Received: 14 September 2022 | Revised: 4 November 2022 | Accepted: 5 November 2022

DOI: 10.1002/ajh.26779

AJH WILEY

CORRESPONDENCE

Efficacy of front-line ibrutinib versus fludarabine, cyclophosphamide, and rituximab in patients with chronic lymphocytic leukemia: A retrospective multicenter "Real-World" study

To The Editor:

In recent years, there has been a dramatic change in the treatment landscape of chronic lymphocytic leukemia (CLL). The chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab (FCR) has been shown to prolong progression-free survival (PFS) and overall survival (OS) compared to FC alone in previously untreated CLL patients.[1] Consequently, until recently FCR has become the treatment of choice in young fit patients with CLL. Ibrutinib, a first-in-class covalent inhibitor of Bruton's tyrosine kinase, improved PFS and OS compared to chlorambucil[2] and prolonged PFS compared to bendamustine plus rituximab, as frontline treatment in older (≥65 years) patients with CLL.[3] In phase the III ECOG-E1912 trial, ibrutinib plus rituximab (IR) has been shown to prolong PFS and OS compared to FCR in treatment-naïve (TN) CLL patients aged <70 years.[4,5] At 3 years, a subgroup analysis showed a PFS superiority with IR compared to FCR only in patients with unmutated (U) immunoglobulin heavy chain variable region gene (IGHV).[4] However, with a longer follow-up of 5 years, an improvement in PFS with IR was apparent in the mutated (M) IGHV subgroup as well.[5] A better PFS in frontline treatment with IR over FCR had also been shown in the phase III NCRI FLAIR trial, yet with no OS difference, and currently, the improved PFS with IR is observed only in the U-IGHV group.[6]

In this retrospective, bi-national, multicenter "real-world" study, we compared the PFS and OS between ibrutinib and FCR in previously untreated CLL patients. Patients with documented del(17p13.1) or TP53 mutations were excluded. Demographics and clinical data were retrieved from the Israeli CLL Study Group database (1996–2020) and the Italian multicenter "Campus CLL" network (2015–2020). The study was approved by the institutional Helsinki ethics committees of the participating centers. In order to fit both treatment groups, the maximum follow-up was censored at 48 months. For controlling differences in patients' characteristics, we use the inverse probability of treatment weighting method. For more details on the statistical analysis, see Supplementary Appendix.

A total of 235 patients treated in first-line either with FCR ($n = 136$, 57.9%) or ibrutinib ($n = 99$, 42.1%), were included (baseline demographic and disease characteristics are listed in Table S1). FCR treated patients were younger compared to patients treated with ibrutinib (mean = 57.6 years [±7.5] versus 71.6 years [±8.7]; $p < .001$). In the entire cohort, most patients were males ($n = 160$, 68.1%), had U-IGHV ($n = 115$, 70.6%) and Binet stage B/C ($n = 191$, 83.8%). The most frequent chromosomal aberration was del(11q) ($n = 45$, 23.1%) followed by trisomy 12 ($n = 34$, 17.4%) and del(13q) ($n = 43$, 22.1%). The median time from CLL diagnosis to first treatment was 29.4 months (IQR, 11.9–56.2) and was not significantly different between the ibrutinib (median = 24.9 months, IQR 10.3–46.6) and FCR cohorts (median = 33.5 months, IQR 13.8–59.3; $p = .164$). The median follow-up for the entire cohort was 48.0 months; 37.2 months for ibrutinib and 48.0 months for the FCR cohort.

During the study follow-up, a total of 66 patients (28.1%) progressed (ibrutinib: $n = 10$, 10.1%; FCR: $n = 56$, 41.2%). The PFS was shorter in patients treated with FCR than with ibrutinib; a 4-year PFS rate of 54.8% versus 87.7%, respectively (hazard ratio (HR) = 3.6, 95% CI [1.84–7.06]; $p < .001$) (Figure 1A, Supplementary Table S3). The PFS difference between these treatments protocols was also noted in 3-year analysis (65.0% vs 89.7%, HR = 3.3, 95% CI [1.63–6.83], $p < .001$). By subgroup analysis, the PFS was significantly longer among patients with age at treatment initiation <65 years compared with age at initiation ≥65 years (HR = 0.6, 95% CI [0.33–0.96], $p = .036$) and among patients without FISH abnormalities (HR = 0.5, 95% CI [0.25–0.95], $p = .036$) (Table S2) Four-year PFS was shorter among U-IGHV patients treated with FCR compared to patients treated with ibrutinib (44.9% vs. 89.5%; HR = 5.8, 95% CI [2.35–14.46]; $p < .001$) (Figure 1B) but it did not reach a statistically significant difference in the M-IGHV group (4-year PFS: 67.0% vs. 83.0%, respectively; HR = 1.5, 95% CI [0.41–5.24]; $p = .551$) (Figure 1C). As expected, 4-year PFS among patients treated with FCR was trendy shorter in the U-IGHV compared with M-IGHV subgroup, but without statistical significance (44.9% vs. 67.0%, respectively; HR = 2.2, 95% CI: 0.89–5.49; $p = .087$), while there was no difference in PFS among patients treated with ibrutinib stratified by IGHV mutational status (4-year PFS: 83.0% vs. 89.5% in M-IGHV and U-IGHV respectively; HR = 0.5, 95% CI [0.15–1.88]; $p = .326$).

In a multivariate analysis, FCR was the only independent variable associated with reduced PFS (HR = 4.3, 95% CI [1.92–9.60], p = <0.001) (Table S3). Given the imbalance in age between the

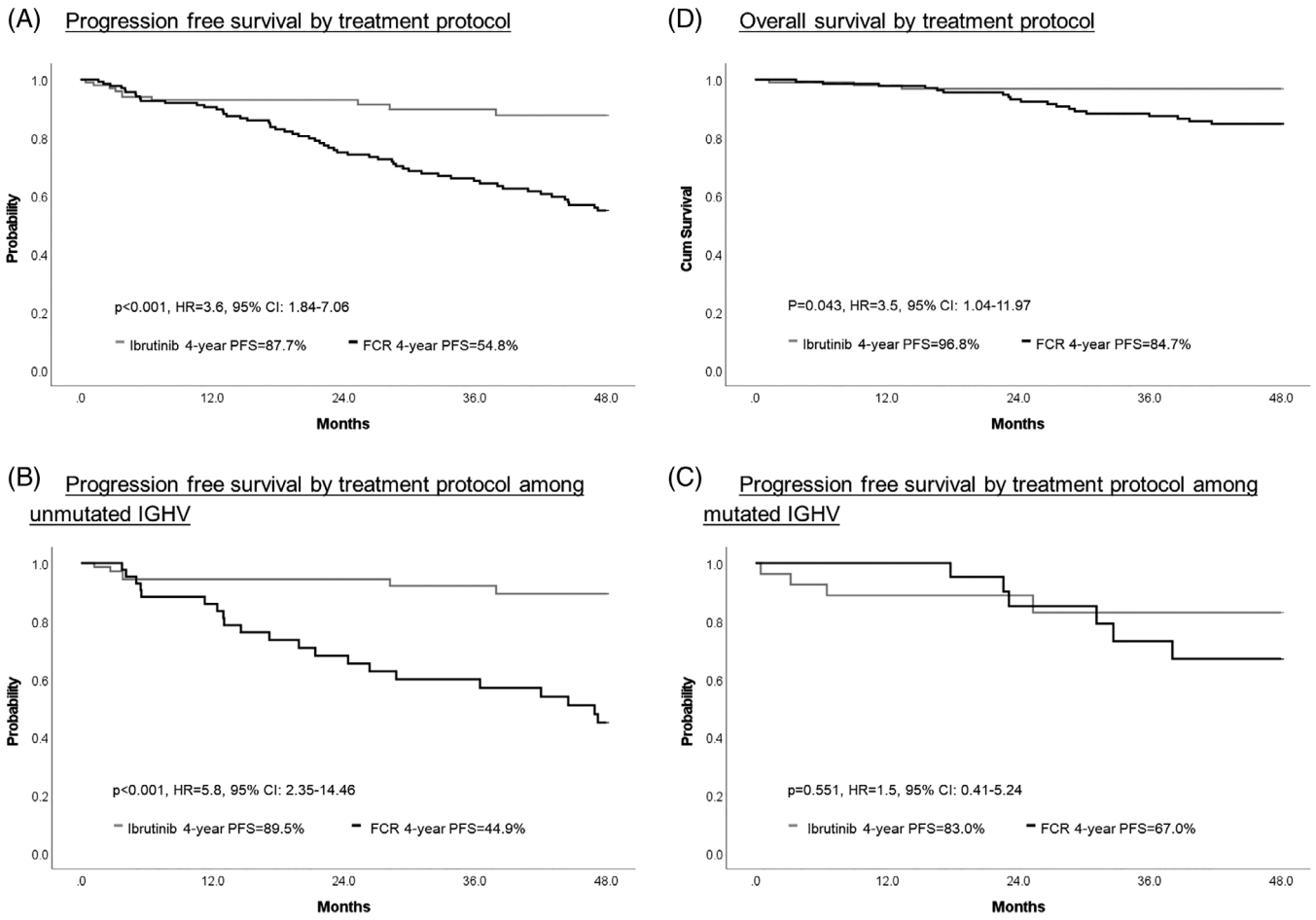

FIGURE 1 Kaplan–Meier curves of progression free survival for the treatment protocols ibrutinib and FCR among all patients (A), unmutated IGHV patients (B) and mutated IGHV patients (C), and overall survival for the treatment protocols among all patients (D)

ibrutinib and FCR groups, we confirmed by inverse probability of treatment weighting the PFS inferiority with FCR compared to ibrutinib (HR = 4.5, 95% CI [2.1–10.0], $p < .001$).

A total of 22 patients (9.4%) died during the 48-months study period (Table S5); 19 (14.0%) in the FCR cohort and 3 (3.0%) in the ibrutinib cohort. OS was shorter in patients treated with FCR compared with ibrutinib, with a 4-year OS rate of 84.7% vs. 96.8%, respectively (HR = 3.5, 95% CI [1.04–11.97]; $p = .043$) (Figure 1D, Table S4). A similar analysis at 3 years showed only a trend toward statistical significance between FCR and ibrutinib (87.4% vs. 96.8%, respectively; HR = 3.1, 95% CI: 0.90–10.63; $p = .073$). By subgroup analysis, none of the variables were found to prolong the OS among the study's cohort, and multivariate analysis was not performed. Using the inverse probability of treatment weighting, we confirmed an OS inferiority with FCR compared to ibrutinib (HR = 5.3, 95% CI [1.5–18.3], $p = .008$). For additional sub-groups statistical analysis, see Supplementary Appendix.

In this multicenter retrospective, real-world study, we show that frontline treatment with ibrutinib improved both PFS and OS over FCR in patients with CLL during 48 months of follow-up. To compare our findings with previous studies, we analyzed our findings also for 3-year of follow-up. Our results seem to be similar to the results reported in the phase III ECOG-E1912 and FLAIR trials, which showed a better PFS with frontline IR compared to FCR,[4-6] whereas OS advantage with IR was observed only in the ECOG-E1912 trial.[4,5] In our study, the 3-year PFS with ibrutinib (89.7%) is comparable to the PFS reported with IR in the ECOG-E1912 trial (89.4%).[4] It has been previously shown that the addition of rituximab to ibrutinib does not improve PFS compared to ibrutinib alone in patients with CLL.[3,7] On the other hand, the 3-year PFS rate in patients treated with FCR (65.0%) in our cohort, seems to be lower than reported in the ECOG-E1912 trial (72.9%).[4] It is important to note that in a real-world setting, more intensive treatment regimens like FCR were often reported to achieve inferior PFS probably due to a lack of patient selection (thus including patients with multiple comorbidities and less fit patients) and more frequent dose reductions.[8] Furthermore, the 3-year OS rates in our patients treated with ibrutinib (96.8%) and FCR (87.4%) are also comparable to those reported with IR and FCR (98.8% and 91.5%, respectively) in the ECOG-E1912 trial.[4] This favorable OS in our FCR-treated patients may have been due to the

introduction of targeted therapies into second-line treatment onwards. In our study, treatment with ibrutinib improved PFS in the U-IGHV but not in the M-IGHV subgroup. No similar differences were observed in the OS analysis. A similar favorable PFS with ibrutinib has been reported in U-IGHV patients both in the ECOG-E1912 and FALIR trials.[4-6] Lack of PFS advantage with ibrutinib in M-IGHV patients had been observed in the first 3 years of follow-up in both the ECOG-E1912 trial as well as in the NCRI FLAIR study,[4,6] yet, with a longer follow-up of 5 years, treatment with IR emerged to improve PFS also in the M-IGHV subgroup, in the ECOG-E1912 trial.[5] Thus, it is indeed possible that with longer follow-up, an improvement in PFS in the M-IGHV subgroup can also be expected in our cohort.

Our study has several limitations; first, our data were retrospectively collected from multiple centers, which may potentially cause lack of uniformity in the data analysis. In addition, there was an age imbalance between the two treatment cohorts, with a younger age among FCR-treated patients versus ibrutinib. However, by inverse probability of treatment weighting, we confirmed that PFS is superior with ibrutinib over FCR. In addition, the older age in the ibrutinib cohort was in fact expected to adversely affect outcomes and therefore reinforce our results.

In conclusion, in a real-world setting frontline treatment with ibrutinib improved PFS and OS compared to FCR in patients with CLL in 48 months of follow-up. The improvement in PFS was preferentially observed in patients with unmutated IGHV. Overall, these real-world results are comparable to the results reported in clinical trials and therefore further support ibrutinib as a preferred option over FCR in first-line treatment in CLL.

AUTHOR CONTRIBUTIONS

SL and YB wrote the manuscript and analyzed the data. TZB analyzed the data. YH initiated and supervised the study, and wrote the manuscript. All co-authors except TZB collected the clinical data.

FUNDING INFORMATION

The present study is supported in part by: Progetto Ricerca Finalizzata PE-2016-02362756, and RF-2018-12 365 790, Italian Ministry of Health, Rome, Italy; Associazione Italiana Ricerca Cancro (AIRC), Investigator Grant IG-21687; Associazione Italiana contro le Leucemie, linfomi e mielomi (AIL), Venezia Section, Pramaggiore/Veneto Orientale Group, Italy; Fundaciò La Maratò de TV3 (Spain); Linfo-check - Bando ricerca - contributo art. 15, comma 2, lett (b) LR 17/2014; "5 × 1000 Intramural Program", Centro di Riferimento Oncologico, Aviano, Italy.

CONFLICT OF INTEREST

Yair Herishanu received honoraria from AstraZeneca, Janssen, Abbe-Vie, Roche and Medison that unrelated to this study. The remaining authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Shai Levi[1], Yotam Bronstein[1], Neta Goldschmidt[2], Fortunato Morabito[3,4], Tomer Ziv-Baran[5], Giovanni Del Poeta[6], Osnat Bairey[7], Maria Ilaria Del Principe[6], Riva Fineman[8], Francesca Romana Mauro[9], Odit Gutwein[10], Gianluigi Reda[11], Rosa Ruchlemer[12], Paolo Sportoletti[13], Luca Laurenti[14], Lev Shvidel[15], Marta Coscia[16], Tamar Tadmor[17], Marzia Varettoni[18], Ariel Aviv[19], Roberta Murru[20], Andrei Braester[21], Annalisa Chiarenza[22], Andrea Visentin[23], Daniela Pietrasanta[24], Giacomo Loseto[25], Antonella Zucchetto[26], Riccardo Bomben[26], Jacopo Olivieri[27], Antonio Neri[28], Davide Rossi[29], Gianluca Gaidano[30], Livio Trentin[23], Robin Foà[9], Antonio Cuneo[31], Chava Perry[1,2], Valter Gattei[26], Massimo Gentile[32], Yair Herishanu[1,5]

[1]*Department of Hematology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[2]*Department of Hematology, Hadassah Medical Center, Jerusalem, Israel*
[3]*Biothechnology Research Unit, AO of Cosenza, Cosenza, Italy*
[4]*Hematology and Bone Marrow Transplant Unit, Hemato-Oncology Department, Augusta Victoria Hospital, Jerusalem, Israel*
[5]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[6]*Division of Hematology, University of Tor Vergata, Rome, Italy*
[7]*Rabin medical Center, Petah Tikva, Israel*
[8]*Rambam Medical Center, Haifa, Israel*
[9]*Hematology, Department of Translational and Precision Medicine, 'Sapienza' University, Rome, Italy*
[10]*Shamir Medical Center, Tsrifin, Israel*
[11]*Ematologia, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy*
[12]*Shaare Zedek Medical Center, Jerusalem, Israel*
[13]*Centro di Ricerca Emato-Oncologica (CREO), University of Perugia, Perugia, Italy*
[14]*Fondazione Universitaria Policlinico A Gemelli di Roma, Roma, Italy*
[15]*Kaplan Medical Center, Rehovot, Israel*
[16]*Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino, Torino, Italy*
[17]*Bnai Zion Medical Center, Haifa, Israel*
[18]*Division of Haematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[19]*Ha'Emek Medical Center, Afula, Israel*
[20]*Hematology and Stem Cell Transplantation Unit, Ospedale A. Businco, ARNAS "G. Brotzu", Cagliari, Italy*
[21]*Galillee Medical Center, Nahariya, Israel*
[22]*Division of Hematology, Policlinico, Department of Surgery and Medical Specialties, University of Catania, Catania, Italy*
[23]*Department of Medicine, Hematology and Clinical Immunology Branch, University of Padova, Padova, Italy*
[24]*Division of Hematology, Azienda Ospedaliera SS Arrigo e Biagio e Cesare Arrigo, Alessandria, Italy*
[25]*Hematology and Cell Therapy Unit, IRCCS-Istituto Tumori 'Giovanni Paolo II', Bari, Italy*
[26]*Clinical and Experimental Onco-Hematology Unit, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy*

[27]*Clinica Ematologica, Centro Trapianti e Terapie Cellulari "Carlo Melzi", Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy*
[28]*Scientific Directorate, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy*
[29]*Department of Hematology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland*
[30]*Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy*
[31]*Hematology Section, Department of Medical Sciences, University of Ferrara, Ferrara, Italy*
[32]*Hematology Unit AO of Cosenza, Cosenza, Italy*

Correspondence
Yair Herishanu, Department of Hematology, Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel-Aviv 6423906, Israel.
Email: yairh@tlvmc.gov.il

Shai Levi and Yotam Bronstein equal contribution to this study.
Valter Gattei, Massimo Gentile and Yair Herishanu Senior authors equal contribution to this study.

ORCID

Shai Levi https://orcid.org/0000-0002-1453-9029
Yotam Bronstein https://orcid.org/0000-0002-3026-8724
Maria Ilaria Del Principe https://orcid.org/0000-0002-3958-0669
Francesca Romana Mauro https://orcid.org/0000-0003-2425-9474
Gianluigi Reda https://orcid.org/0000-0003-4687-7089
Paolo Sportoletti https://orcid.org/0000-0002-5630-9862
Luca Laurenti https://orcid.org/0000-0002-8327-1396
Marzia Varettoni https://orcid.org/0000-0001-7304-1629
Andrea Visentin https://orcid.org/0000-0003-0271-7200
Antonella Zucchetto https://orcid.org/0000-0003-3678-5957
Yair Herishanu https://orcid.org/0000-0002-7864-0089

REFERENCES

1. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174. doi:10.1016/S0140-6736(10)61381-5
2. 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
3. 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
4. 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
5. 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
6. Hillmen PPA, Bloor A, Broom A, et al. Ibrutinib plus rituximab is superior to FCR in previously untreated CLL: results of the phase III NCRI FLAIR trial. *Blood*. 2021;138(Supplement 1). doi:10.1182/blood-2021-152319
7. Burger JA, Sivina M, Jain N, et al. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. *Blood*. 2019;133(10):1011-1019. doi:10.1182/blood-2018-10-879429
8. Herishanu Y, Goldschmidt N, Bairey O, et al. Efficacy and safety of front-line therapy with fludarabine-cyclophosphamide-rituximab regimen for chronic lymphocytic leukemia outside clinical trials: the Israeli CLL study group experience. *Haematologica*. 2015;100(5):662-669. doi:10.3324/haematol.2014.115808

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.