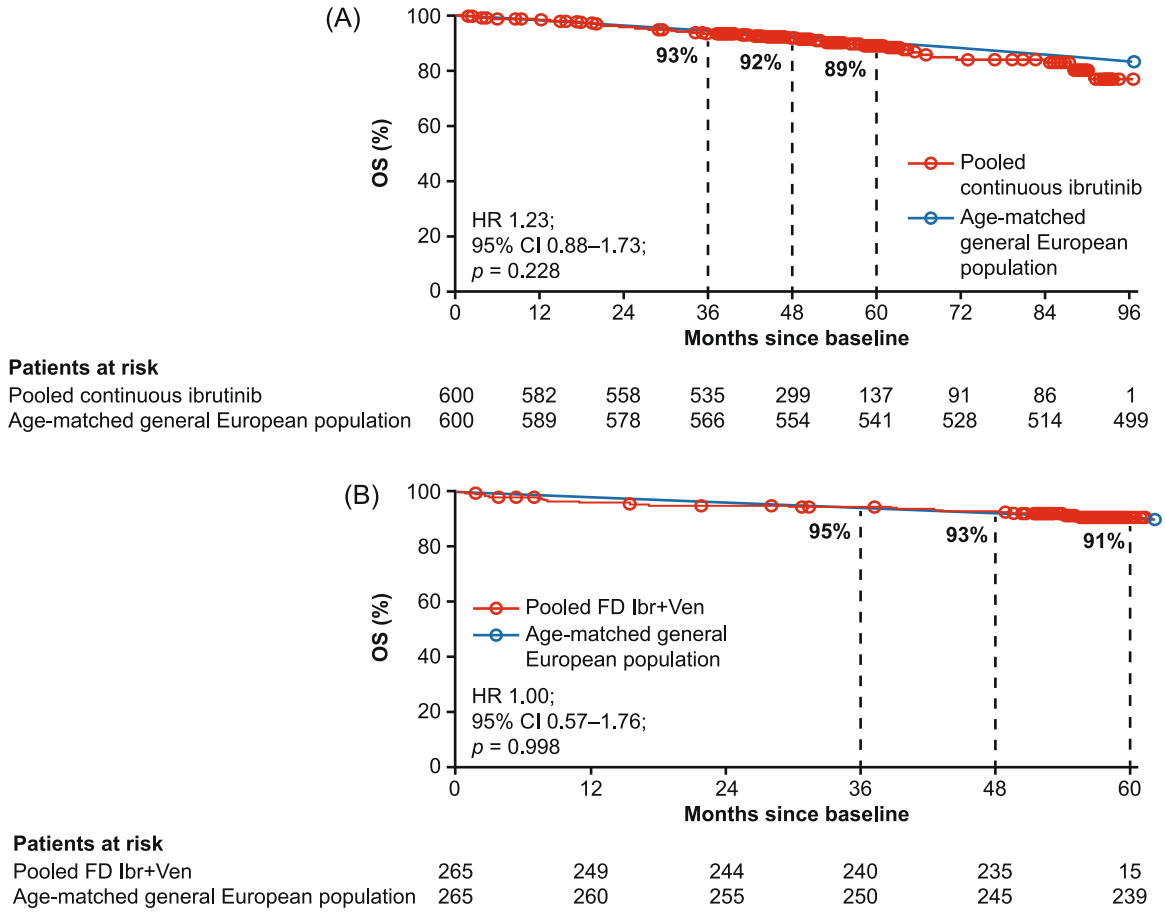

FIGURE 1 **OS estimates for ibrutinib-based regimens versus age-matched general European population. (A)** Pooled continuous ibrutinib-based regimens. **(B)** Fixed-duration ibrutinib-venetoclax. HR < 1 favors ibrutinib. CI, confidence interval; HR, hazard ratio; OS, overall survival.

Analysis/subgroup	Estimated OS rates (%) 36 months	48 months	60 months	HR	95% CI + probability
Age-matched European population	94	92	90		
Pooled continuous ibrutinib	93	92	89	1.23	0.88–1.73; $p = 0.228$
Pooled FD Ibr+Ven	95	93	91	1.00	0.57–1.76; $p = 0.998$
Continuous single-agent ibrutinib	88	86	83	0.93	0.58–1.49; $p = 0.766$
Pooled continuous ibrutinib + anti-CD20 mAb	95	94	91	1.18	0.72–1.94; $p = 0.511$
Pooled continuous ibrutinib (≥ 65 years)	89	87	83	1.02	0.70–1.48; $p = 0.916$
Pooled continuous ibrutinib (< 65 years)	97	96	93	1.35	0.65–2.82; $p = 0.428$
Pooled FD Ibr+Ven (≥ 65 years)	92	90	88	0.83	0.42–1.62; $p = 0.582$
Pooled FD Ibr+Ven (< 65 years)	97	96	93	1.64	0.55–4.88; $p = 0.377$
Pooled continuous ibrutinib (unmutated IGHV)	94	92	88	1.23	0.76–1.98; $p = 0.397$
Pooled continuous ibrutinib (mutated IGHV)	93	93	93	1.12	0.57–2.21; $p = 0.736$
Pooled FD Ibr+Ven (unmutated IGHV)	92	92	88	1.18	0.59–2.35; $p = 0.633$
Pooled FD Ibr+Ven (mutated IGHV)	99	98	97	0.40	0.11–1.49; $p = 0.171$

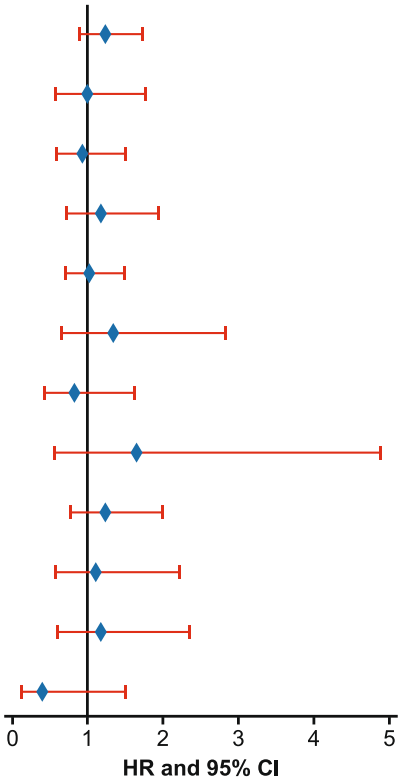

FIGURE 2 **Summary of hazard ratios and OS estimates by treatment distribution for the overall population, patients aged ≥65 and <65 years, and patients based on IGHV mutation status.** HR < 1 favors treatment. CI, confidence interval; HR, hazard ratio; OS, overall survival.

with previously untreated CLL comparable with those of an age-matched general European population. These findings were consistent, regardless of age group (<65 and ≥65 years), IGHV gene mutation status, or the specific continuous ibrutinib-based treatment regimen used. The 2019 WHO life tables utilized in this analysis reflect survival benefits using pre-COVID-19 data, including a general population with a variety of comorbidities.

Our analysis offers insight into key treatment approaches for CLL. Treatment recommendations typically vary depending on patient characteristics. Recent guidelines suggest that elderly patients with comorbidities are more likely to be recommended continuous BTKi monotherapy, whereas younger patients without comorbidities are more likely to receive fixed-duration treatments such as ibrutinib-venetoclax.[20] This study demonstrates that both treatment approaches—continuous ibrutinib-based regimens and fixed-duration ibrutinib-venetoclax—show comparable survival with an age-matched general European population regardless of age and the presence of high-risk genomic features, such as IGHV gene mutation status.

Our findings are consistent with previous estimates[18] comparing ibrutinib-based regimens with the general US population. However, the OS estimate in that study[18] (HR: 0.87) appeared slightly more favorable than that of this study (HR: 1.23) in the overall pooled population; for patients aged <65 years, the previous study reported an HR of 0.51, while this study showed an HR of 1.35. This may have been due to different mortality rates between US and European populations as well as to methodological differences across the two studies. For the previous study, age-matching was performed at diagnosis and annually, instead of using daily probability calculations.

Our findings provide valuable context for ongoing research in CLL treatment. Notably, they may inform the interpretation of results from the ongoing CLL17 (NCT04608318) trial, which compares fixed-duration venetoclax-obinutuzumab, fixed-duration ibrutinib-venetoclax, and continuous ibrutinib monotherapy in previously untreated CLL patients. Our results demonstrated comparable survival rates with the general population for continuous and fixed-duration ibrutinib-based regimens, supporting the efficacy of ibrutinib-based therapies across different administration strategies. Our subgroup analyses, especially in older or comorbid patients with unmutated IGHV genes, offer valuable comparisons for similar subgroups in the CLL17 trial.

Limitations include the use of a simulated age-matched general European population rather than an observed healthy control group, and the use of pooled data from several trials with a variety of specific inclusion and exclusion criteria and with relatively short follow-up. Survival data were matched only for age and may potentially be biased by confounding factors. Additionally, the global nature of the trials may limit direct comparability with European population data, potentially resulting in a more conservative estimate of the relative survival benefit of ibrutinib-based therapies due to lower life expectancy in some trial recruitment regions compared with Europe.

Finally, the results cannot be extrapolated to other high-risk patients, such as those with del(17p) or *TP53* mutations, due to the low sample size of this analysis.

In conclusion, this analysis shows that first-line ibrutinib-based regimens, whether administered as monotherapy, in combination with anti-CD20 mAbs, or as fixed-duration therapy with venetoclax, offer patients with CLL similar OS to that of the age-matched general European population. The consistency across different treatment modalities (continuous ibrutinib-based regimens, or fixed-duration ibrutinib-venetoclax) suggests the effectiveness of ibrutinib as a first-line targeted treatment for previously untreated patients with CLL. These findings provide valuable insights on the OS benefits in the evolving CLL treatment landscape.

ACKNOWLEDGMENTS

This study was sponsored by Johnson & Johnson. Writing assistance was provided by Jennifer L. Venzie, PhD, and Noopur Mandrekar, PhD, of Parexel, and was funded by Johnson & Johnson. Open access funding provided by BIBLIOSAN.

AUTHOR CONTRIBUTIONS

Paolo Ghia: Conceptualization; formal analysis; writing—review and editing; methodology; supervision. **Loic Ysebaert**: Conceptualization; methodology; formal analysis; supervision; writing—review and editing. **Ann Janssens**: Conceptualization; methodology; formal analysis; supervision; writing—review and editing. **Stephan Stilgenbauer**: Conceptualization; methodology; formal analysis; supervision; writing—review and editing. **Mohamed Fouad**: Conceptualization; methodology; formal analysis; supervision; writing—review and editing. **Claudio A. Schioppa**: Conceptualization; methodology; formal analysis; supervision; writing—review and editing. **José-Ángel Hernández-Rivas**: Conceptualization; methodology; formal analysis; supervision; writing—review and editing. **Alessandra Tedeschi**: Conceptualization; methodology; formal analysis; supervision; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

Paolo Ghia: research funding and honoraria from AbbVie, AstraZeneca, Bristol Myers Squibb, and Janssen; honorarium from BeiGene, Bristol Myers Squibb, Galapagos, Lilly/Loxo Oncology, MSD, and Roche. Loic Ysebaert: advisory board member and research grants from AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Gilead Sciences, Janssen, and Roche. Ann Janssens: advisory board member, consultant, and/or speaker for AbbVie, Amgen, Argenx, AstraZeneca, BeiGene, Eli Lilly, Janssen, MSD, Novartis, Sobi, and Takeda; travel expenses paid for by AbbVie and AstraZeneca. Stephan Stilgenbauer: advisory board member and received research/travel support and speaker fees from AbbVie, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, Galapagos, Gilead Sciences, GlaxoSmithKline, Hoffmann-La Roche, Janssen, Lilly, Novartis, and Sunesis. Mohamed Fouad: employee and shareholder of Johnson & Johnson. Claudio Schioppa: employee and shareholder of Johnson & Johnson. José-Ángel Hernández-Rivas: speaker for AbbVie, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb-Celgene, Gilead Sciences, Janssen, Lilly, Roche, and Takeda; advisory board member for AbbVie, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb-Celgene, Gilead Sciences, Incyte, Janssen, Jazz Pharmaceuticals, Lilly, MSD, Roche, Rovi, and Takeda; grant/research support from Bristol Myers Squibb-Celgene. Alessandra Tedeschi: advisory board member and/or speaker for AstraZeneca, AbbVie, BeiGene, Janssen, and Eli Lilly.

DATA AVAILABILITY STATEMENT

Janssen Pharmaceutical Companies of Johnson & Johnson's data sharing policy is available at https://www.janssen.com/clinical-trials/transparency.

ETHICS STATEMENT

This work included the use of pooled data from multiple trials. Ethical consideration was not applicable for this study.

FUNDING

This work was supported by Johnson & Johnson.

SUPPORTING INFORMATION

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

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