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High rate of durable responses with undetectable minimal residual disease with frontline venetoclax and rituximab in young and fit patients with chronic lymphocytic leukemia and an adverse biologic profile: results of the gimema phase II LLC1518 - 'Veritas' study

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High rate of durable responses with undetectable minimal residual disease with frontline venetoclax and rituximab in young and fit patients with chronic lymphocytic leukemia and an adverse biologic profile: results of the gimema phase II LLC1518 – 'Veritas' study

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CONTRIBUTIONS

FRM, AC and RF developed the concept and design of the study interpreted data and wrote the manuscript. MM, VA, PF, MV, and AP managed data collection and assembly; performed the statistical analysis and interpreted data. IDS, FA, AN, LDN, MSDP, MN, and IDG performed biological and molecular studies and analyzed and interpreted data. GR, LT, MC, PS, LO, GMC, RoMa, RoMu, LuLa, FI, CS, DM, MaMa, GMR, LS, MoMa, LuLe, MT, AA, GM, MD, PG, VBP, DG, AML, AG, MCM, DP, VM, AV, CV managed patients participated in the collection of clinical data. All authors critically revised the manuscript and reviewed and approved the final version.

Data sharing statement. The data presented in this study are available on request. Details on sharing criteria and processes for requesting access to data can be required at a.piciocchi@gimema.it.

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ABSTRACT (word count: 243/250)

The GIMEMA phase II LLC1518 VERITAS trial investigated the efficacy and safety of frontline, fixed-duration venetoclax and rituximab (VenR) combination in young (≤65 years) and fit patients with chronic lymphocytic leukemia (CLL) and unmutated IGHV and/or *TP*53 disruption. Treatment consisted of the Ven ramp-up, six-monthly courses of the VenR combination, followed by six monthly courses of Ven single agent. A centralized assessment of measurable minimal residual disease (MRD) was performed on the peripheral blood (PB) and bone marrow (BM) by ASO-PCR at the end of treatment (EOT) and during the follow-up. The primary endpoint was the complete remission (CR) rate at the EOT. Seventy-five patients were enrolled; the median age was 54 years (range 38-65), 96% had unmutated IGHV, 9 (12%) *had TP*53 disruption, and 4% were IGHV mutated with *TP53* disruption. The overall response rate (ORR) at the EOT was 94.7%, with a CR rate of 76%. An undetectable (u) MRD was recorded in 69.3% of patients in the PB and 58.7% in the BM. The 12-month MRD-free survival in the 52 patients with uMRD in the PB at the EOT was 73.1%. After a median follow-up of 20.8 months, no disease progressions were observed. Three patients have died, two due to Covid-19 and 1 to tumor lysis syndrome. The first report of the VERITAS study shows that frontline VenR was associated with a high rate of CRs and durable responses with uMRD in young patients with CLL and unfavorable genetic characteristics.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most frequent leukemia in western countries and affects predominantly elderly subjects, with a median age of 72 years at presentation[1]. Patients under 65 are less frequently diagnosed but more likely to have CLL as a cause of mortality than the elderly population[2, 3.]

In recent years, relevant advances in our understanding of the biology of CLL have led to the development of targeted agents, namely the Bruton tyrosine kinase (BTK) inhibitors and the B-cell lymphoma 2 (BCL2) inhibitor venetoclax (Ven). The excellent therapeutic activity of these agents has radically changed the treatment approach of CLL, partially overcoming the unfavorable prognostic impact of adverse biologic characteristics, including the unmutated configuration of the variable portion of the immunoglobin gene heavy chain gene (*IGHV*) and *TP*53 disruption (deletion and, or mutation of the *TP*53 gene).

Continuous treatment with ibrutinib has demonstrated its high efficacy regardless of high-risk biologic features and its superiority over chemoimmunotherapy in relapsed/refractory (R/R) CLL and previously untreated patients[4-12]. Recent studies have shown similar efficacy with a better toxicity profile of the covalent BTK inhibitors acalabrutinib[13-15] and zanubrutinib[16-18]. The effectiveness of the non-covalent BTK inhibitor, pirtobrutinib, in patients with resistance to ibrutinib due to BTK mutation has also been described[19]. Ven, a selective oral BCL2 inhibitor, restores activation of CLL apoptosis[20]. In several studies that included relapsed/refractory (R/R) and treatment-naïve patients with CLL, fixed-duration treatment with Ven in combination with an anti-CD20 monoclonal antibody led to responses with undetectable minimal residual disease (uMRD) in a large proportion of patients, including those with adverse genetic aberrations[21-26].

The updated results of the randomized CLL14 study showed a superior 5-year progression-free survival (PFS) in unfit patients treated frontline with Ven and obinutuzumab fixed-duration therapy compared to those who received chlorambucil and obinutuzumab (62.6% vs 27.0%,

respectively)[21,23]. The randomized Murano trial for R/R patients with CLL demonstrated a significant improvement in PFS and overall survival (OS) with fixed-duration therapy with the combination of Ven and rituximab (VenR) as compared to chemoimmunotherapy[24-26]. In addition, a high rate of deep responses with uMRD was recorded with VenR, which was associated with a highly favorable impact on PFS. Moreover, the safety profile of fixed-duration VenR was favorable, and severe rituximab-related infusion reactions did not occur. In addition, late adverse events, a relevant issue in treating younger patients with CLL and a long-life expectancy, were not observed.

Although BTK inhibitors are effective agents, fixed-duration therapy with Ven, capable of inducing profound and durable responses followed by a therapy-free period, is more appealing than continuous therapy, particularly for younger patients.

Based on the efficacy of fixed-duration VenR in the setting of R/R patients with CLL, including those with unmutated IGHV and *TP*53 disruption, the GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) group investigated the efficacy and safety of the frontline VenR regimen in young (≤65 years) and fit patients with CLL and an unfavorable biologic profile. Herein, we report the first results of the GIMEMA phase II, single-arm, multicenter LLC1518 VERITAS study in 75 previously untreated and young patients with CLL and an unmutated IGHV profile and/or a *TP*53 disruption.

METHODS (498/500 words)

Patients

The VERITAS study included previously untreated patients with CLL requiring treatment according to the International Workshop on CLL (iwCLL) criteria[27]. The study was approved by Comitato Etico Università Sapienza comitato.etico@policlinicoumberto1.it date of approval 07/06/2018 approval file number CE 497/18 (Rif 5049).

Patients were required to be ≤65 years, have a cumulative illness rating scale score (CIRS) ≤6[28], have a creatinine clearance ≥30 mL/min, an unmutated immunoglobulin heavy chain (IGHV) gene and, or a *TP*53 disruption (17p deletion and, or *TP*53 mutation)[29-31]. The IGHV profile and the *TP*53

status were assessed centrally at the Hematology Center of the Sapienza University of Rome. The cytogenetic profile was investigated by fluorescence in situ hybridization (FISH) at four reference laboratories (Rome, Ferrara, Bari, Milan).

Treatment

Study treatment consisted of a Ven ramp-up and six monthly courses of the VenR combination, followed by six monthly courses of Ven given as a single agent. Patients received Ven according to a 5-week escalation schedule of a gradual increase in the dose from 20 mg per day to 400 mg per day[22]. Once the five weeks of the ramp-up phase were completed, the following six cycles of venetoclax and rituximab started on day 1 of cycle 1. Rituximab was administered on day 1 of each cycle. Ven was continued at 400 mg per day in combination with R at 375 mg/m² on month 1, day 1, and on months 2-6, day 1 at the dose of 500 mg/m². After the end of the combination therapy (EOCT), patients continued Ven monotherapy until day 28 of cycle 13, or unacceptable toxicity or disease progression. The risk of tumor lysis syndrome (TLS) was assessed according to the presence of bulky lymphadenopathy (diameter ≥5 cm) and the peripheral absolute lymphocyte count (≥25 × 10□/L)[32]. Patients received TLS prophylaxis with urate-reducing agents and oral or iv hydration. TLS events were classified according to Howard's criteria [32]. Adverse events (AEs) were graded according to the CTCAE criteria v.5[33].

Response

The response was assessed according to the iwCLL guidelines[27] at the end of combination therapy (EOCT, month 7) and the end of treatment (EOT, month 15). Response assessment included clinical examination, PB evaluation, BM aspirate, BM biopsy, and CT scan. A centralized MRD assessment was carried out at the Hematology Center in Rome on PB and BM cells by allele-specific oligonucleotide polymerase-chain-reaction (ASO-PCR) assay as previously reported[34,35]. MRD was categorized as undetectable (uMRD) with a cut-off of <1 cell in 10,000 leukocytes. During the follow-up, MRD was monitored every six months.

Study endpoints

The primary endpoint of this study was the complete remission (CR) rate at the EOT. The secondary endpoints included the overall response rate (ORR) and the rate of responses with

uMRD at the EOT, the PFS, and the OS. Further secondary endpoints included the time to MRD conversion from undetectable to detectable, the time from the re-emergence of detectable leukemic cells to clinical progression of the disease, and the time to a new CLL treatment.

Details on the supportive treatment, statistical analysis, and ethics are reported in the Supplementary material file.

RESULTS

Patients

Between October 2018 and May 2020, 75 young patients with CLL and an unfavorable biologic profile requiring frontline therapy from 28 Italian centers were included in this study and represented the intention-to-treat population assessed for treatment response and safety. The patients' disposition is described in Supplementary Fig. 1. The baseline clinical and biological characteristics are summarized in Table 1. The median age was 54 years (range 38-65). Thirty-eight % of patients had advanced III-IV Rai stage disease; 41% had an increased beta-2 microglobulin, and 25% had bulky lymphadenopathy. The TLS risk at baseline was high in 44% of patients. Seventy-two patients (96%) had an unmutated IGHV gene profile, with a *TP*53 disruption in 6 (*TP*53 mutation, 5; *TP*53 mutation and deletion, 1), while three patients (4%) were IGHV mutated and carried a *TP*53 disruption (*TP*53 mutation and deletion, 3). The median CIRS was 1 (range, 0-6), with 9 (12%) patients with a CIRS value >3.

Response to treatment

Response at the end of the combination therapy (EOCT)

Seventy-two patients (96%) achieved a response at the EOCT (month 7). Responses included a CR/CRi in 41 patients (CR, 52%; CRi, 2.7%), and PR in 31 (41.3%) (Fig. 1A). Three patients discontinued treatment due to an AE and were censored as treatment failures. The ASO-PCR

assay demonstrated an uMRD at the EOCT in the PB and BM of 70.7% and 46.7% of patients, respectively (Fig. 2A). The proportion of CR patients with no measurable MRD by ASO-PCR in the PB and BM was 78% and 61%, respectively (Fig. 2A). In patients who achieved a PR, an uMRD status was observed in the PB and the BM of 68% and 32% patients, respectively.

Response at the end of treatment (EOT)

At the EOT (month 15), after six further months of treatment with Ven single agent, the ORR was 94.7%, and the CR rate increased from 54.2% to 76% (57 patients) (Fig. 1B). A PR was recorded in 14 patients (18.7%) who showed residual lymph nodes (median longitudinal lymph node diameter, 1.95 cm; range, 1.5-4.5 cm). Two patients discontinued treatment due to an AE and were censored as treatment failures. A significantly lower CR rate at the EOT rate was observed in older patients (p=0.032) and those with a higher CIRS (p=0.009) (Supplementary Table 1). However, the only factor that retained a borderline statistical significance in multivariate analysis was the CIRS (p=0.054). A response with uMRD by ASO-PCR was recorded in 69.3% of patients in the PB and 58.7% in the BM (Fig. 2B). Six of the nine patients with *TP*53 disruption achieved a response with uMRD in the PB and BM. We analyzed the impact of the baseline characteristics of patients and the iwCLL response measured at the EOCT on the probability of achieving an uMRD in the PB and BM at the EOT. While no factors showed a significant impact on the rate of responses with uMRD in the PB, the only factor associated with a higher probability of achieving uMRD was a CD38 cut-off level <30% in the BM (Fig. 3). MRD was monitored during the follow-up in 52 patients with a response and uMRD in the PB at the EOT. Thirty-eight (73%) patients maintained an uMRD in the PB, 13 (25%) converted to detectable MRD, and one patient died due to an AE. The 12-month MRD-free survival was 73.1% (95%CI, 62-86.2) (Fig. 4). There was no significant difference in the proportion of patients with CR or PR and uMRD in the BM who lost the response at month 21 (uMRD at month 21: PR vs CR, 0/10 *vs.* 4/33).

Survival

After a median follow-up of 20.8 months (range, 0.2-36.5), no patient has shown a clinical progression, and three patients have died due to an AE. The 24-month OS was 96% (95%CI, 91.6-100) (Fig. 5).

Safety

The grade ≥3 adverse reactions are described in Supplementary Table 2. Thirty-four patients (45.3%) experienced at least one grade ≥3 AE. Granulocytopenia was recorded in 28 patients (37.3%), and 26 (35%) received granulocyte colony-stimulating factors. Grade ≥3 infections were observed in 9 patients (12%), including five patients (6.7%) who developed Covid-19 at the time of the first SARS-CoV2 pandemic when vaccination was unavailable. The nine patients who developed grade ≥3 infections (COVID-19 in 5/9 cases) were not characterized by increased risk factors for severe infections such as older age, increased CIRS, an increased risk factor for TLS, low creatinine clearance, or granulocyte count at baseline. A fungal infection has been reported in two patients. One patient showed clinical signs suggestive of sinusitis whose fungal etiology has been suspected but not documented. The second one with steroid-controlled hemolytic anemia developed an Aspergillus pulmonary infection which was successfully treated with voriconazole.
A transient increase in liver enzymes was reported in 3 patients (4%). Thirty-three patients (44%) were at high risk of TLS. Two patients showed creatinine clearance <60 ml/min at baseline but none developed TLS. Despite hospitalization, intravenous hydration, and the administration of anti-uric agents, a patient at increased risk of TLS developed a grade 5 TLS during the ramp-up phase. This patient with severe osteoporosis suffered from severe pain due to a vertebral fracture and used self-administered fentanyl patches for analgesic purposes (More details about the clinical case are reported in the Supplementary file). A patient was diagnosed with follicular lymphoma 24 months after the start of treatment. No Richter's syndromes nor non-hematologic cancers were recorded. Three patients died due to an AE, 1 with a clinical TLS, and 2 with Covid-19.

DISCUSSION

The first analysis of the VERITAS study showed that 94.7% of previously untreated, young patients with CLL and an adverse biologic profile achieved a response with the VenR fixed-duration treatment. Moreover, no evidence of residual disease was detected in the PB of 69.3% of patients and BM of 58.7%. After a median follow-up of 20.8 months, no disease progressions were observed so far. These data confirm in previously untreated patients the efficacy of the VenR combination described in R/R patients with CLL in the Murano trial[24-26].

The primary endpoint of this study, the CR rate at the EOT, was met with a 76% CR rate, which compares favorably with that reported in fit patients treated with FCR chemoimmunotherapy in the CLL10 trial (40%) and the ECOG1912 study (30.3%)[9,36], and also in the CLL14 trial in unfit patients treated with Ven plus obinutuzumab (49.5%)[21-23]. High CR rates were also described with ibrutinib and Ven in the Flair trial (59.6%)[38] and the MRD and the fixed duration cohorts of the Captivate trial (46% and 52.2%)[37-39].

Our study included young and fit patients of 65 years or less with a CIRS ≤6. The presence of comorbidities, even with a CIRS <6, was associated with a lower CR rate. Interestingly, in a real-world study, an increased CIRS was also associated with an adverse impact on the outcome of patients with CLL who received ibrutinib[40].

The follow-up of this study, 20.8 months, is relatively short, and PFS data are, therefore premature. A valid surrogate of the efficacy of VenR is represented by the rate of patients with uMRD in the PB, as observed by ASO-PCR in the CLL14 trial[21]. The 69.3% rate of uMRD PB responses recorded in our study compares favorably with the uMRD rates observed with FCR in the CLL10 and ECOG1912 trials, 49% and 59.2%, respectively[9,36]. In the CLL13 trial that included patients with a favorable genetic profile, a similar schedule produced uMRD responses in 57% of cases[41].

Higher rates of responses with uMRD in the PB have been reported in the CLL14 and CLL13 trials with the venetoclax and obinutuzumab combination (76% and 86.5%)[21,41]. Obinutuzumab, a more potent CD20 monoclonal antibody with a higher capacity for direct B cell killing and a glycoengineered Fc-fragment for improved effector cell recruitment, has shown an advantage over rituximab as a partner of Ven. Although in the CLL13 trial infusion-related reactions associated with obinutuzumab were more severe than those seen with rituximab, patients treated with Ven and

obinutuzumab compared to those treated with Ven and rituximab showed a higher rate of responses with uMRD and more prolonged PFS[41].

In the Glow trial that included elderly/unfit patients with CLL, the Ven plus ibrutinib resulted in 54.7% responses with uMRD in the PB[42], while higher rates were observed in the Flair trial (71.3%)[37], in the MRD and fixed duration cohorts of the Captivate study (75% and 77%)[38,39]. In the CLL13 trial, the triplet Ven, ibrutinib, and obinutuzumab was associated with the highest rate of responses with uMRD in the PB, 92.2%[41]. A comparison between the rates of uMRD in the different studies is hampered by the technique used, ASO-PCR in some studies [21,42], like ours, and flow cytometry in others [38-39;41].

Although cross-trial comparison must be interpreted with caution, it is important to underline that in our study, 96% of patients had an unmutated IGHV gene profile, whereas the proportion of patients with unmutated IGHV ranged between 43.5%% and 60.5% in the studies mentioned above.

Longer follow-up of this and other studies may show whether patients with these same unfavorable genetic characteristics may benefit from different and, more prolonged Ven-based treatments.

CD38 positivity, recorded in 51% of patients, emerged as the only factor with an unfavorable impact on the uMRD rate in the BM. CD38, a surface multifunctional transmembrane glycoprotein[43], is associated with an IGHV unmutated status, advanced-stage disease, poor response to chemotherapy, shorter time to first treatment, and survival[44-46]. To the best of our knowledge, the prognostic impact of CD38 expression has not yet been tested in patients treated with Ven. In a study by Sargent et al.[47], a significant inverse relationship has been observed in vitro between the proportion of CD38 positive cells and the level of BCL2 expression. Based on this finding, we could speculate that CD38-negative patients could express higher levels of the anti-apoptotic BCL2 protein, resulting in a more pronounced activity of Ven.

Due to the number of patients included in this trial the predictive value of novel mutations occurring in a minority of patients was not analyzed.

Patients with unmutated IGHV show a more rapid reemergence of MRD after FCR than mutated IGHV patients[48]. In our study, which included mainly patients with unmutated IGHV, 73% of patients who achieved a response with uMRD maintained an uMRD in the PB at 12 months from

the EOT. Despite the unfavorable genetic characteristics, the MRD-free survival in our analysis is in line with that observed in unfit patients treated with Ven and obinutuzumab in the CLL14 trial[23]. VenR treatment was well tolerated. Notably, no grade ≥3 infusion reactions to rituximab were recorded. The most frequent AE was granulocytopenia, easily manageable with granulocyte growth factors. Unfortunately, our study was carried out during the outbreaks of the SARS-CoV-2 pandemic before vaccines were introduced, and 5 of the 9 grade ≥3 infections were due to the SARS-CoV-2 infection. About half of the patients in this study had a high risk of TLS. However, a single case of lethal clinical TLS was observed in a patient who underwent the ramp-up phase while on treatment for analgesic purposes of a drug that may have interfered with the metabolism of Ven. A patient discontinued therapy due to the diagnosis of indolent lymphoma, while no cases of Richter transformation or second malignancies were observed.

In conclusion, this first report of the VERITAS study shows that the frontline VenR combination is easily manageable, well-tolerated, and associated with a high rate of CRs and durable responses with uMRD in younger patients with CLL and unfavorable genetic characteristics.

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Table 1. Baseline patient characteristics

	N = 75 (100%)
Gender M/F	56 (75)/19 (25)
Median age, years (range)	54 (38- 65)
ECOG performance status 0/1	65 (87) /10 (13)
Median CIRS (range)	1.00 (0.00, 6.00)
CIRS >3	9 (12)
Median Hb g/dl (range)	12.50 (7.5-16.6)
Median lymphocyte count $x10^9$/L (range)	96 (5.3, 556)
Median platelet count $x10^9$/L (range)	150 (54, 425)
B symptoms	16 (22)
Beta-2 microglobulin >3.5 mg/L	27 (41)
Increased LDH	26 (35)
CD38 >30%	38 (51)
Rai stage III/IV	9 (12)/19 (26)
Bulky lymph nodes (≥5 cm in diameter)	18 (25)
TLS risk	
• Low	10 (13)
• Intermediate	32 (43)
• High	33 (44)
IGHV mutated	3 (4)
IGHV unmutated	72 (96)
FISH aberrations	
• Del 13q	22 (30)
• Tris 12	12 (16)
• Del 11q	16 (22)
• Del 17p	4 (5.5)
• No aberrations	19 (26)
*TP*53 disruption	9 (12)
• *TP*53 mutation only	5 (6.6)
• *TP*53 mutation and deletion	4 (5.5)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; CIRS, Cumulative Illness Rating Scale; Hb, hemoglobin; LDH, lactate dehydrogenase, TLS, tumor lysis syndrome; IGHV, immunoglobulin heavy chain variable region gene; *TP*53 gene, tumor protein p53 gene; Del, deletion; Tris, trisomy.

LEGEND TO FIGURES

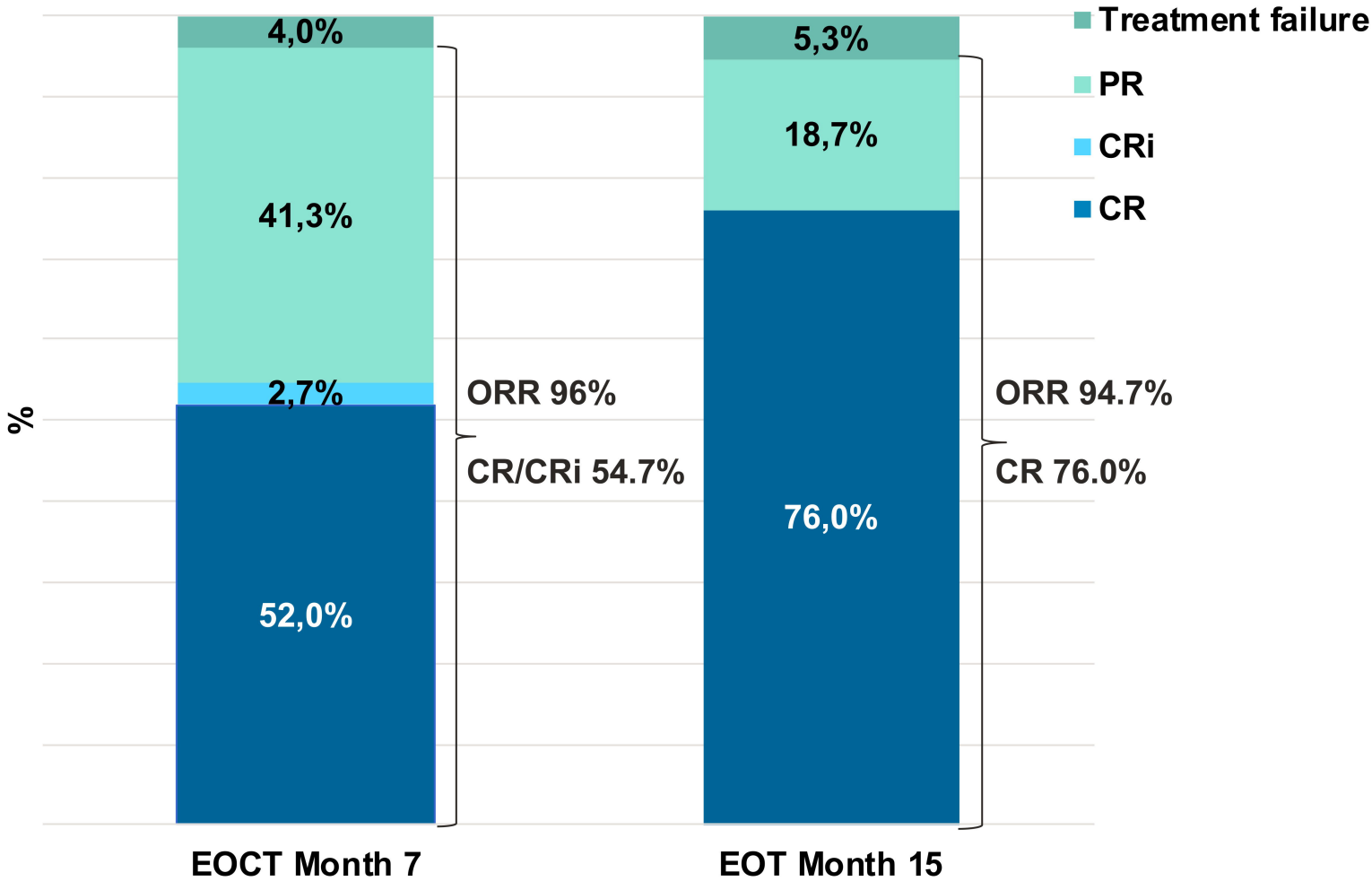
Figure 1. iwCLL response at the end of combination therapy (EOCT) and end of therapy (EOT).

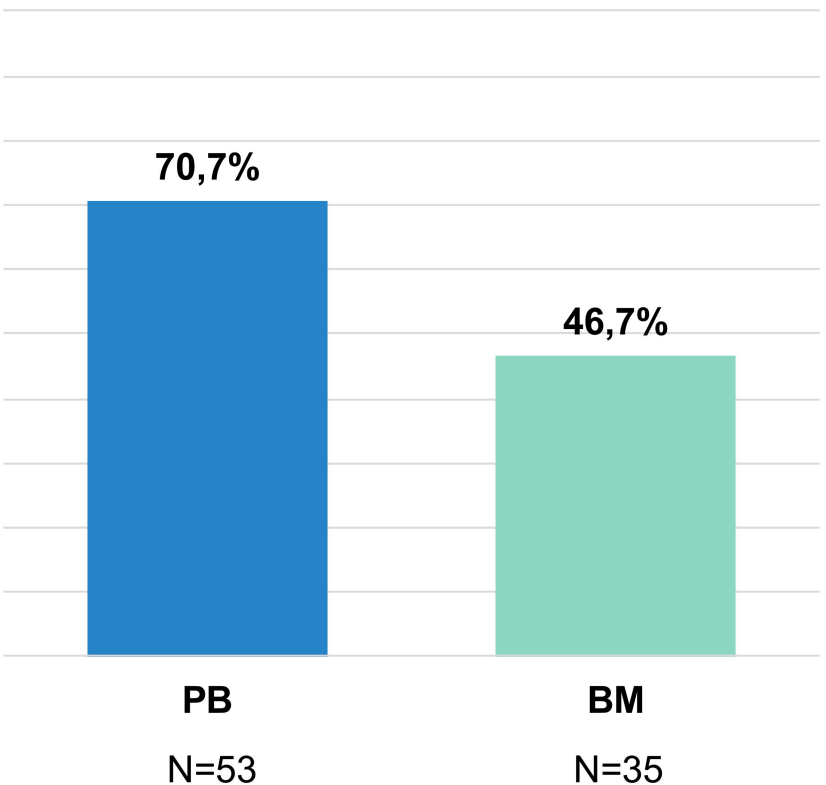
Figure 2. Response rates with undetectable MRD (uMRD, 10^{-4}) in the PB and BM by ASO-PCR at the end of combination therapy (EOCT) and end of treatment (EOT).

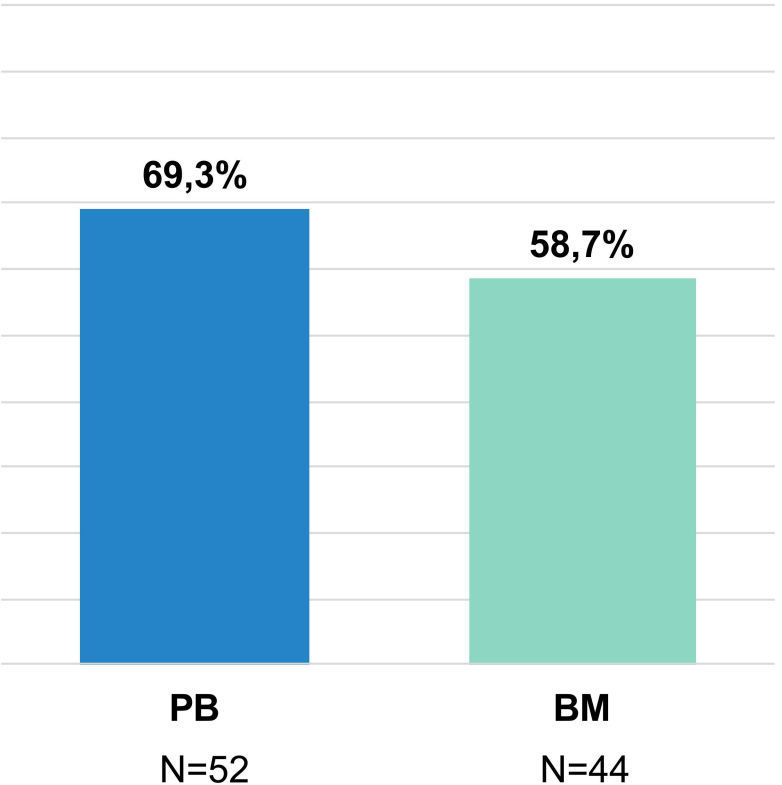
Figure 3. Impact of baseline factors and CRs measured at the end of combination therapy on responses with uMRD in the BM at end of treatment (OR; 95% CI).

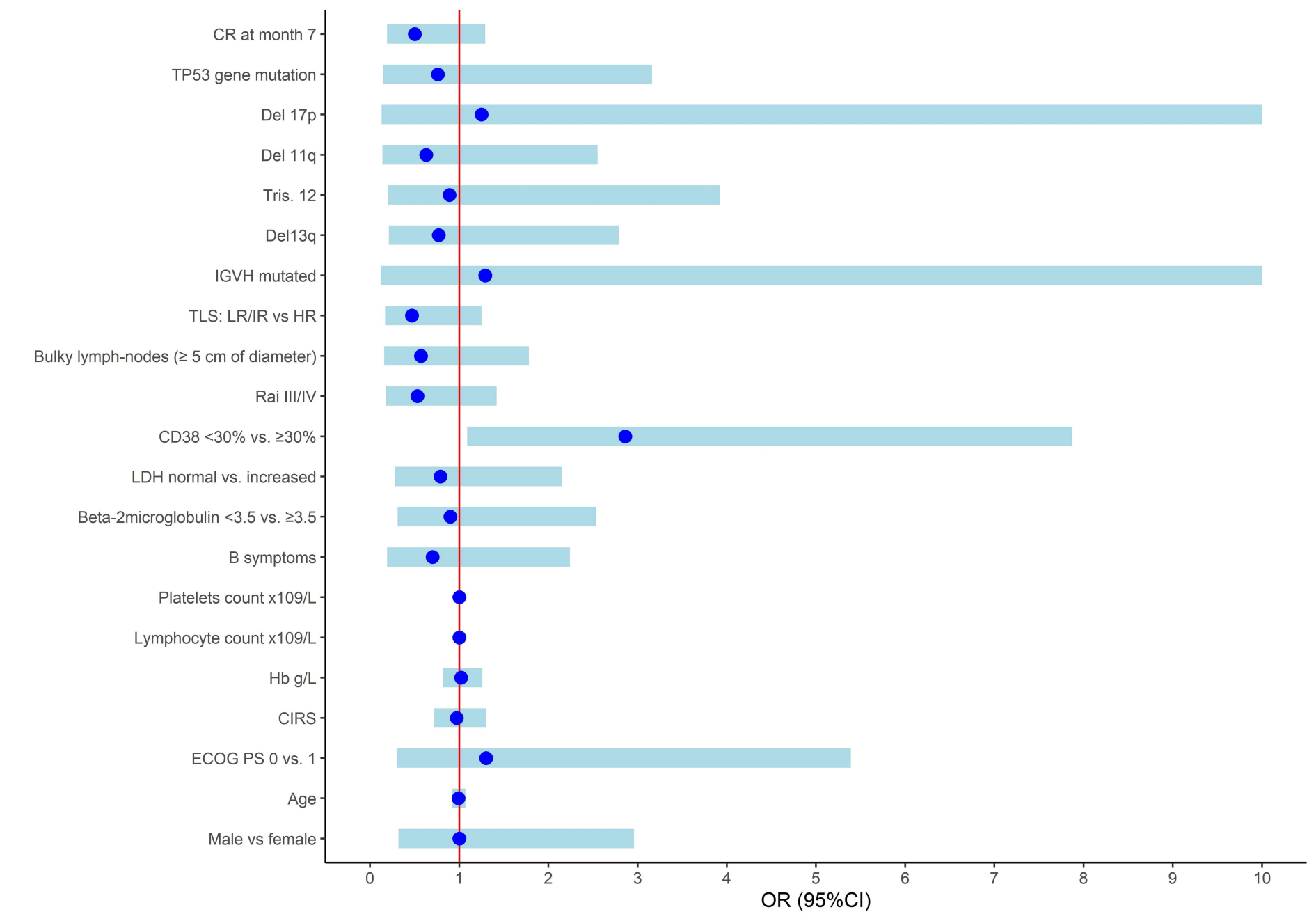
Figure 4. Undetectable MRD (uMRD) free survival .

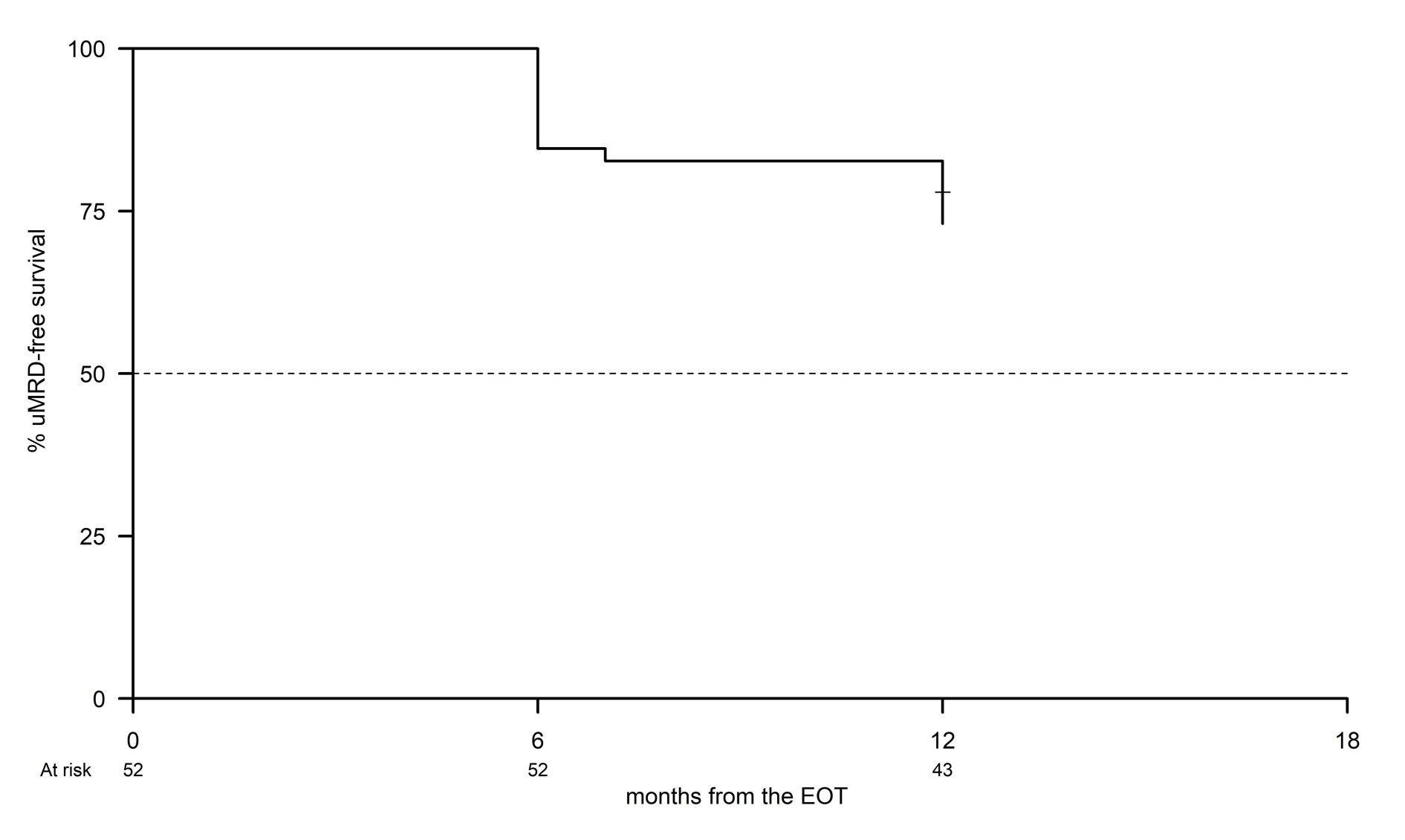
Figure 5. Overall Survival.

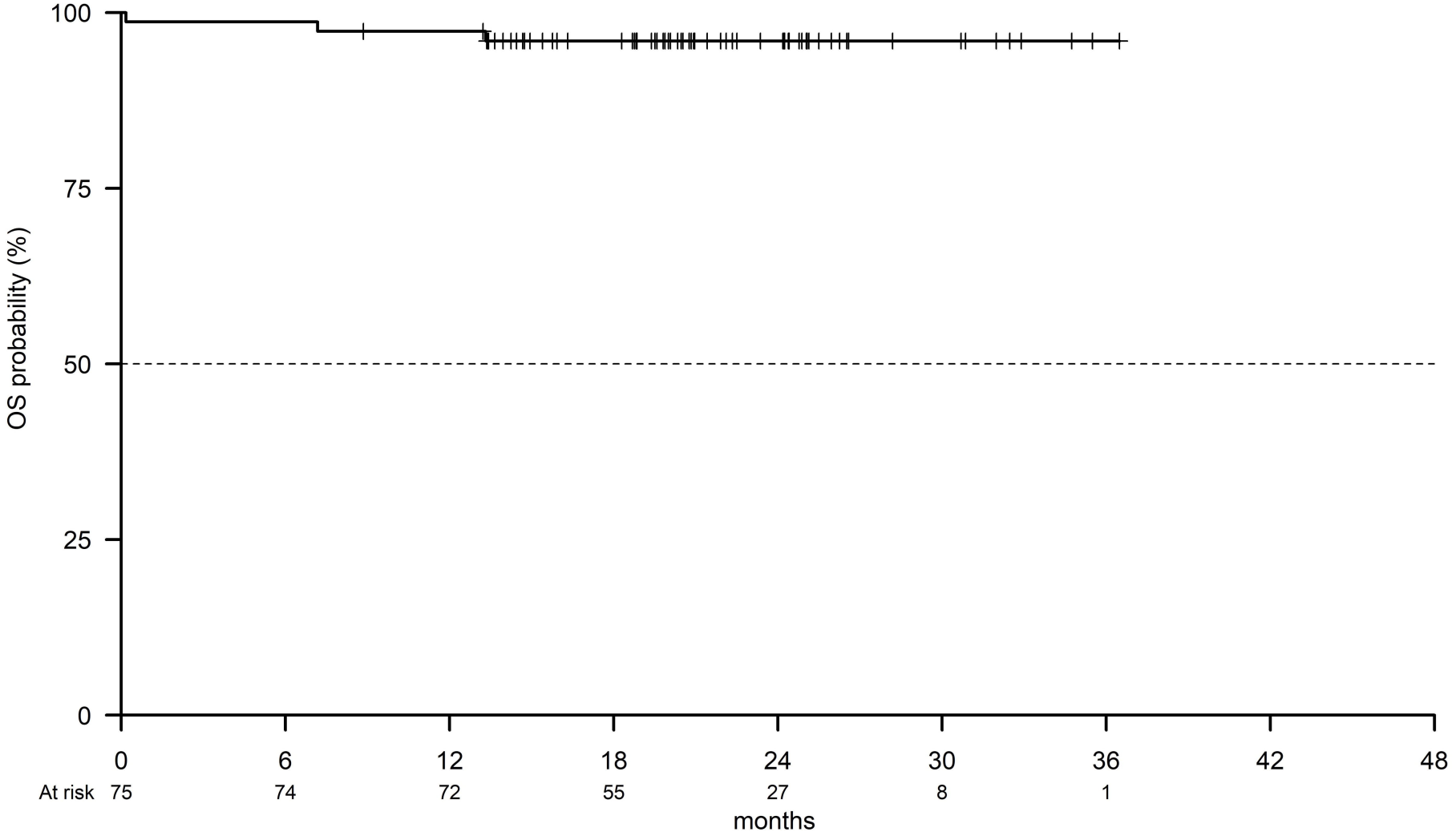

Treatment failure
PR
CRi
CR
%
4,0%
41,3%
2,7%
52,0%
ORR 96%
CR/CRi 54.7%
5,3%
18,7%
76,0%
ORR 94.7%
CR 76.0%
EOCT Month 7
EOT Month 15


70,7%
46,7%
PB
BM
N=53
N=35
EOCT Month 7


69,3%
58,7%
PB
BM
N=52
N=44
EOT Month 15


CR at month 7
TP53 gene mutation
Del 17p
Del 11q
Tris. 12
Del13q
IGVH mutated
TLS: LR/IR vs HR
Bulky lymph-nodes (≥ 5 cm of diameter)
Rai III/IV
CD38 <30% vs. ≥30%
LDH normal vs. increased
Beta-2microglobulin <3.5 vs. ≥3.5
B symptoms
Platelets count x109/L
Lymphocyte count x109/L
Hb g/L
CIRS
ECOG PS 0 vs. 1
Age
Male vs female
0
1
2
3
4
5
6
7
8
9
10
OR (95%CI)


100
75
50
25
0
% uMRD-free survival
0
6
12
18
At risk
52
52
43
months from the EOT


100
75
50
25
0
OS probability (%)
0
6
12
18
24
30
36
42
48
At risk
75
74
72
55
27
8
1
months

SUPPLEMENTARY MATERIAL

HIGH RATE DURABLE RESPONSES WITH UNDETECTABLE MRD WITH FRONTLINE VENETOCLAX AND RITUXIMAB IN YOUNG AND FIT PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND AN ADVERSE BIOLOGIC PROFILE: RESULTS OF THE

PATIENTS AND METHODS

Supportive treatment

Treatment was stopped in patients with febrile neutropenia and grade ≥3 toxicities. Myeloid growth factors were allowed in patients with grade ≥3 neutropenia. All patients received *Pneumocystis Carinii* prophylaxis with co-trimoxazole.

Statistical analysis

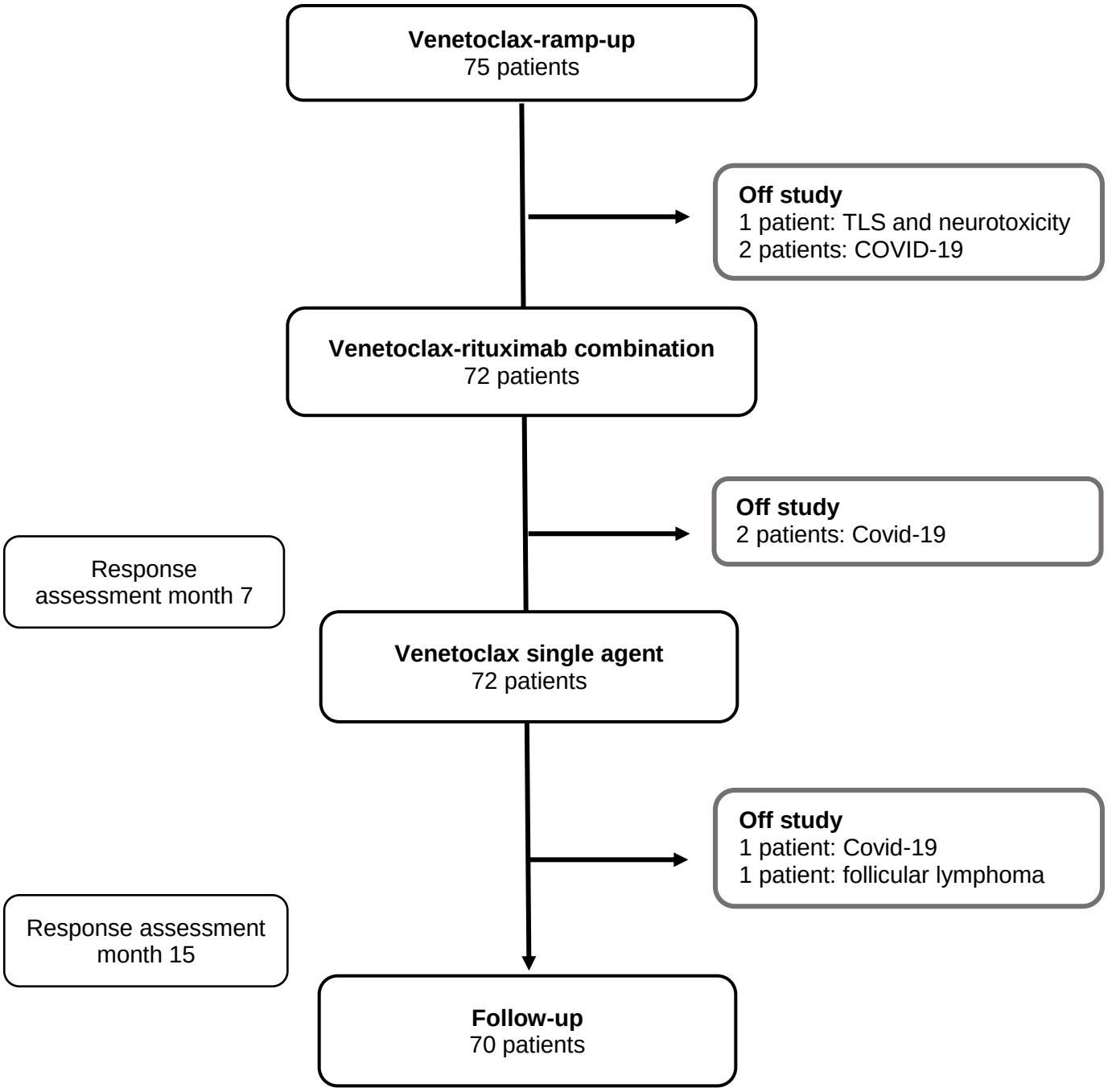
Patients' characteristics have been summarized using cross-tabulations for categorical variables or using quantiles for continuous variables. In univariate analysis, non-parametric tests were performed for comparisons between groups (Chi-Squared and Fisher Exact test in case of categorical variables or response rate, Mann-Whitney and Kruskal-Wallis test in case of continuous variables). Survival distributions have been estimated using the Kaplan-Meier Product Limit estimator. Differences in survival curves have been evaluated using the Log-Rank test. Cox regression models have been performed in univariate and multivariate analyses to assess the effect of clinical and biologic factors on PFS and OS. Hazard Ratios (HR) and 95% Confidence Interval have been reported as parameter results of the Cox regression models. The multivariate models have considered all relevant clinical/biologic variables or covariates with a p-value less than 0.15 in the univariate analysis. Cumulative Incidence curves have been estimated using the proper non-parametric method. The Gray test has been applied for significance tests on cumulative incidence curves, and the Fine and Gray model has been used in the univariate and multivariate analyses. All analyses have been analyzed on an intention-to-treat basis. All tests were 2-sided, accepting $p<0.05$ as indicating a statistically significant difference. Confidence intervals have been

calculated at the 95% level. All analyses were performed using the SAS software (release 9.4) and R (R Foundation for Statistical Computing, Vienna, Austria) system software.

Ethics

This study was carried out in accordance with the *Helsinki Declaration* and was approved by the Ethical Committee of all participating centers. All participants provided written informed consent. This study is registered at ClinicalTrials gov, Identifier: NCT03455517.

Supplementary Figure 1. Patients' disposition



Supplementary Table 1. Impact of clinical and biologic characteristics of the patients at baseline on the iwCLL CR assessed at the EOT: univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
Baseline characteristics	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value
Gender male *vs.* female	0.59	0.19, 1.97	0.37			
Age continuous variable	0.90	0.81, 0.99	0.032	0.90	0.80, 1.00	0.067
ECOG PS 0 *vs*. 1	0.70	0.17, 3.55	0.63			
CIRS continuous variable	0.64	0.45, 0.89	0.009	0.71	0.49, 1.00	0.054
Hb g/dl continuous variable	0.91	0.70, 1.16	0.45			
Lymphocyte count x10^9/L continuous variable	1.00	1.00, 1.01	0.72			
Platelet count x10^9/L continuous variable	1.00	0.99, 1.01	0.93			
B symptoms present *vs.* absent	2.50	0.60, 17.1	0.26			
Beta-2 microglobulin <3.5 *vs*. ≥3.5	0.90	0.27, 3.10	0.87			
LDH normal *vs.* increased	2.26	0.71, 8.79	0.19			
CD38 <30% *vs.* ≥30%	0.57	0.19, 1.66	0.31			
Rai III/IV absent *vs*. present	1.89	0.62, 6.54	0.28			
Bulky lymph nodes (≥5 cm in diameter) absent *vs*. present	1.11	0.33, 4.44	0.87			
TLS risk assessment Low and intermediate *vs.* high	0.40	0.13, 1.17	0.10	0.45	0.13, 1.48	0.19

	Univariate analysis			Multivariate analysis		
Baseline characteristics	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value
IGVH mutated *vs*. unmutated	1.62	0.07, 17.9	0.70			
FISH aberrations ~~according to the Dohner classification~~						
Del13q present *vs*. no aberration	0.50	0.09, 2.25	0.38			
Tris. 12 present *vs*. no aberration	2.06	0.23, 44.8	0.55			
Del11q present *vs*. no aberration	0.24	0.04, 1.10	0.078			
Del17p present *vs*. no aberration t	0.56	0.05, 13.5	0.66			
*TP*53 gene mutation present *vs*. absent	0.59	0.14, 3.04	0.49			

[1]OR = Odds Ratio, CI = Confidence Interval

Abbreviations: CIRS, Cumulative Illness Rating Scale; ECOG PS, Eastern Cooperative Oncology Group Performance Status Scale; Hb, hemoglobin; LDH, Lactate dehydrogenase¸ TLS, tumor lysis syndrome; IGHV, immunoglobulin heavy chain variable region gene; *TP*53 gene, tumor protein p53 gene; Del., deletion; Tris., trisomy.

Supplementary Table 2. Grade ≥3 adverse events

	No of AEs	No of the patients with an AE	% of patients with an AE
Blood and lymphatic system disorders	**66**	**34**	**45.3**
• Anemia	1	1	
• Febrile neutropenia	4	2	**37.3**
• Neutropenia	49	26	
• Leukopenia	6	2	
• Lymphopenia	2	1	
• Thrombocytopenia	4	2	
Gastrointestinal disorders	**2**	**2**	**2.6**
• Diarrhea	1	1	
• Nausea	1	1	
Infections and infestations	**9**	**9**	**12**
• Fungal infections	2	2	
• Bacterial infection	1	1	
• Herpes zoster	1	1	
• COVID-19 pneumonia	5	5	
Hepatobiliary disorders	**3**	**3**	**4**
• Increased alanine aminotransferase	1	1	
• Increased gamma-glutamyltransferase	1	1	
• Increased transaminases	1	1	
Metabolism and nutrition disorders	**1**	**1**	**1.3**
• Clinical tumor lysis syndrome	1	1	
Neoplasm benign malignant and unspecified	**1**	**1**	**1.3**
• Prostate cancer	1	1	
Skin and subcutaneous tissue disorders	**1**	**1**	**1.3**
• Erythema	1	1	
Total	**83**	**51**	**68**

TUMOR LYSIS SYNDROME (TLS) IN A PATIENT INCLUDED IN THE GIMEMA 1518 TRIAL 'VERITAS'.

NN/CC, a 60-year-old male patient with CLL, showed an unmutated IGHV, wild-type *TP*53, and a high-risk TLS due to enlarged lymph nodes (longitudinal size of 10.5 cm). Baseline renal function, sodium, potassium, calcium, and phosphorus levels were normal- at baseline, showed: creatinine clearance, 0.6 /ml; uric acid, 0.5 mg/dl (normal values <6 mg/dl). Given the high risk of TLS, the patient was hospitalized, and IV hydration combined with rasburicase were given before the start of venetoclax at the dose of 20 mg daily on day 1. On day 2, 8 hours from the start of venetoclax, the patient showed a loss of consciousness. Venetoclax was discontinued, while IV hydration and allopurinol were continued. The patient developed progressive hypoxemia and renal insufficiency with increased creatinine, potassium, calcium, and phosphorus levels. The patient died on day + 6.

This patient with severe osteoporosis suffered from severe pain due to a vertebral fracture and used self-administered fentanyl patches for analgesic purposes. This clinical case has been discussed extensively. As venetoclax and fentanyl are metabolized by the same hepatic cytochromes (CYP3A4/5), a metabolic interference could have resulted in severe toxicity[1,2].

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2. Drug Bank online; Venetoclax https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwj377T4ipD7AhUL_qQKHVpdCF4QFnoECDYQAQ&url=https%3A%2F%2Fgo.drugbank.com%2Fdrugs%2FDB11581&usg=AOvVaw2CQDtwe0Rf6a83Ya0l3H_V