Efficacy of bendamustine and rituximab in unfit patients with previously untreated chronic lymphocytic leukemia. Indirect comparison with ibrutinib in a real-world setting. A GIMEMA-ERIC and US study

Antonio Cuneo | Anthony R. Mato | Gian Matteo Rigolin | Alfonso Picciocchi | Massimo Gentile | Luca Laurenti | John N. Allan | John M. Pagel | Danielle M. Brander | Brian T. Hill | Allison Winter | Nicole Lamanna | Constantine S. Tam | Ryan Jacobs | Frederick Lansigan | Paul M. Barr | Mazyar Shadman | Alan P. Skarbnik | Jeffrey J. Pu | Alison R. Sehgal | Stephen J. Schuster | Nirav N. Shah | Chaitra S. Ujjani | Lindsey Roeker | Ester Maria Orlandi | Atto Billio | Livio Trentin | Martin Spacek | Monia Marchetti | Alessandra Tedeschi | Fiorella Ilariucci | Gianluca Gaidano | Michael Doubek | Lucia Farina | Stefano Molica | Francesco Di Raimondo | Marta Coscia | Francesca Romana Mauro | Javier de la Serna | Angeles Medina Perez | Isacco Ferrarini | Giuseppe Cimino | Maurizio Cavallari | Rosalba Cucci | Marco Vignetti | Robin Foà | Paolo Ghia | the GIMEMA, European Research Initiative (ERIC) on CLL, US study group

1Hematology, Department of Medical Sciences, St. Anna University Hospital, Ferrara, Italy
2Division of Hematological Oncology, CLL Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA
3Italian Group for Adult Hematologic Diseases (GIMEMA), Data Center and Health Outcomes Research Unit, Rome, Italy
4Department of Onco-Hematology, Hematology Unit, A.O. of Cosenza, Cosenza, Italy
5Weill Cornell Medicine, New York, NY, USA
6Center for Blood Disorders and Stem Cell Transplantation, Swedish Cancer Institute, Seattle, WA, USA
7Division of Hematologic Malignancies and Cellular Therapy, Duke University, Durham, NC, USA
8Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA
9Columbia University Medical Center, New York, NY, USA
10University of Melbourne, Melbourne, Victoria, Australia
11Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC, USA
12Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA
13Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA

Antonio Cuneo, Anthony R. Mato and Gian Matteo Rigolin contributed equally.
Robin Foà and Paolo Ghia contributed equally.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. Cancer Medicine published by John Wiley & Sons Ltd.
Abstract

Limited information is available on the efficacy of front-line bendamustine and rituximab (BR) in chronic lymphocytic leukemia (CLL) with reduced renal function or coexisting conditions. We therefore analyzed a cohort of real-world patients and performed a matched adjusted indirect comparison with a cohort of patients treated with ibrutinib. One hundred and fifty-seven patients with creatinine clearance (CrCl) <70 mL/min and/or CIRS score >6 were treated with BR. The median age was 72 years; 69% of patients had ≥2 comorbidities and the median CrCl was 59.8 mL/min. 17.6% of patients carried TP53 disruption. The median progression-free survival (PFS) was 45 months; TP53 disruption was associated with a shorter PFS (P = 0.05).

The overall survival (OS) at 12, 24, and 36 months was 96.2%, 90.1%, and 79.5%, respectively. TP53 disruption was associated with an increased risk of death (P = 0.01).

Data on 162 patients ≥65 years treated with ibrutinib were analyzed and compared with 165 patients ≥65 years treated with BR. Factors predicting for a longer PFS at multivariable analysis in the total patient population treated with BR and ibrutinib were age (HR 1.06, 95% CI 1.02-1.10, P < 0.01) and treatment with ibrutinib (HR 0.55, 95% CI 0.33-0.93, P = 0.03). In a post hoc analysis of patients in advanced...
INTRODUCTION

With 20,720 estimated new cases and 3930 deaths in 2019 in the United States, chronic lymphocytic leukemia (CLL) is the most frequent leukemia in western countries.1 Because the median age at diagnosis is around 70 years and many patients carry one or more comorbidities, the most effective chemoinmunotherapy (CIT) regimen, fludarabine, cyclophosphamide, and rituximab (FCR), cannot be safely administered, thus making other options like a combination of the anti CD20 monoclonal antibody rituximab with bendamustine (BR) or chlorambucil2 a widely employed therapeutic strategy in the clinical practice. The efficacy and safety of these combinations in the front-line setting have been documented in phase-2 and phase-3 trials including fit patients randomized to either FCR or BR,3-5 or patients deemed ineligible for fludarabine due to coexisting conditions and/or reduced renal function who were treated with chlorambucil and anti CD20 monoclonal antibodies.6-10 The BR combination was also tested in a limited number of patients not deemed fit to receive fludarabine-based regimens at physician’s discretion9 and in older patients with preserved or moderately impaired renal function.11

In recent years, evidence has been provided that a longer progression-free survival (PFS) can be achieved with ibrutinib than with CIT in previously untreated CLL10-12 and expert opinions recommended ibrutinib upfront, especially in older patients with CLL and in younger patients with TP53 disruption or less favorable unfavorable immunogenetic characteristics, that is, unmutated configuration of the variable portion of the immunoglobulin (IGHV) gene.13-15

Interestingly, an observational study of CIT in the “real-world” setting showed that these regimens may prove safe and effective,16-18 even though dose reductions may occur commonly in clinical practice and may impact on outcome.19 Likewise, the rates of ibrutinib discontinuation and survival are likely to be worse in a real-world setting than in a clinical trial possibly due to inclusion of patients with poorer performance status and more comorbidities.20-22 A matched-adjusted indirect comparison of patients who had received BR or ibrutinib as first salvage treatment outside of clinical trials showed no OS difference.17

Because limited information is available on the efficacy and safety of BR in unfit patients, we analyzed the efficacy of this regimen in a cohort treated outside clinical trials and we carried out an indirect comparison with a cohort of older patients treated with ibrutinib front-line in a real-world setting.23

METHODS

2.1 | Patients

The patients included in this report were retrospectively selected as outlined below from a cohort of patients treated front-line with BR between 2008 and 2014 at GIMEMA and European Research Initiative on CLL (ERIC) centers and from a cohort of CLL patients treated front-line with ibrutinib at 20 community and academic US centers.16,22

2.2 | BR regimen in unfit CLL

Inclusion criteria in this analysis were (a) CLL progression according to the NCI criteria24 (b) no previous treatment for CLL, (c) creatinine clearance <70 mL/min and/or CIRS > 6, that is unfit patients as previously defined,6 (d) and received at least 1 day of treatment with the BR regimen.25 Patients were excluded from the study if they had transformation of CLL into Richter’s syndrome before starting treatment, known HIV infection, active and uncontrolled HCV and/or HBV infections. Treatment response and disease progression were assessed according to the NCI criteria.24 The primary endpoint was 12-month progression-free survival (PFS). Secondary endpoints were overall response rate (ORR), time to next anti-leukemic treatment (TTNT), and overall survival (OS) as previously defined.17 Safety data were reported according to the NCI Common Terminology Criteria for Adverse Events version 4.0. The study was registered at ClinicalTrials.gov (NCT02491398). The study was approved by the institutional review board of each participating institution.
2.3 | Indirect comparison with ibrutinib

For the purpose of this analysis, we retrieved pertinent data by reviewing clinical charts, electronic medical records, and related databases in patients ≥65 years enrolled in the GIMEMA ERIC study who had received BR in first line and in patients ≥65 years of a US study who had received single agent ibrutinib. The patients with del(17p) or TP53 mutations were excluded. The endpoints for this analysis were the PFS and OS.

2.4 | Statistical analysis

The analyses were performed following the intention-to-treat principle as previously described. All analyses were performed using the SAS software (version 9.4 or later); all tests were two-sided, at a significance level of 0.05. Study data were collected and managed using REDCap electronic data capture tools. The data that support the findings of this study are available from the corresponding author upon reasonable request.

3 | RESULTS

3.1 | Treatment with BR in unfit patients

One hundred fifty-seven patients treated at 31 centers (24 GIMEMA centers and 7 ERIC centers) were included. The demographic data at baseline have been outlined in Table 1. The median age was 72 years; 80.9% of patients was >65 years; 69.2% had 2 or more comorbidities, the median creatinine clearance was 59.8 mL/min and 58.9% had Binet stage B-C. Fifty-one percent (data available in 56.7% of the patients) had β2 microglobulin ≥3.5/ <3.5 mg/L. ECOG PS 0/1/ ≥2 (n = 154) 68 (43.3)/70 (44.6)/ 16 (10.2).

One hundred and fourteen of 157 patients (73.1%) received the planned number of cycles; treatment was discontinued as a result of toxicity in 18% patients (n = 28), withdrawal of consent in 2% (n = 3), or other reasons in 7% (n = 11). The number of cycles actually administered to patients who discontinued treatment was >4 in 71% of cases. The starting dose of bendamustine was 90 mg/m² in 45.8% of the patients, 70 mg/m² in 33.1% of the patients and 50-70 mg/m² in 21.1% of the patients. A dose reduction >10% of the planned dose of bendamustine was recorded in 24.2% of cases; treatment delay occurred in 22.9% of patients.

Second-line treatment was offered at symptomatic progression according to local guidelines.

3.2 | Efficacy

The ORR to BR was 91.7%. The probability of attaining a response was significantly lower in patients with del(17p)/TP53 mutations as compared to patients without del(17p)/TP53 mutations (50% vs 85.1%, P = 0.02). Other variables had no significant impact on the ORR (Table S2).

The median PFS was 45 months (Figure 1(A)), with a 12-month PFS rate of 93% (95% CI 89.0%-97.1%). The estimated PFS at 24 and at 36 months were 81% (95% CI 74.5%-88.2%) and 66.8% (95% CI 74.5%-88.2%), respectively. Factors associated with a shorter PFS in univariate analysis were represented by del(17p)/TP53 mutations, ECOG performance status and by the presence of 2 or more comorbidities, as shown in Table 2, whereas an intermediate/advanced stage and an IGHV-unmutated status were of borderline significance. Age (cut-off 65 years) and other clinicobiologic parameters had no impact on PFS. del(17p)/TP53 mutations represented the only adverse parameter in multivariable analysis (Table 2, Figure 1(B)).

A second-line treatment was administered to 3.2% (95% CI 1.2%-6.9%), 8.3% (95% CI 4.3%-13.9%), and 21.5% (95% CI 13.1%-31.1%) of patients at 12, 24, and 36 months, respectively (Figure S1). A shorter TTNT was associated with del(17p)/TP53 mutation (P < 0.01; Table S2).

The OS at 12, 24, and 36 months were 96.2% (95% CI 93.2%-99.2%), 90.1% (95% CI 85.0%-95.5%), and 79.5% (95% CI 70.0%-90.5%), respectively, with a median OS that was not reached with a 26-month median follow-up (Figure 2). The presence of del(17p)/TP53 mutation (P < 0.01) and lack of response to treatment (P < 0.01) were associated with a shorter OS in univariate as well as
in multivariate analysis (Table 3). Other clinicobiologic parameters had no impact on OS. Twenty-two patients died (n = 2 due to CLL, 9.1%; n = 12 infection with or without active CLL, 54.6%; n = 3 second primary tumors, 13.6%; 1 each cardiac disease and sudden death). In three patients, the cause of death was not reported.

### 3.3 Safety

Forty-two percent of the BR patients reported at least one grade 3-4 adverse event. Overall, cytopenias were recorded in 34% of patients. Grade 3-4 neutropenia occurred in 24% of cases. Grade 3-4 infections including febrile neutropenia were recorded in 11% of patients. One case of fatal infection was reported. Grade 3-4 rash and/or dermatitis were reported 3% of patients.

### 3.4 Comparison of BR in the GIMEMA-ERIC dataset and ibrutinib in the US dataset

Data on 165 and 162 older patients without del(17p)/TP53 aberrations treated with BR and ibrutinib, respectively, were analyzed. The median follow-up in the BR and in the ibrutinib cohorts was 29 months (95% CI 26-31) and 13 months (95% CI 10-14), respectively. As shown in Table 4, the two cohorts were comparable in terms of age and frequency of del(11q). Patients with advanced Rai stage were more frequently represented in the ibrutinib cohort than in the BR cohort, and the interval between diagnosis and treatment was significantly longer in the ibrutinib cohort.

Factors associated with a longer PFS in multivariate analysis in the combined patient population treated with BR and ibrutinib were represented by age as a continuous
variable and by treatment with ibrutinib (Table 5). Age was the only factor predicting for shorter OS at multivariate analysis (HR 1.10, 95% CI 1.04 - 1.15, \( P < 0.01 \)).

In a post hoc analysis including patients in advanced stage (ie Rai III-IV), the ibrutinib cohort (\( n = 96 \) patients), and the BR cohort (\( n = 46 \) patients) were comparable in terms of age (cut-off 70 years) and interval between diagnosis and first-line treatment (cut-off 36 months), as shown in Table 6. A significant PFS advantage was observed in the ibrutinib cohort (\( P = 0.03 \)), which also showed a trend for an advantage in terms of OS (\( P = 0.08 \), Figure 3(A) and (B)). Patients in early/intermediate stage in the BR (\( n = 79 \)) and in the ibrutinib cohort (\( n = 59 \)) had similar age and similar interval between diagnosis and first-line treatment characteristics (Table 6). No difference was noted in terms of PFS (\( P = 0.89 \)) and OS (\( P = 0.66 \)) in these patients (Figure 4(A) and (B)).

4 | DISCUSSION

This is the first robust report of the efficacy and safety of BR in unfit patients treated outside clinical trials, as these patients were usually enrolled in trials using chlorambucil and an anti CD20 monoclonal antibody.\(^6,27\) Even though chlorambucil is the preferred option as chemotherapy backbone in this subset.
| Variable                          | Univariate HR (95% CI) | P     | Multivariate HR (95% CI) | P     |
|----------------------------------|------------------------|-------|--------------------------|-------|
| Age > 65 vs ≤ 65 years           | 3.95 (0.53-29.50)      | 0.18  | 4.47 (1.37-14.56)        | 0.01  |
| Binet B-C vs Binet A             | 2.42 (0.79-7.41)       | 0.12  | —                        | —     |
| β2 microglobulin ≥ 3·0.5 vs < 3.5 mg/L | 4.11 (0.55-30.92)     | 0.17  | —                        | —     |
| IGHV unmutated vs mutated        | 0.81 (0.22-3.05)       | 0.76  | —                        | —     |
| NR vs CR or PR                   | 8.43 (3.52-20.19)      | <0.01 | 15.21 (5.72-40.74)       | <0.01 |
| Gender female vs male            | 0.68 (0.29-1.64)       | 0.39  | —                        | —     |
| ECOG 0 vs 1                      | 2.28 (0.79-6.59)       | 0.13  | —                        | —     |
| ECOG 0 vs ≥ 2                    | 4.90 (1.48-16.19)      | 0.01  | —                        | —     |
| Comorbidities 0-1 vs ≥ 2         | 1.79 (0.60-5.29)       | 0.29  | —                        | —     |
| Creatinine clearance ≤ 70 vs > 70 mL/min | 3.02 (1.01-9.09)   | 0.05  | —                        | —     |
| no-aberrations vs 13q            | 0.74 (0.12-4.45)       | 0.74  | —                        | —     |
| 11q- vs 13q                      | 3.18 (0.52-19.37)      | 0.21  | —                        | —     |
| +12 vs 13q                       | 3.88 (0.90-16.71)      | 0.07  | —                        | —     |
| 17p- vs 13q                      | 11.29 (2.08-61.14)     | <0.01 | 4.47 (1.37-14.56)        | 0.01  |

Legend: NR, no response; CR, complete response; PR, partial response.

### TABLE 3
Overall survival (OS): univariate and multivariate analyses in the bendamustine and rituximab (BR) cohort

### TABLE 4
Baseline characteristics of the bendamustine and rituximab (BR) and the ibrutinib cohorts

### TABLE 5
Univariate and multivariable analysis of PFS in the total patient population treated with bendamustine and rituximab (BR) and ibrutinib
of CLL, BR is a widely adopted front-line regimen in the clinical practice for elderly CLL patients with coexisting conditions. Even though this study is not based on a registry reporting the efficacy of BR and ibrutinib in all the incident CLL cases and accepting the limitations of a retrospective analysis, to ensure

### TABLE 6 Baseline characteristics in patients with advanced (Rai III-IV) and early/intermediate stage (Rai 0-II) in the bendamustine and rituximab (BR) and ibrutinib cohorts

|                  | Advanced stage | Early/intermediate stage |
|------------------|----------------|--------------------------|
|                  | BR n = 46 (%)  | ibrutinib n = 96 (%)     | BR n = 79 (%)  | ibrutinib n = 59 (%) |
| Age              |                |                          |                |
| ≤70 years        | 16 (34.8)      | 27 (28.1)                | 31 (39.2)      | 22 (37.3)              |
| >70 years        | 30 (65.2)      | 69 (71.9)                | 48 (60.8)      | 37 (67.2)              |
| Gender           |                |                          |                |
| Male             | 31 (67.4)      | 58 (60.4)                | 49 (62.0)      | 38 (64.4)              |
| Female           | 15 (32.6)      | 38 (39.6)                | 30 (38.0)      | 21 (35.6)              |
| Time dx-trx*     |                |                          |                |
| <36 months       | 25 (54.3)      | 35 (36.5)                | 50 (63.3)      | 30 (50.8)              |
| ≥36 months       | 21 (45.7)      | 61 (63.5)                | 29 (36.7)      | 29 (49.2)              |
| del11q           |                |                          |                |
| No               | 26 (78.8)      | 77 (88.5)                | 55 (96.5)      | 41 (83.7)              |
| Yes              | 7 (21.2)       | 10 (11.5)                | 2 (3.5)        | 8 (16.3)               |

*Time dx-trx: Interval between diagnosis and treatment.

**FIGURE 3** PFS (A) and OS (B) in the BR and in the ibrutinib cohort in (Rai stage III-IV)

**FIGURE 4** PFS (A) and OS (B) in the BR and in the ibrutinib cohort in (Rai stage 0-II)
accuracy in data collection we encouraged each participating
center to include all patients who started BR and we performed
consistency checks on each case report form. Furthermore, we
included, in addition to PFS, objective measures of efficacy
such as OS and TTNT. Because bone biopsy was not manda-
tory, we were not able to assess complete response.

Our BR cohort resembled closely patients with CLL
treated in the daily clinical practice in terms of age, crea-
tinine clearance, performance status and comorbidities.30
The percentage of patients with early stage disease in our
analysis (41.1%) was higher than in GCLLSG and in UK
trials, where 23% and 33% of the patients, were in Binet
stage A, respectively.6,31 This finding reflects the tendency
to initiate treatment in the presence of a short lymphocyte
doubling time or of symptomatic disease in this unfit pa-
tient population.

The proportion of patients who completed the planned
therapy in our analysis (73.1%) is in line with the data form
the MABLE trial that compared chlorambucil and ritux-
imab with the BR regimen in a fludarabine-ineligible CLL
population.9

Grade 3-4 infections in this study (11%) occurred at a
similar frequency as in clinical trials (7.7%-19%).9,11,25 We
observed a lower incidence of grade 3-4 cytopenia (34%)
compared to other studies reporting a 52.1%-56% incidence
of cytopenia due to fact that many investigators did not per-
form a blood count at the nadir time point.

With a median PFS of 45.1 months and a projected OS
rate at 24 and 36 months of 90.1% and 79.5%, respectively,
our data show that BR is an effective front-line treatment
option for an unfit patient population treated outside of
clinical trials. The only baseline characteristics with a significant
negative impact on the efficacy endpoints in this study were
represented by the *TP53* disruption and, interestingly, failure
to respond to BR was an independent dynamic prognostic
factor for OS, a finding probably reflecting the lack of effective
salvage treatment for a proportion of patients during the
study period. The *IGHV*-unmutated configuration was asso-
ciated with a shorter PFS, that was of borderline significant
probably as a consequence of the limited number of patients
assessed.

In our analysis PFS is similar to that observed in the
MABLE trial (median 39.6 months).9 Interestingly, a median
PFS of 33.9 months was observed in the subset of patients
with creatinine clearance <70 in a phase-2 study25 and a me-
dian PFS of 43 months with a 74% PFS rate at 24 months
was reported in a trial enrolling older CLL patients.11 Notably,
OS was similar in our analysis and in prospective trials which
reported an OS rate of approximately 80% at 36 months and
an OS rate of 90%-95% at 24 months.11,25

It is worth noting that chlorambucil and rituximab pro-
duced an 87% ORR with an OS rate at 48 and 60 months of
86.1% (95% CI: 79.4-93.5) and 81.2% (95% CI: 72.4-91.2),
respectively, in elderly patients treated outside clinical tri-
als.18 Likewise, an 80.3% ORR and estimated 2-year OS of
88% was recorded by the Israeli end ERIC group in elderly
patients who received chlorambucil and obinutuzumab, with-
out unexpected adverse events.32 Taken together, these data
show that the efficacy and safety of different CIT regimens
in routine clinical practice are consistent with those reported
in clinical trials.

Because there is evidence that treatment continuation and
efficacy with ibrutinib may be inferior outside of clinical
trials,21,22 and given the growing importance of real world
evidence which can provide invaluable information to sup-
plement randomized clinical studies,33 we elected to compare
PFS and OS in a cohort treated with ibrutinib in a real-world
experience in the USA23 with a similar patient population
received with BR at the GIMEMA-ERIC centers.

Although the two groups were treated in different time pe-
riods with consequent difference in follow-up time, we per-
formed an indirect comparison trying to minimize the effect
of the heterogeneity of patient populations.

First, we documented that in the total study population
(excluding patients with 17p-) age and treatment with ibrut-
inib were associated with a longer PFS in multivariate
analysis.

When restricting our analysis to patients with advanced
stage (Rai III-IV) with comparable baseline characteristics,
we were able to show that ibrutinib was associated with a
longer PFS and a trend of longer OS as compared with BR,
whereas no difference was observed in patients with early in-
termediate stage. Though caution should be exercised when
interpreting these data, as they were obtained in quite a small
number of patients treated outside of clinical trial, it is note-
worthy that similar findings were reported in a randomized
prospective study.34

Taken together our data show that (a) BR is a safe and
effective first-line regimen in a real-world cohort of unfit
CLL patients, with the exception of patients with unfavor-
able genetic characteristics (ie del(17p)/*TP53* aberrations and
*IGHV*-unmutated configuration, (b) there are no appreciable
differences in terms of efficacy and safety between BR in
clinical trials that enrolled older patients with CLL and this
real world experience on unfit patients with reduced renal
function and with coexisting conditions and, (ci) and ibrut-
inib provided more durable disease control than BR in the
front-line setting in patients treated outside of clinical trials,
especially in patients with advanced disease stage.

While providing evidence that BR is an effective first-line
regimen in unfit patients, these data reinforce the notion that
ibrutinib has an established place in the front-line treatment
of older patients with CLL.11,15,35 These findings may have
practical implications in the definition of treatment algo-
rithms, especially in those countries with restrictions to the
use of ibrutinib or other oral agents.36,37
ACKNOWLEDGMENTS

Work supported by Ricerca Finalizzata project RF-2011-02349712 Ministero della Salute, Rome, Italy to AC, GG; MIUR-PRIN 2015 ZMRFEA_004, Rome, Italy to AC, AIL-Ferrara, Italy to AC; Beat Leukemia to AC, Ministry of Health, Czech Republic, grant VFN64165 to MS.

CONFLICT OF INTEREST

- Antonio Cuneo: advisory board and lecturing for Janssen, Gilead, Abbvie, Roche.
- Anthony R. Mato: consultancy for TG Therapeutics (in addition DSMB), Abbvie, PharmaMacys, Johnson & Johnson, Regeneron, AstraZeneca, and Celgene and research funding from TG Therapeutics, Abbvie, PharmaMacys, Johnson & Johnson, Regeneron, Portola, DTRM, and Acerta.
- Gian Matteo Rigolin: lecturing for Abbvie, Gilead and research funding from Gilead.
- Luca Lauretti advisory board and lecturing for Janssen, Gilead, Abbvie, Roche and AstraZeneca.
- John N. Allan Advisory board/Consultant for Sunesis, PCYC, Abbvie, Genentech and research funding from Janssen, Genentech.
- John M. Pagel: Consultancy for AstraZeneca, Pharmacyclys, and Gilead.
- Constantine S. Tam honorarium and research funding from Janssen.
- Paul M. Barr: consultancy for from Abbvie/Pharmacyclys, Gilead, Janssen, TG therapeutics, AstraZeneca, Celgene, Morphosys, Seattle Genetics.
- Alan P. Skarbnik: consultancy for Abbvie, Pharmacyclys, Celgene, Kite, AstraZeneca, Genentech, Seattle Genetics; Speakers Bureau for Abbvie, Pharmacyclys, Celgene, Kite, Gilead Sciences, Jazz Pharma, Beigene, AstraZeneca, Genentech, Seattle Genetics, Verastem, Novartis; Stock Ownership in COTA Healthcare.
- Nirav N. Sha: honoraria, travel support, and research funding from Miltenyi Biotec, honoraria and travel support from Incyte, and Celgene; advisory boards for Kite, Celgene, and Cellectar; research support for clinical trials from BMS.
- Chaitra S. Ujjani: research support from Pharmacyclys, Astra Zeneca and Abbvie; consulting for Astra Zeneca and Abbvie.
- Lindsey Roeker: ASH grant funding for work outside of this manuscript, minority ownership interest in AbbVie and Abbott Laboratories.
- Gianluca Gaidano: Advisory Boards for Janssen, Abbvie, Astra-Zeneca, Sunesis.
- Michael Doubek: Honoraria and Research grants from Roche, AbbVie, AOP Orphan, Janssen-Cilag, Gilead and Amgen.
- Lucia Farina: advisory board for Janssen; lecturing for Abbvie.
- Marta Coscia: advisory board and lecturing from Janssen for Gilead, Abbvie, and research funding from Janssen and Karyopharm Therapeutics.
- Robin Foà34: Editorial boards and/or speaker's bureau for Janssen, AbbVie, Amgen, Novartis, Roche, Pfizer.
- Paolo Ghia: honoraria from AbbVie, Adaptive, ArQule, Beigene, Celgene/Juno, Dyname, Gilead, Janssen, Sunesis and research funding from AbbVie, Gilead, Janssen, Novartis.

AUTHORS' CONTRIBUTIONS

AC, ARM, GMR, AP, MV, RF and PG designed the study and interpreted the data. AC, ARM, GMR, MG, LL, JNA, JMP, DMB, BTH, AW, NL, CST, RJ, FL, PMB, MS, APS, JIP, ARS, SJS, NNS, CSU, LR, EMO, AB, LT, MS, MM, AT, FI, GG, MD, LF, SM, FDR, MC, FRM, JdlS, AMP, IF, GC and PG collected data. AP and RC performed statistical analyses. AC and GMR wrote the manuscript. All the authors reviewed the manuscript for important intellectual contents and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

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

ORCID

Anthony R. Mato https://orcid.org/0000-0001-8724-1875
Gian Matteo Rigolin https://orcid.org/0000-0002-8370-5190
Allison Winter https://orcid.org/0000-0002-8437-7539
Frederick Lansigan https://orcid.org/0000-0001-6027-3359
Jeffrey J. Pu https://orcid.org/0000-0001-7498-3159
Nirav N. Shah https://orcid.org/0000-0002-4336-1071
Monia Marchetti https://orcid.org/0000-0001-7615-0572
Stefano Molica https://orcid.org/0000-0003-2795-6507
Francesca Romana Mauro https://orcid.org/0000-0003-2425-9474

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.
2. Zoellner A-K, Höhler T, Fries S, et al. Altered treatment of chronic lymphocytic leukemia in Germany during the last decade. Ann Hematol. 2016;95(6):853-861.
3. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol. 2005;23(18):4079-4088.
4. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016;127(2):208-215.
5. Eichhorst B, Fink A-M, Bahlo J, et al. First-line chemoimmuno-
therapy with bendamustine and rituximab versus fludarabine, cy-
clophosphamide, and rituximab in patients with advanced chronic
lymphocytic leukaemia (CLL10): an international, open-label,
randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016;17(7):928-942.

6. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlor-
ambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014;370(12):1101-1110.

7. Foà R, Del Giudice I, Cuneo A, et al. Chlorambucil plus ritux-
imab with or without maintenance rituximab as first-line treatment
for elderly chronic lymphocytic leukemia patients. Am J Hematol. 2014;89(5):480-486.

8. Hillmen P, Gribben JG, Follows GA, et al. Rituximab plus chlor-
ambucil as first-line treatment for chronic lymphocytic leuke-
emia: final analysis of an open-label phase II study. J Clin Oncol. 2014;32(12):1236-1241.

9. Michallet A-S, Aktan M, Hiddemann W, et al. Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. Haematologica. 2018;103(4):698-706.

10. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinu-
tuzumab versus chlorambucil plus obinutzumab in first-line treatment
of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(1):43-56.

11. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimen
versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med. 2018;379(26):2517-2528.

12. 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.

13. Jain N. Selecting front-line therapy for CLL in 2018. Hematology Am Soc Hematol Educ Program. 2018;2018(1):242-247.

14. Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leu-
kaemia. Nat Rev Dis Primers. 2017;3:16096.

15. Hallek M. Chronic lymphocytic leukaemia: 2020 update on
diagnosis, risk stratification and treatment. Am J Hematol. 2019;94(11):1266-1287.

16. Gentile M, Zirlik K, Cioli S, et al. Combination of bendamustine and rituximab as front-line therapy for patients with chronic lym-
phocytic leukemia: multicenter, retrospective clinical practice experi-
ence with 279 cases outside of controlled clinical trials. Eur J Cancer. 2016;60:154-165.

17. Cuneo A, Follows G, Rigolin GM, et al. Efficacy of bendam-
ustine and rituximab as first salvage treatment in chronic lym-
phocytic leukaemia and indirect comparison with ibrutinib: a GIMEMA, ERIC and UK CLL FORUM study. Haematologica. 2018;103(7):1209-1217.

18. Laurenti L, Innocenti I, Autore F, et al. Chlorambucil plus ritux-
imab as front-line therapy for elderly and/or unfit chronic lymphocytic leukemia patients: correlation with biologically-
based risk stratification. Haematologica. 2017;102(9):e352-e355.

19. Herishanu Y, Goldschmidt N, Bairey O, et al. Efficacy and safety of front-line therapy with fludarabine-cyclophosphamide-ritux-
imab regimen for chronic lymphocytic leukaemia outside clinical trials: the Israeli CLL Study Group experience. Haematologica. 2015;100(5):662-669.

20. UK Cll Forum. Ibrutinib for relapsed/refractory chronic lympho-
cytic leukaemia: a UK and Ireland analysis of outcomes in 315 pa-
tients. Haematologica. 2016;101(12):1563-1572.

21. Ghia P, Cuneo A. Ibrutinib in the real-world patient: many lights
and some shades. Haematologica. 2016;101(12):1448-1450.

22. Mato AR, Roeker LE, Allan JN, et al. Outcomes of front-line ibrut-
inib treated CLL patients excluded from landmark clinical trial. Am J Hematol. 2018;93(11):1394-1401.

23. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and out-
comes of 616 ibrutinib-treated patients in the United States: a re-
al-world analysis. Haematologica. 2018;103(5):874-879.

24. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diag-
nosis and treatment of chronic lymphocytic leukaemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guide-
lines. Blood. 2008;111(12):5446-5456.

25. Fischer K, Cramer P, Busch R, et al. Bendamustine in combina-
tion with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2012;30(26):3209-3216.

26. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-381.

27. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutu-
zumab in patients with CLL and coexisting conditions. N Engl J Med. 2019;380(23):2225-2236.

28. Al-Sawaf O, Cramer P, Goede V, Hallek M, Pflug N. Bendamustine and its role in the treatment of unfit patients with chronic lym-
phocytic leukaemia: a perspective review. Ther Adv Hematol. 2017;8(6):197-205.

29. Mato A, Nabhan C, Kay NE, et al. Real-world clinical experience in the Connect chronic lymphocytic leukaemia registry: a pro-
spective cohort study of 1494 patients across 199 US centres. Br J Haematol. 2016;175(5):892-903.

30. Knauf W, Abenhardt W, Dörfler S, et al. Routine treatment of pa-
tients with chronic lymphocytic leukaemia by office-based haema-
tologists in Germany-data from the prospective tumour registry lymphatic neoplasms. Hematol Oncol. 2015;33(1):15-22.

31. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatu-
zumab versus chlorambucil alone in previously untreated pa-
tients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. Lancet. 2015;385(9980):1873-1883.

32. Herishanu Y, Shaulov A, Fineman R, et al. Frontline treatment with the combination obinutuzumab + chlorambucil for chronic lymphocytic leukaemia outside clinical trials: results of a multinational, multicenter study by ERIC and the Israeli CLL study group. Am J Hematol. 2020;95(6):604-611.

33. Islam P, Mato AR. Real-world evidence for chronic lympho-
cytic leukaemia in the era of targeted therapies. Cancer J. 2019;25(6):442-448.

34. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy
for patients with chronic lymphocytic leukaemia. N Engl J Med. 2015;373(25):2425-2437.

35. Brown JR, Wierda WG. Evolving strategies in first-line chronic lymphocytic leukaemia: is there a role for chemoimmunotherapy? J Natl Compr Canc Netw. 2019;17(11.5):1408-1410.
36. Chen Q, Jain N, Ayer T, et al. Economic burden of chronic lymphocytic leukemia in the era of oral targeted therapies in the United States. *J Clin Oncol*. 2017;35(2):166-174.

37. Iovino L, Shadman M. Novel therapies in chronic lymphocytic leukemia: a rapidly changing landscape. *Curr Treat Options Oncol*. 2020;21(4):24.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

---

**How to cite this article:** Cuneo A, Mato AR, Rigolin GM, et al; the GIMEMA, European Research Initiative (ERIC) on CLL, US study group. Efficacy of bendamustine and rituximab in unfit patients with previously untreated chronic lymphocytic leukemia. Indirect comparison with ibrutinib in a real-world setting. *Cancer Med*. 2020;9:8468–8479. [https://doi.org/10.1002/cam4.3470](https://doi.org/10.1002/cam4.3470)