

RESEARCH ARTICLE

Frontline treatment with the combination obinutuzumab ± chlorambucil for chronic lymphocytic leukemia outside clinical trials: Results of a multinational, multicenter study by ERIC and the Israeli CLL study group

Yair Herishanu^{1,2}  | Adir Shaulov³ | Riva Fineman⁴ | Sandra Bašić-Kinda⁵ | Ariel Aviv^{6,7} | Ewa Wasik-Szczepanek⁸ | Ozren Jaksic⁹ | Mihnea Zdrengea¹⁰ | Uri Greenbaum¹¹ | Inga Mandac¹² | Martin Simkovic¹³ | Marta Morawska¹⁴ | Ohad Benjamini^{2,15} | Martin Spacek¹⁶ | Anatoly Nemets¹⁷ | Osnat Bairey¹⁸ | Livio Trentin¹⁹ | Rosa Ruchlemer²⁰ | Luca Laurenti²¹ | Oana Stanca Ciocan²² | Michael Doubek²³ | Lev Shvidel^{24,25} | Nagib Dali²⁶ | Fátima Mirás²⁷ | Anne De Meûter²⁸ | Maria Dimou²⁹ | Francesca R. Mauro³⁰ | Marta Coscia³¹ | Horia Bumbea³² | Róbert Szász³³ | Tamar Tadmor³⁴ | Odit Gutwein³⁵ | Massimo Gentile³⁶ | Lydia Scarfò^{37,38} | Alessandra Tedeschi³⁹ | Paolo Sportoletti⁴⁰ | Eva Gimeno Vázquez⁴¹ | Juan Marquet⁴² | Sarit Assouline⁴³ | Maria Papaioannou⁴⁴ | Andrei Braester⁴⁵ | Luciano Levato⁴⁶ | Michael Gregor⁴⁷ | Gian M. Rigolin⁴⁸ | Javier Loscertales⁴⁹ | Angeles Medina Perez⁵⁰ | Marten R. Nijziel⁵¹ | Viola M. Popov⁵² | Rosa Collado⁵³ | Irma Slavutsky⁵⁴ | Gilad Itchaki¹⁸ | Shimrit Ringelstein⁴ | Neta Goldschmidt³ | Chava Perry^{1,2} | Shai Levi¹ | Aaron Polliack³ | Paolo Ghia^{37,38}

¹Department of Hematology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

²Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel

³Hadassah Hebrew University Medical Center, Jerusalem, Israel

⁴Department of Hematology, Rambam Health Care Campus, Haifa, Israel

⁵University Hospital Centre Zagreb, Zagreb, Croatia

⁶Department of Hematology, HaEmek Medical Center, Afula, Israel

⁷Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel

⁸Department of Hematooncology, and Bone Marrow Transplantation Medical University, Lublin, Poland

⁹Dubrava University Hospital, Zagreb, Croatia

¹⁰Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

¹¹Ben-Gurion University, Soroka University Medical Center, Beer Sheva, Israel

¹²Clinical Hospital Merkur, Zagreb, Croatia

¹³University Hospital and Medical School Hradec Kralove, Hradec Kralove, Czech Republic

¹⁴St. John's Cancer Center, Lublin, Poland

¹⁵Hematology Division, Chaim Sheba Medical Center, Ramat Gan, Israel

¹⁶Charles University and General Hospital in Prague, Prague, Czech Republic

¹⁷Barzilai University Medical Center, Ashkelon, Israel

- ¹⁸Rabin Medical Center, Beilinson Hospital; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
- ¹⁹Hematology Unit, University of Padua, Padua, Italy
- ²⁰Department of Hematology, Shaare Zedek Medical Center, Jerusalem, Israel
- ²¹Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
- ²²Coltea Clinical Hospital, Bucharest, Romania
- ²³Department of Internal Medicine-Hematology and Oncology, Medical Faculty of Masaryk University and University Hospital Brno, Brno, Czech Republic
- ²⁴Department of Hematology, Kaplan Medical Center, Rehovot, Israel
- ²⁵Hebrew University of Jerusalem, Jerusalem, Israel
- ²⁶Ziv Medical Center, Safed, Israel
- ²⁷Hospital 12 de Octubre, Madrid, Spain
- ²⁸Institut Jules Bordet, Brussels, Belgium
- ²⁹Hematology Section - 1st Department Of Propaedeutic Internal Medicine, Laikon Hospital, Athens, Greece
- ³⁰Hematology, Department of Translational and Precision Medicine, Sapienza University, Policlinico Umberto I, Rome, Italy
- ³¹Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy
- ³²Emergency University Clinical Hospital, Bucharest, Romania
- ³³Division of Hematology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
- ³⁴Hematology, Bnai Zion Medical Center, Haifa, Israel
- ³⁵Assaf Ha'Rofeh, Tsrifin, Israel
- ³⁶Hematology Unit and Biotechnology Research Unit, A.O. of Cosenza, Cosenza, Italy
- ³⁷Division of Experimental Oncology, IRCCS Ospedale San Raffaele, Milan, Italy
- ³⁸Università Vita-Salute San Raffaele, Milan, Italy
- ³⁹Department of Haematology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
- ⁴⁰Institute of Hematology and Center for Hemato-Oncological Research, Ospedale S. Maria della Misericordia, University of Perugia, Perugia, Italy
- ⁴¹Hospital del Mar, Barcelona, Spain
- ⁴²Hematology and Hemotherapy, Hospital Universitario Ramón y Cajal, Madrid, Spain
- ⁴³Division of Hematology, Jewish General Hospital, Montreal, Quebec, Canada
- ⁴⁴First Department of Internal Medicine, Division of Haematology, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
- ⁴⁵Galilee Medical Center, Nahariya, Israel
- ⁴⁶Department Hematology-Oncology, Azienda Ospedaliera Pugliese-Ciaccio, Catanzaro, Italy
- ⁴⁷Division of Hematology, Cantonal Hospital of Lucerne, Lucerne, Switzerland
- ⁴⁸Hematology Section, Department of Medical Sciences, University of Ferrara-Azienda Ospedaliera-Universitaria di Ferrara, University of Ferrara, Ferrara, Italy
- ⁴⁹IIS-IP, Hospital Universitario de La Princesa, Madrid, Spain
- ⁵⁰Hospital Costa del Sol, Marbella, Spain
- ⁵¹Maxima Medical Center Eindhoven/Veldhoven, Eindhoven, Netherlands
- ⁵²Hematology, Colentina Clinical Hospital, Bucharest, Romania
- ⁵³Hospital General Universitario, Valencia, Spain
- ⁵⁴Hospital Alvarez, Buenos Aires, Argentina

Correspondence

Yair Herishanu, Department of Hematology,
Tel Aviv Sourasky Medical Center,
6 Weizmann Street, Tel-Aviv 64239, Israel.
Email: yairh@tasmc.health.gov.il

Abstract

In recent years, considerable progress has been made in frontline therapy for elderly/physically unfit patients with CLL. The combination of obinutuzumab and chlorambucil (O-Clb) has been shown to prolong progression free survival (PFS, median PFS-31.5 months) and overall survival (OS) compared to chlorambucil alone. More recently, obinutuzumab given in combination with either ibrutinib or venetoclax improved PFS but not OS when compared to O-Clb. In this retrospective multinational, multicenter co-operative study, we evaluated the efficacy and safety of frontline treatment with O ± Clb in unfit patients with CLL, in a “real-world” setting.

Patients with documented del (17p13.1)/*TP53* mutation were excluded. A total of 437 patients (median age, 75.9 years; median CIRS score, 8; median creatinine clearance, 61.1 mL/min) were included. The clinical overall response rate was 80.3% (clinical complete and partial responses in 38.7% and 41.6% of patients, respectively). Median observation time was 14.1 months and estimated median PFS was 27.6 months (95% CI, 24.2-31.0). In a multivariate analysis, high-risk disease [del (11q22.3) and/or IGHV-unmutated], lymph nodes of diameter > 5 cm, obinutuzumab monotherapy and reduced cumulative dose of obinutuzumab, were all independently associated with shorter PFS. The median OS has not yet been reached and estimated 2-year OS is 88%. In conclusion, in a "real-world" setting, frontline treatment with O-C1b achieves PFS comparable to that reported in clinical trials. Inferior outcomes were noted in patients with del (11q22.3) and/or unmutated IGHV and those treated with obinutuzumab-monotherapy. Thus, O-C1b can be still considered as legitimate frontline therapy for unfit CLL patients with low-risk disease.

1 | INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characteristically diagnosed in older individuals with a median age of 72 years.¹ In recent years, there has been considerable progress in frontline therapy of elderly and physically unfit patients with CLL. The German CLL11 trial^{2,3} showed that addition of obinutuzumab to chlorambucil (O-C1b) prolongs progression free survival (PFS) and overall survival (OS) compared to C1b given alone or in combination with rituximab in unfit patients (defined as Cumulative Illness Rating Scale (CIRS) > 6 or a creatinine clearance (CCT) of 30-69 mL/min). In addition, the Resonate-2 trial⁴ demonstrated that ibrutinib improves PFS and OS compared to chlorambucil in patients with CLL/small lymphocytic lymphoma (SLL) aged ≥65. More recently, the iLLUMINATE trial⁵ randomized patients with CLL/SLL (either ≥65 years or unfit <65 years) to receive either ibrutinib plus obinutuzumab or O-C1b, while the CLL14 trial⁶ compared fixed-duration treatment with venetoclax plus obinutuzumab to O-C1b in unfit patients. In the latter two studies, combinations of obinutuzumab with either ibrutinib or venetoclax were superior to O-C1b in regard to PFS, but showed no advantage in OS. Until now, all studies comparing first-line therapy with novel agents to chemoimmunotherapy in CLL, show that improved PFS is more consistently achieved in patients with high-risk features such as del (17p13.1), del (11q22.3) and/or unmutated immunoglobulin heavy-chain variable-region (IGHV) gene.⁵⁻⁸

Treatment of CLL in general practice may have different outcomes and safety signals than those evident in clinical trials. Outside of clinical trials, patient adherence to a given protocol is compromised more frequently,⁹ and treating physicians appear to be more readily tempted to decrease individual dose intensity.^{9,10} Furthermore, older patients with multiple co-morbidities, worse performance status and obvious renal dysfunction are generally underrepresented or excluded from planned clinical trials. As a result, there may well be considerable differences in outcome for patients

treated with O ± C1b informal clinical trials compared to cases treated in routine daily practice.

The aim of our study was to examine the efficacy and safety of frontline treatment for CLL with O ± C1b outside clinical trials and determine the relevance of this combination in the chemotherapy-free era, particularly for in patients with low-risk disease.

2 | METHODS

2.1 | Study design and patients

This retrospective, multinational, multicenter co-operative study of the European Research Initiative on CLL (ERIC) and the Israeli CLL Study Group (ICLLSG) included 437 patients from 51 centers in Europe, Israel, Canada and Argentina, treated during 2014-2019. Our analysis excluded cases with documented del (17p13.1) or *TP53* mutations, who are no longer treated with chemotherapy.

Data was extracted from the medical records and included: baseline demographics, CIRS score, complete blood count, creatinine clearance, Binet stage, available imaging results (abdominal ultrasound or CT scan of neck, chest and abdomen), analyses of genomic aberrations by fluorescent in situ hybridization (FISH), categorized according to the hierarchical model reported by Döhner et al.,¹¹ and mutational status of IGHV gene (using a cut off of 98% identity to the germ-line sequence).¹² We also obtained data regarding dose modifications, number of treatment cycles, adverse events [documented and graded according to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.], and the incidence of second malignancies. The study was approved by the institutional Helsinki ethics committee of the participating centers.

The relative dose intensity (RDI) of obinutuzumab and chlorambucil in our study was calculated with regarding to the O-C1b regimen in the CLL11 trial study.² That included intravenous administration of obinutuzumab for six cycles (starting with 100 mg on day

1 and 900 mg on day 2, 1000 mg on day 8, and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles two through six) and oral chlorambucil given at 0.5 mg/kg on days 1 and 15 of each cycle for six cycles.²

2.2 | Evaluation of outcomes

Clinical response was assessed 2-3 months after completion of therapy and was defined according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2018 criteria for general clinical practice,¹³ essentially based only on physical examination and complete blood count. The PFS was defined as the period from commencing therapy to the date of first disease progression, or death from any cause or the last follow-up. Time to next treatment (TTNT) was defined as the first date of treatment to the date of initiation of next anti-CLL therapy. The OS was calculated from the first date of treatment to the date of death from any cause or the last follow-up.

2.3 | Statistical analysis

Statistical significance was determined at $P < .05$. IBM SPSS version 25.0 was used to perform the following: Descriptive statistics, including, the median of numeric values, range, mean, standard deviation (SD). Binary logistic regression for univariate and multivariate analyses regarding clinical complete response (CR) Kaplan-Meier method was used for examining the PFS and OS. This included an application of Log-Rank test to compare the hazard functions in cases of categorical variables. Proportional hazard model (Cox regression) for univariate and multivariate analyses regarding PFS and OS. Winpepi version 11.65 was used to perform the Sidak-adjusted test. For more details of the statistical methods see Appendix S1. Microsoft Excel version 14.0 was used to create forest plots and tables.

3 | RESULTS

3.1 | Trial population

In total, 437 therapy-naïve patients with CLL who received treatment with O ± Clb from November 2014 through April 2019, at 51 medical centers in 13 countries were included in this study (baseline demographic and disease characteristics are listed in Table 1). The median age was 75.9 years (range, 57.1-95.8); 59.7% were men; median CIRS total score was 8 (0-46) and estimated creatinine clearance 61.1 mL/min (range, 42.8-79.4). Seventy four patients had Binet stage A (17.2%), 167 (38.8%) stage B and 190 (44.1%) stage C. Results of FISH analysis and IGHV mutational status were available for 332 and 115 patients, respectively. High-risk cytogenetics del(11q22.3) was documented in 18.6% of patients and the unmutated IGHV gene in 64.3%. Median time from diagnosis to first treatment was 37 months (range, <1-461).

TABLE 1 Baseline characteristics

	N	%
Age at Start of treatment		
Median (range)	75.9	(57.1-95.8)
Male sex (N, %)	261	59.7
Binet (available = 431)		
A	74	17.2
B	167	38.8
C	190	44.1
Cumulative Illness Rating Scale (CIRS) (available = 337)		
Median CIRS Score (range)	8 (0-46)	
Total CIRS Score > 6	231	68.5
Calculated creatinine clearance (available = 363)		
Median, mL/min	61.1 (0.2-151.2)	
<70 mL/min	231	63.6
β -2-microglobulin (mg/L) (available = 274)		
Median (mg/L)	4.3 (1.6-18.5)	
FISH (available = 333)		
Normal	134	40.2
del13q	92	27.6
Trisomy 12	45	13.5
del11q	62	18.6
IGHV mutational status (available = 115)		
Mutated	41	35.7
Unmutated	74	64.3
Bulky disease (available = 431)		
Lymph nodes diameter \leq 5 cm	337	78.2
Lymph nodes diameter > 5 cm	94	21.8
Median follow-up time from initial diagnosis, months (range)	37	(<1-461)

Most of the patients were treated with O-Clb (N = 408) and the remaining 29 patients with obinutuzumab monotherapy (O-monotherapy). Out of the pre-treatment parameters, the only significant difference between patients treated with O-Clb compared to O-monotherapy was a higher percentage of patients with Binet stage B among patients treated with O-Clb, compared to patients treated with O-monotherapy (Binet stage A; 15.9% vs 35.7%, stage B; 40.9% vs 7.1% and stage C; 43.2% vs 57.1%, respectively, Table S1).

The mean and median number of treatment courses administered were 4.3 ± 2.2 and 6 (range, 1-6), respectively. The median RDI was 100% (range, 1.3-112.5) for obinutuzumab and 75.1% (range, 1.9-175.0) for chlorambucil. Overall, the chlorambucil dose was reduced in 119 patients (27.2%).

3.2 | Efficacy

By intention-to-treat, the overall rate of clinical response was 80.3% (95% CI, 76.3%-83.9%), including 169 patients (38.7%) who achieved clinical CR, and 182 patients (41.6%) with clinical PR.

In univariate analysis of all baseline and treatment characteristics, male gender, Binet stage C, lymph nodes of diameter > 5 cm and reduced obinutuzumab RDI were associated with an increased risk for

failure to achieve clinical CR (Figure S1). In multivariate analysis, all the above mentioned parameters maintained statistical significance (Table S2).

After a median follow-up of 14.1 months (range, 0.1 to 50.3), 96 of the patients had a disease progression or relapse, with estimated median PFS of 27.6 months (95% CI, 24.2-31.0, Figure 1A). PFS was longer with O-C1b than O-monotherapy (HR, 0.38; 95% CI, 0.22-0.67, $P = .001$), and the 2-year PFS estimates were 61.8% and

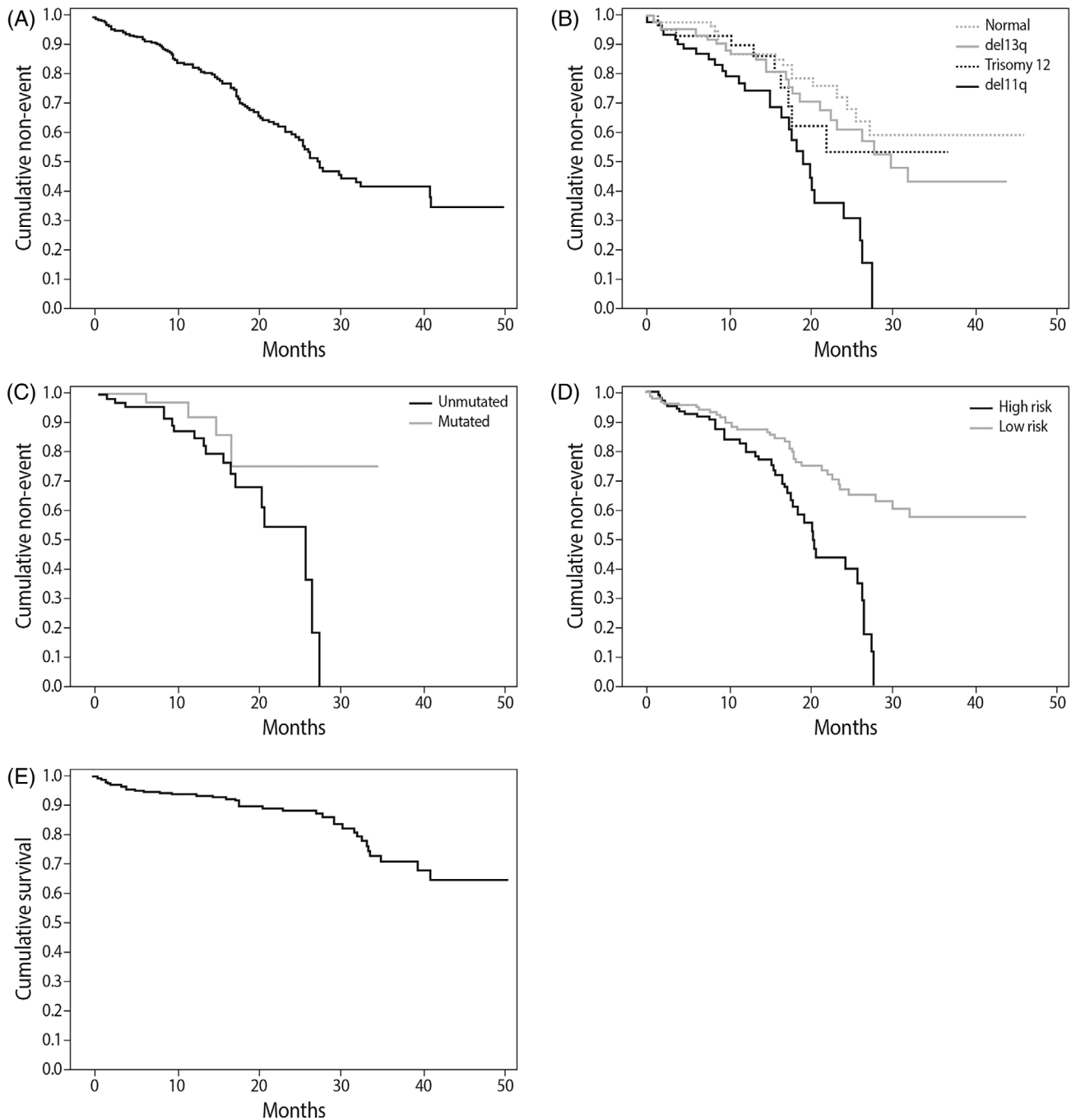


FIGURE 1 Progression free survival and overall survival. A, Shown Kaplan-Meier curves for progression free survival of the entire cohort, and according to; B, FISH subgroups, C, IGHV mutational status and D, risk features (11q22.3 and/or unmutated IGHV vs non-11q22.3 and mutated IGHV). E, Shown a Kaplan-Meier curve for overall survival of the entire cohort

TABLE 2 Multivariate analysis for progression free survival (PFS) and overall survival (OS)

Variable	Hazard ratio	95% CI	P value
A. Multivariate analysis for PFS			
High-risk disease (del [11q22.3] or unmutated-IGHV)	2.52	1.61-3.94	<.001
Lymph nodes diameter > 5.0 cm	1.66	1.04-2.65	.032
Obinutuzumab monotherapy	4.30	1.83-10.14	.001
<100% Obinutuzumab RDI	2.71	1.74-4.20	<.001
B. Multivariate analysis for OS			
Lymph node diameter > 5 cm	2.37	1.30-4.33	.005
Obinutuzumab monotherapy	2.14	1.01-4.55	.048
<100% Obinutuzumab RDI	4.63	2.42-8.85	<.001

52.8% respectively. Patients with lymph node diameter of >5 cm had close to a 2 fold increase in the risk of progression (HR, 1.87; 95% CI, 1.27-2.75, $P = .001$), as well as an eventual decrease in estimated PFS from 32.0 months (95% CI, 20.4-43.6), for those with lymph node of diameter ≤ 5 cm) to 22.1 months (95% CI, 14.8-29.4). The median PFS was significantly shorter for patients with del(11q22.3) (19.2 months, 95% CI, 16.0-22.3) compared to those with normal FISH (not reached), del(13q) (29.9 months, 95% CI, 22.8-36.9) and trisomy12 (not reached) (HR, 1.5; 95% CI, 1.23-1.75, $P < .001$, Figure 1B). Patients with unmutated IGHV had a trend for shorter PFS compared to those with mutated IGHV gene (estimated median PFS 25.6 months, 95% CI, 18.7-32.5 vs not reached. Also, HR, 2.79; 95% CI, 0.92-8.47, $P = .06$, Figure 1C,D). Additional factors associated with shorter PFS included high-risk disease (del [11q22.3] and/or unmutated IGHV), obinutuzumab's RDI < 100% and chlorambucil RDI < 80% (Figure S2). In a multivariate analysis, high risk-disease, lymph nodes diameter > 5 cm, O-monotherapy and reduced RDI of obinutuzumab, were independently associated with shorter PFS (Table 2A).

During the study follow-up period, alternative, second line therapy was administered to 69 patients (15.7%). Median time to next treatment was not reached. The most common second-line therapy used was ibrutinib (66.7%) followed by chemo \pm immunotherapy (18.8%).

The median OS for the entire cohort has not yet been reached and the 2-year OS estimate is 88% (Figure 1E). Patients treated with O-C1b had longer OS than those receiving O-monotherapy (HR, 0.26; 95% CI, 0.12-0.53, $P < .001$). Additional factors associated with shorter OS included lymphadenopathy >5 cm (HR 1.85; 95% CI, 1.02-3.34, $P = .04$), elevated β -2-microglobulin levels (HR 4.49; 95% CI, 1.04-19.39, $P = .027$), obinutuzumab RDI <100% (HR 4.47; 95% CI, 2.41-8.29, $P < .001$) and chlorambucil RDI <80% (HR 3.04; 95% CI, 1.33-6.97, $P = .006$), (Figure S3). In a multivariate analysis, lymph node diameter > 5 cm, O-monotherapy and reduced obinutuzumab RDI, were independently associated with shorter OS (Table 2B). Richter transformation occurred in four patients (0.9%) with a median time to onset of 27.2 months (range, 18.1-28).

TABLE 3 Grade ≥ 3 adverse events

	Grade ≥ 3 (incl. G5) N (%)	Grade 5 N (%)
Adverse events of grade ≥ 3	153 (35.0)	7 (1.6)
Adverse events of grade ≥ 3 that occurred in $\geq 3\%$ of the patients and/or grade 5		
Hematologic toxicity	89 (20.4)	
Neutropenia	63 (14.4)	
Thrombocytopenia	16 (3.7)	
Pancytopenia	5 (1.1)	
Anemia	5 (1.1)	
Infusion related reaction	38 (8.7)	
Infections	34 (7.8)	6 (1.4)
Neutropenia febrile	5 (1.1)	
Sepsis	7 (1.6)	5 (1.1)
Osteomyelitis	1 (0.2)	1 (0.2)
Tumor lysis syndrome	13 (3.0)	
Gastrointestinal bleeding	1 (0.2)	1 (0.2)

3.3 | Safety

All AEs are summarized in Table S3. At least one adverse event of any grade occurred in 72.5% of patients, and the most common Grade ≥ 3 AEs are summarized in Table 3. Hematologic toxicities were the most frequent grade ≥ 3 AEs ($n = 89$, 20.4%), in particular neutropenia, occurring in 63 (14.4%) patients. The second most common Grade ≥ 3 AEs were infections ($n = 30$, 7.8%). Grade ≥ 3 infusion-related reactions and tumor lysis syndrome were reported in 38 (8.7%) and 13 (3.0%) patients, respectively. Additional events of clinical interest included reactivation of cytomegalovirus (CMV) in two patients (0.45%), hepatitis B (HBV) infection in one patient (0.23%), and JC virus infection (PML) in two patients (0.45%). Fatal events (Grade 5 AEs) occurred in 7 (1.6%) patients and of these, 6 (1.4%) were related to infections.

4 | DISCUSSION

In this large real-world study, frontline treatment with O \pm C1b in elderly/unfit patients with CLL requiring treatment had comparable efficacy and safety to that reported in earlier formal clinical trials. In our study the estimated median PFS was 27.6 months, whereas the median PFS reported with O-C1b was 31.5 months in the CLL11 trial,^{2,3} 19 months in the iLLUMINATE study⁵ and 64.1% at 24 months in CLL14.⁶ The differences in PFS in these studies can probably be attributed to a number of factors; including length of follow-up reported, duration of treatment with chlorambucil (6 vs 12 months) and to the nature of post-treatment surveillance (periodic CT scans vs clinical assessment). In addition, our study further highlights the efficacy of O-C1b therapy in patients with low-risk CLL compared to high-risk disease. Patients with lymph nodes of >5 cm, del

(11q22.3) and/or unmutated IGHV achieved shorter PFS compared to those with lower tumor mass and favorable genomic features of non-del(11q22.3) and mutated IGHV gene status.

As frequently reported from studies outside formal clinical trials,⁹ dose modifications were often made, especially in relation to chlorambucil. In this respect, close to 7% of patients were actually treated with obinutuzumab alone, in about a third of the cases chlorambucil dose was reduced and the median chlorambucil RDI was 75.1% compared to 100% with obinutuzumab. In comparison, in the German CLL14 study the median chlorambucil RDI was 95.4%,⁶ which further emphasizes that in real-life clinical practice, treating physicians tend to reduce the dose of chemotherapy given. Our results show the importance of the addition of chlorambucil to obinutuzumab and adherence to the maximal dose intensity of obinutuzumab. We found these two parameters to be independent variables associated not only with better PFS but also with longer OS. Notably, Gay et al¹⁴ retrospectively analyzed 20 naïve patients with previously untreated CLL, who were treated with obinutuzumab monotherapy and achieved a median PFS of 33.5 months. In contrast to our O-monotherapy cohort, in the study by Gay et al¹⁴ most patients were in early Binet stage with only 15% in stage C, a difference which may explain the discrepancy in the PFS between the two studies.

The OR and CR rates evident in our study were higher than those reported in other clinical studies with O-C1b (OR-80.3% and CR-38.7% vs 71.3%-81% and 8%-23.1%, respectively).^{2,5,6} This is not surprising as response assessment in real-life generally follows the IWCLL 2018 criteria for general clinical practice,¹³ which are essentially based only on physical examination and complete blood count results, whereas assessment in formal clinical studies require CT scan and confirmation of CR with a bone marrow biopsy.

The 2-year OS of our cohort was 88%, while in previously reported clinical trials the two and five-year survival rates in patients treated with O ± C1b were 91-93.3% and 84%, respectively.^{2,3,5,6} The fact that there is no OS advantage for frontline treatment in elderly patients with CLL using ibrutinib or venetoclax plus obinutuzumab compared to O-C1b, is probably related to the fact that that targeted-therapy can still efficiently salvage patients after frontline O-C1b. This is also evident from our study where during follow-up, 15.7% of patients required a subsequent second line of treatment and in two thirds of these cases this was ibrutinib. The median time to next treatment in our study was not reached, while it was 56.4 months with O-C1b in the CLL11 trial^{2,3} and 42.7 months in the iLLUMINATE trial.⁵ Thus, it seems that O-C1b treatment can achieve a reasonable treatment-free period (approximately 3.5-4.5 years) until requiring therapy again, with a longer period expected in patients with low-risk disease.

In terms of safety our findings were consistent with those of reported in earlier clinical trials,^{2,5,6} and no new safety signals were identified. Grade ≥ 3 adverse effects were encountered in about one third of patients, with the most common being neutropenia, infusion-related reactions and infections. Treatment-related Grade 5 adverse events occurred in 7 (1.4%) patients and mostly related to infections.

The main limitations of this study, beyond its retrospective design, are that only 26.3% patients had IGHV mutation status studies available, the number of patients who received single-agent obinutuzumab was 6.6% of the overall cohort, no minimal residual disease data are available, and that median follow-up was very short (14.1 months), making assertions regarding time to next therapy and long-term overall survival more difficult to interpret.

Taken together, although the use of O-C1b is decreasing over time, due to the rise of targeted therapies, it appears that treatment with O-C1b can still be an efficient therapeutic tool in elderly patients with CLL, with low-risk features and low tumor mass. Beyond its benefits of fixed-duration and the limited financial toxicity of this regimen compared to continuous, indefinite Bruton's tyrosine kinase inhibitor therapy, O-C1b can induce both durable PFS and TTNT, in patients with low-risk disease, without compromising OS.

CONFLICT OF INTEREST

YH- has reported honoraria from AbbVie, Janssen, Astra-Zeneca and Roche. MD has reported honoraria and research grants from Roche, AbbVie, AOP Orphan Pharmaceuticals, Gilead, Novartis and Janssen. JL-AdBoards/honoraria: Janssen, Abbvie. AdBoard: AstraZeneca. Honoraria: Roche, Gilead. RGM- has reported grants: Gilead, Janssen. Research support: Gilead and honoraria: Gilead, Abbvie. PG has reported Honoraria/advisory board: AbbVie, Acerta/AstraZeneca, Adaptive, ArQule, BeiGene, CelGene/Juno, Dynamo, Gilead, Janssen, Sunesis. Research Funding: AbbVie, Gilead, Janssen, Novartis, Sunesis.

AUTHOR CONTRIBUTIONS

Y.H.-initiated, planned and designed the study, provided the clinical data and wrote the final manuscript. A.S., R.F., S.B.K., A.A., E.W.S., O.J., M.Z., U.G., I.M., M.S., M.M., O.B., M.S., A.N., O.B., L.T., R.R., L.L., O.C., M.D., L.S., N.D., F.M., A.D.M., M.D., F.R.M., M.C., H.B., R.S., T.T., O.G., M.G., L.S., A.T., P.S., E.G.V., J.M.P., S.A., M.P., A.B., L.L., M.G., G.M.R., J.L., A.M.P., M.R.N., V.M.P., R.C., I.S., G.I., S.R. and N.G.- provided the clinical data for the study. SL-collected, maintained and proofread the data and performed the statistical analyses. C.P., A.P. and P.G.-critical reading of the manuscript and comments.

ORCID

Yair Herishanu  <https://orcid.org/0000-0002-7864-0089>

REFERENCES

- Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic leukemia. *N Engl J Med*. 2005;352:804-815.
- Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014; 370:1101-1110.
- Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. *Leukemia*. 2015;29:1602-1604.
- Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373: 2425-2437.

5. 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;20:43-56.
6. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380:2225-2236.
7. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381:432-443.
8. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379:2517-2528.
9. Herishanu Y, Goldschmidt N, Bairey O, et al; Israeli CLL Study Group. 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;100:662-669.
10. Bouvet E, Borel C, Oberic L, et al. Impact of dose intensity on outcome of fludarabine, cyclophosphamide, and rituximab regimen given in the first-line therapy for chronic lymphocytic leukemia. *Haematologica*. 2013;98:65-70.
11. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med*. 2000;343:1910-1916.
12. Ghia P, Stamatopoulos K, Belessi C, et al; European Research Initiative on CLL. ERIC recommendations on IGHV gene mutational status analysis in chronic lymphocytic leukemia. *Leukemia*. 2007;21:1-3.
13. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131:2745-2760.
14. Gay ND, Kozin E, Okada C, Danilov AV, Spurgeon S. Obinutuzumab monotherapy in previously untreated chronic lymphocytic leukemia. *Leuk Lymphoma*. 2018;59:2258-2260.

SUPPORTING INFORMATION

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

How to cite this article: Herishanu Y, Shaulov A, Fineman R, et al. Frontline treatment with the combination obinutuzumab ± chlorambucil for chronic lymphocytic leukemia outside clinical trials: Results of a multinational, multicenter study by ERIC and the Israeli CLL study group. *Am J Hematol*. 2020;95:604-611. <https://doi.org/10.1002/ajh.25766>