High rate of durable responses with undetectable minimal residual disease with front-line venetoclax and rituximab in young, fit patients with chronic lymphocytic leukemia and an adverse biological profile: results of the GIMEMA phase II LLC1518 – VERITAS study

Francesca R. Mauro,[1] Irene Della Starza,[1,2] Monica Messina,[2] Gianluigi Reda,[3] Livio Trentin,[4] Marta Coscia,[5] Paolo Sportoletti,[6] Lorella Orsucci,[7] Valentina Arena,[2] Gloria Margiotta Casaluci,[8] Roberto Marasca,[9] Roberta Murru,[10] Luca Laurenti,[11] Fiorella Ilariucci,[12] Caterina Stelitano,[13] Donato Mannina,[14] Massimo Massaia,[15] Gian Matteo Rigolin,[16] Lydia Scarfò,[17] Monia Marchetti,[18] Luciano Levato,[19] Monica Tani,[20] Annalisa Arcari,[21] Gerardo Musuraca,[22] Marina Deodato,[23] Piero Galieni,[24] Valeria Belsito Patrizi,[25] Daniela Gottardi,[26] Anna Marina Liberati,[27] Annamaria Giordano,[28] Maria Chiara Molinari,[1] Daniela Pietrasanta,[18] Veronica Mattiello,[3] Andrea Visentin,[4] Candida Vitale,[5] Francesco Albano,[28] Antonino Neri,[3] Lucia Anna De Novi,[1] Maria Stefania De Propris,[1] Mauro Nanni,[1] Ilaria Del Giudice,[1] Anna Guarini,[1] Paola Fazi,[2] Marco Vignetti,[2] Alfonso Piciocchi,[2] Antonio Cuneo[16,#] and Robin Foà[1,#]

[1]Hematology, Department of Translational and Precision Medicine, Sapienza University, Rome; [2]GIMEMA Foundation, Rome; [3]Hematology Department, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Milan; [4]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padua, Padua; [5]Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino and Department of Molecular Biotechnology and Health Sciences, University of Turin, Turin; [6]Department of Medicine and Surgery, Institute of Hematology, Centro di Ricerca Emato Oncologica (CREO), University of Perugia, Perugia; [7]Department of Hematology, Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Turin; [8]Division of Hematology, Department of Translational Medicine, Università del Piemonte Orientale and AOU Maggiore della Carità, Novara; [9]Hematology Unit, Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena; [10]Hematology and Stem Cell Transplantation Unit, Ospedale A. Businco, ARNAS "G. Brotzu", Cagliari; [11]Fondazione Policlinico Universitario A Gemelli, IRCCS, Rome; [12]Hematology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia; [13]Department of Hematology, Azienda Ospedaliera Bianchi Melacrino Morelli, Reggio Calabria; [14]Division of Hematology, Azienda Ospedaliera Papardo, Messina; [15]Division of Hematology, Santa Croce e Carle Hospital, Cuneo; [16]Hematology Section, St. Anna University Hospital, Ferrara; [17]Strategic Research Program on CLL, IRCCS Ospedale San Raffaele and Università Vita-Salute San Raffaele, Milan; [18]Hematology and Transplant Unit, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, University of Eastern Piedmont, Alessandria; [19]Department of Hematology, Pugliese Ciaccio Hospital, Catanzaro; [20]Division of Hematology, Santa Maria delle Croci Hospital, Ravenna; [21]Division of Hematology, Guglielmo da Saliceto Hospital, Piacenza; [22]Istituto Scientifico Romagnoli per lo Studio e la Cura dei Tumori-IRST, Meldola; [23]ASST Grande Ospedale Metropolitano Niguarda, Milan; [24]Hematology, Mazzoni Hospital, Ascoli Piceno; [25]Hematology Department, Umberto I Hospital, Nocera Inferiore; [26]A.O. Ordine Mauriziano di Torino, Turin; [27]Università degli Studi di Perugia, Azienda Ospedaliera Santa Maria di Terni, Terni and [28]University of Bari "Aldo Moro," Hematology and Stem Cell Transplantation Unit, Department of Emergency and Organ Transplantation, Bari, Italy.

[#]AC and RF contributed equally as last authors.

Correspondence: F.R. Mauro
mauro@bce.uniroma1.it

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Abstract

The GIMEMA phase II LLC1518 VERITAS trial investigated the efficacy and safety of front-line, fixed-duration venetoclax and rituximab (VenR) in combination in young (≤65 years), fit patients with chronic lymphocytic leukemia and unmutated IGHV and/or *TP*53 disruption. Treatment consisted of the venetoclax ramp-up, six monthly courses of the VenR combination,

followed by six monthly courses of venetoclax as a single agent. A centralized assessment of minimal residual disease (MRD) was performed by allele-specific oligonucleotide polymerase chain reaction assay on the peripheral blood and bone marrow at the end of treatment (EOT) and during the follow-up. The primary endpoint was the complete remission rate at the EOT. Seventy-five patients were enrolled; the median age was 54 years (range, 38-65), 96% had unmutated IGHV, 12% had *TP*53 disruption, and 4% had mutated IGHV with *TP*53 disruption. The overall response rate at the EOT was 94.7%, with a complete remission rate of 76%. MRD was undetectable in the peripheral blood of 69.3% of patients and in the bone marrow of 58.7% of patients. The 12-month MRD-free survival in the 52 patients with undetectable MRD in the peripheral blood at the EOT was 73.1%. After a median follow-up of 20.8 months, no cases of disease progression were observed. Three patients had died, two due to COVID-19 and one due to tumor lysis syndrome. The first report of the VERITAS study shows that front-line VenR was associated with a high rate of complete remissions and durable response with undetectable MRD in young patients with chronic lymphocytic leukemia and unfavorable genetic characteristics. ClinicalTrials.gov identifier: NCT03455517.

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. The excellent therapeutic activity of these agents has radically changed the treatment approach for CLL, partially overcoming the unfavorable prognostic impact of adverse biological characteristics, including the unmutated configuration of the variable portion of the immunoglobin gene heavy chain (IGHV) gene and *TP*53 disruption (deletion and/or mutation of the *TP*53 gene).

Continuous treatment with ibrutinib has demonstrated efficacy regardless of high-risk biological features and superiority over chemoimmunotherapy in relapsed/refractory 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 a non-covalent BTK inhibitor, pirtobrutinib, in patients resistant to ibrutinib due to a BTK mutation has also been described.[19] Venetoclax, a selective oral BCL2 inhibitor, restores activation of CLL apoptosis.[20] In several studies that included relapsed/refractory and treatment-naïve patients with CLL, fixed-duration treatment with venetoclax in combination with an anti-CD20 monoclonal antibody led to responses with undetectable minimal residual disease (MRD) 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 in unfit patients treated front-line with venetoclax 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 patients with relapsed/refractory CLL demonstrated a significant improvement in progression-free survival and overall survival with venetoclax and rituximab (VenR) as compared to chemoimmunotherapy.[24-26] In addition, a high rate of deep responses with undetectable MRD was recorded with VenR, which was associated with a highly favorable impact on progression-free survival. 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 when treating younger patients with CLL and a long-life expectancy, were not observed.

Although BTK inhibitors are effective agents, fixed-duration therapy with venetoclax, 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 patients with relapsed/refractory CLL, including those with unmutated IGHV and *TP*53 disruption, the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) investigated the efficacy and safety of a front-line VenR regimen in young (≤65 years), fit patients with CLL and an unfavorable biological profile. Here we report the first results of the GIMEMA phase II, single-arm, multicenter LLC1518 VERITAS study in 75 previously untreated, young patients with CLL and an unmutated IGHV profile and/or a *TP*53 disruption.

Methods

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 the ethics committee of La Spaienza University (date of approval 07/06/2018; approval file number CE 497/18; reference 5049).

Patients were required to be ≤65 years, have a cumulative

illness rating scale (CIRS) score ≤6,[28] have a creatinine clearance ≥30 mL/min, an unmutated IGHV gene and, or a *TP*53 disruption (17p deletion and/or *TP*53 mutation).[29-31] The IGHV profile and *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 at four reference laboratories (Rome, Ferrara, Bari, Milan).

Treatment

Study treatment consisted of a venetoclax ramp-up and six monthly courses of the VenR combination, followed by six monthly courses of venetoclax given as a single agent. During the ramp-up phase, patients were given venetoclax according to a 5-week escalation schedule with a gradual increase in the dose from 20 mg/day to 400 mg/day.[22] Once the 5 weeks of the ramp-up phase had been completed, the following six cycles of VenR started on day 1 of cycle 1. Rituximab was administered on day 1 of each cycle. Venetoclax was continued at the dose of 400 mg/day in combination with rituximab at the dose of 375 mg/m^2 on day 1 of cycle 1 (month 1) and at the dose of 500 mg/m^2 on day 1 of cycles 2-6 (months 2-6). After the end of the combination therapy (EOCT), patients continued venetoclax monotherapy until day 28 of cycle 13, or unacceptable toxicity or disease progression. The risk of tumor lysis syndrome was assessed according to the presence of bulky lymphadenopathy (diameter ≥5 cm) and the peripheral absolute lymphocyte count (≥25×10^9/L).[32] Patients received prophylaxis against tumor lysis syndrome with urate-reducing agents and oral or intravenous hydration. Tumor lysis syndrome events were classified according to Howard's criteria.[32] Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.[33]

Table 1. Patients' baseline characteristics.

Characteristics	
Patients, N (%)	75 (100)
Gender M/F, N (%)	56 (75)/19 (25)
Age, years, median (range)	54 (38-65)
ECOG performance status 0/1, N (%)	65 (87) /10 (13)
CIRS score, median (range)	1.00 (0.00-6.00)
CIRS score >3, N (%)	9 (12)
Hb g/dL, median (range)	12.50 (7.5-16.6)
Lymphocyte count x10^9/L, median (range)	96 (5.3-556)
Platelet count x10^9/L, median (range)	150 (54-425)
B symptoms, N (%)	16 (22)
β_2 microglobulin >3.5 mg/L, N (%)	27 (41)
Increased LDH, N (%)	26 (35)
CD38 expression >30%, N (%)	38 (51)
Rai stage III/IV, N (%)	9 (12)/19 (26)
Bulky lymph nodes (≥5 cm in diameter), N (%)	18 (25)
Risk of TLS, N (%)	
Low	10 (13)
Intermediate	32 (43)
High	33 (44)
IGHV status, N (%)	
Mutated	3 (4)
Unmutated	72 (96)
FISH aberrations, N (%)	
Del 13q	22 (30)
Tris 12	12 (16)
Del 11q	16 (22)
Del 17p	4 (5.5)
No aberrations	19 (26)
*TP*53 disruption, N (%)	9 (12)
*TP*53 mutation only	5 (6.6)
*TP*53 mutation and deletion	4 (5.5)

M: male; F: female; ECOG: Eastern Cooperative Oncology Group; CIRS: Cumulative Illness Rating Scale; Hb: hemoglobin; LDH: lactate dehydrogenase; TLS: tumor lysis syndrome; IGHV: immunoglobulin heavy chain variable region gene; Del: deletion; Tris: trisomy; FISH: fluorescence *in situ* hybridization; *TP*53 gene: tumor protein p53 gene.

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, peripheral blood evaluation, bone marrow aspirate and biopsy, and computed tomography scan. A centralized MRD assessment was carried out at the Hematology Center in Rome on peripheral blood and bone marrow cells by allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) assay as previously reported.[34,35] MRD was categorized as undetectable with a cut-off of <1 cell in 10,000 leukocytes. During the follow-up, MRD was monitored every 6 months.

Study endpoints

The primary endpoint of this study was the complete remission rate at the EOT. The secondary endpoints included the overall response rate, the rate of responses with undetectable MRD at the EOT, progression-free survival, and overall survival. Further secondary endpoints were the time to MRD conversion from undetectable to detectable, the time from the re-emergence of detectable leukemic cells to clinical progression of disease, and the time to a new CLL treatment.

Details on supportive treatment, statistical analysis, and ethics are reported in the *Online Supplementary Material*.

Results

Patients

Between October 2018 and May 2020, 75 young patients with CLL and an unfavorable biological profile requiring front-line therapy from 28 Italian centers were included in this study and formed the intention-to-treat population

assessed for treatment response and safety. The patients' disposition is illustrated in *Online Supplementary Figure S1*. The patients' baseline clinical and biological characteristics are summarized in Table 1. Their median age was 54 years (range, 38-65). Thirty-eight percent of the patients had advanced III-IV Rai stage disease; 41% had an increased level of β_2 microglobulin, and 25% had bulky lymphadenopathy. The risk of tumor lysis syndrome was high at baseline in 44% of patients. Seventy-two patients (96%) had an unmutated IGHV gene profile, with a *TP*53 disruption in six (*TP*53 mutation, n=5; *TP*53 mutation and deletion, n=1), while three patients (4%) were IGHV-mutated and carried a *TP*53 disruption (*TP*53 mutation and deletion, n=3). The median CIRS score was 1 (range, 0-6), with nine (12%) patients having a CIRS score >3.

Response to treatment

Response at the end of the combination therapy

Seventy-two patients (96%) achieved a response at the EOCT (month 7). Responses included a complete response with or without blood count recovery in 41 patients (complete response, 52%; complete response with incomplete blood count recovery, 2.7%), and partial response in 31 (41.3%) (Figure 1). Three patients discontinued treatment because of an adverse event and were censored as treatment failures. The ASO-PCR assay demonstrated undetectable MRD at the EOCT in the peripheral blood and bone marrow of 70.7% and 46.7% of patients, respectively (Figure 2). The proportion of patients in complete remission with no measurable MRD by ASO-PCR in the peripheral blood and bone marrow was 78% and 61%, respectively (Figure 2). In patients who achieved a partial response, MRD could not be detected in the peripheral blood and bone marrow of 68% and 32% patients, respectively.

Response at the end of treatment

At the EOT (month 15), after a further 6 months of treatment with venetoclax as a single agent, the overall response rate was 94.7%, and the complete response rate increased from 54.2% to 76% (57 patients) (Figure 1). A partial response 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 because of an adverse event and were censored as treatment failures. A significantly lower complete response rate at the EOT was observed in older patients (*P*=0.032) and those with higher CIRS scores (*P*=0.009) (*Online Supplementary Table S1*). However, the only factor that retained a borderline statistical signifi-

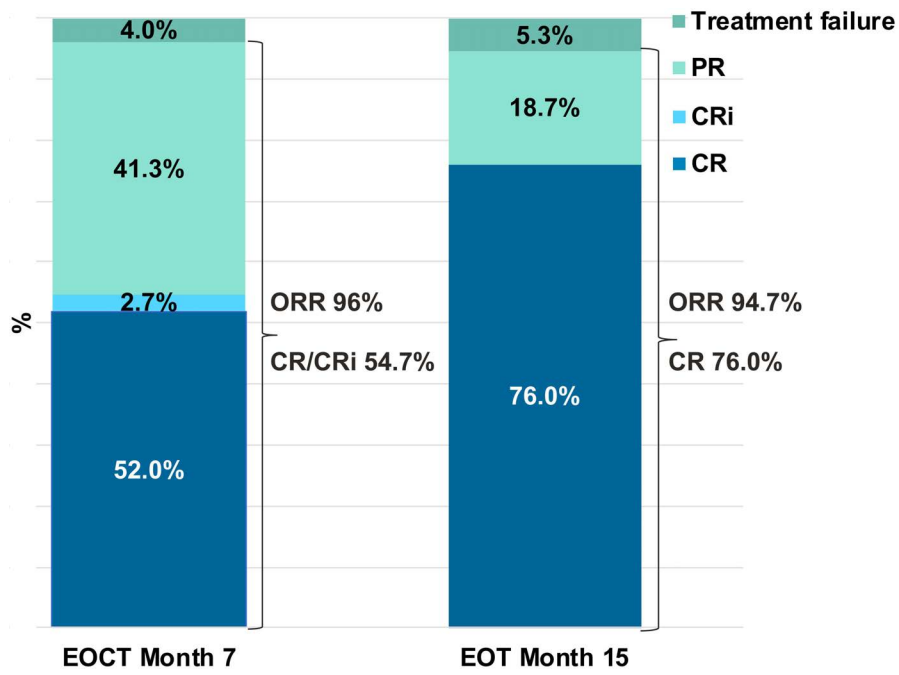

Figure 1. Responses at the end of combination therapy and end of treatment according to International Working Group Chronic Lymphocytic Leukemia criteria. EOCT: end of combination therapy; EOT: end of treatment; ORR: overall response rate; CR: complete response; CRI: complete response with incomplete blood count recovery; PR: partial response.

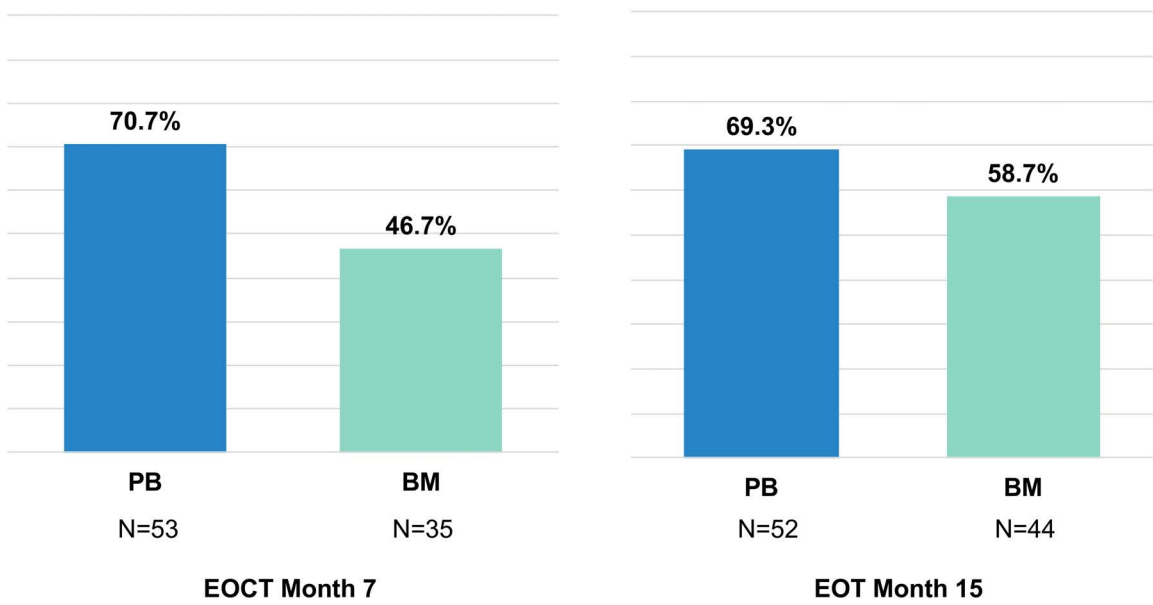

Figure 2. Rates of responses with undetectable minimal residual disease (10^{-4}) in the peripheral blood and bone marrow by allele-specific oligonucleotide polymerase chain reaction at the end of combination therapy and end of treatment. EOCT: end of combination therapy; EOT: end of treatment; PB: peripheral blood; BM: bone marrow.

cance in multivariate analysis was the CIRS score (*P*=0.054). A response with undetectable MRD by ASO-PCR was recorded in 69.3% of patients when examining peripheral blood and in 58.7% when bone marrow was tested (Figure 2). Six of the nine patients with *TP*53 disruption achieved a response with undetectable MRD in the peripheral blood and bone marrow. We analyzed the impact of the patients' baseline characteristics and iwCLL-defined response measured at the EOCT on the probability of achieving undetectable MRD in the peripheral blood and bone marrow at the EOT. While no factors showed a significant impact on the rate of responses with undetectable MRD in the peripheral blood, the only factor associated with a higher probability of achieving undetectable MRD was a cut-off level of CD38 expression <30% in the bone marrow (Figure 3). MRD was monitored during the follow-up in 52 patients with a response and undetectable MRD in the peripheral blood at the EOT. MRD remained undetectable in the peripheral blood in 38 (73%) patients, 13 (25%) converted to detectable MRD, and one patient died from an adverse event. The 12-month MRD-free survival was 73.1% (95% confidence interval [95% CI]: 62-86.2) (Figure 4). There was no significant difference in the proportion of patients with complete or partial response and undetectable MRD in the bone marrow who lost the response at month 21 (undetectable MRD at month 21: partial response, 0/10 *vs.* complete response, 4/33).

Survival

After a median follow-up of 20.8 months (range, 0.2-36.5), no patient showed clinical progression, and three patients had died from adverse events. The 24-month overall survival was 96% (95% CI: 91.6-100) (Figure 5).

Safety

The grade ≥3 adverse reactions are described in *Online*

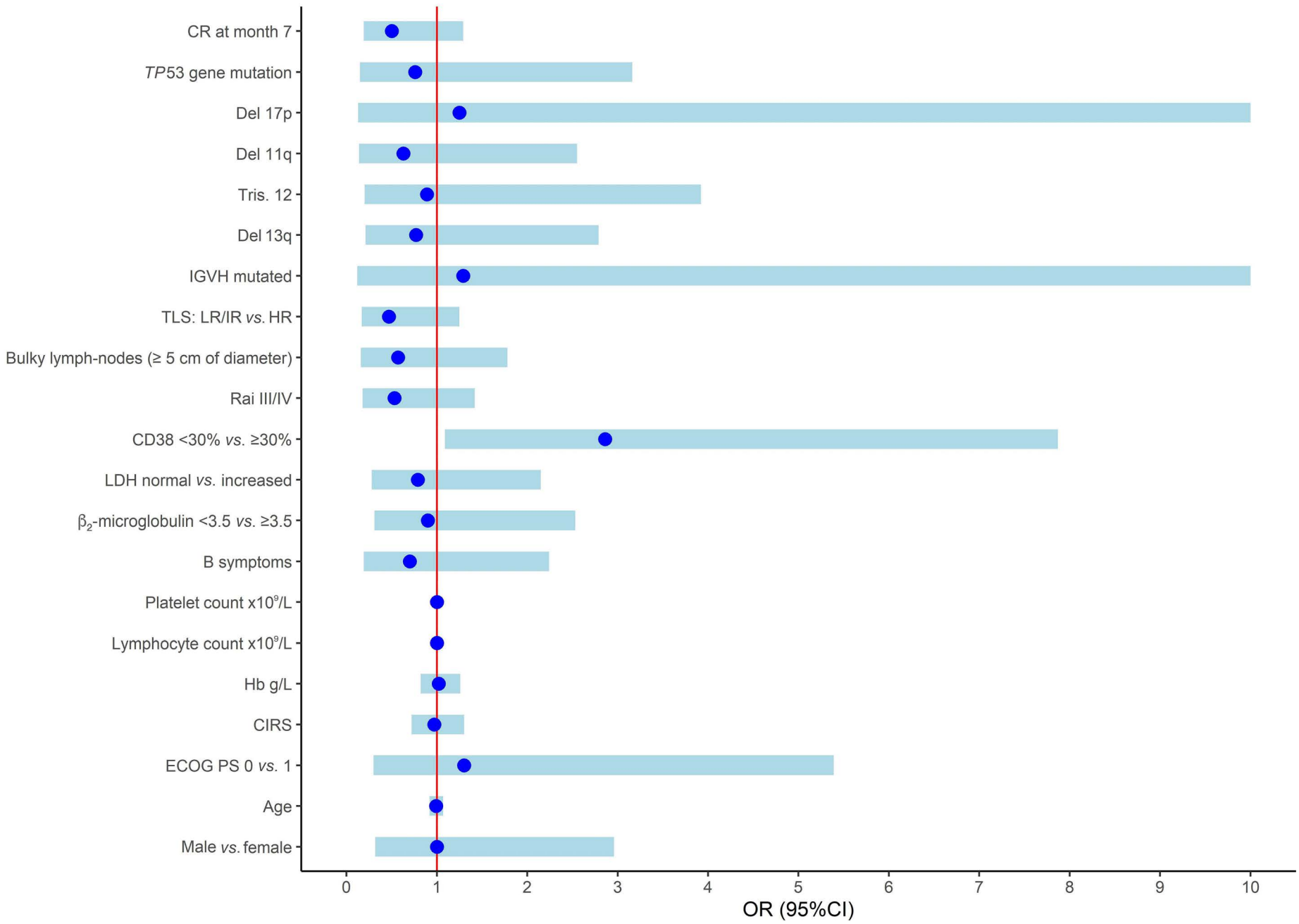

Figure 3. Impact of baseline factors and complete response measured at the end of combination therapy on responses with undetectable minimal residual disease in the bone marrow at the end of treatment. CR: complete response; *TP*53 gene: tumor protein p53 gene; Del: deletion; Tris: trisomy; IGHV: immunoglobulin heavy chain variable region gene; TLS: tumor lysis syndrome; LR: low risk; IR: intermediate risk; HR: high risk; LDH: lactate dehydrogenase; Hb: hemoglobin; CIRS: Cumulative Illness Rating Scale; ECOG: Eastern Cooperative Oncology Group; OR: odds ratio; 95% CI: 95% confidence interval.

Supplementary Table S2. Thirty-four patients (45.3%) experienced at least one grade ≥3 adverse event. Granulocytopenia was recorded in 28 patients (37.3%), and 26 (35%) received granulocyte colony-stimulating factors. Grade ≥3 infections were observed in nine patients (12%), including five patients (6.7%) who developed coronavirus disease 2019 (COVID-19) at the time of the first SARS-CoV-2 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, high CIRS score, increased risk factor for tumor lysis syndrome, low creatinine clearance, or low granulocyte count at baseline. A fungal infection was reported in two patients. One patient showed clinical signs suggestive of sinusitis of suspected, but not documented, fungal etiology. The other patient 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 three patients (4%). Thirty-three patients (44%) were at high risk of tumor lysis syndrome. Two patients had a creatinine clearance <60 mL/min at baseline but neither of them developed tumor lysis syndrome. Despite hospitalization, intravenous hydration, and the administration of anti-uric agents, one patient at increased risk of tumor lysis syndrome developed a grade 5 syndrome 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

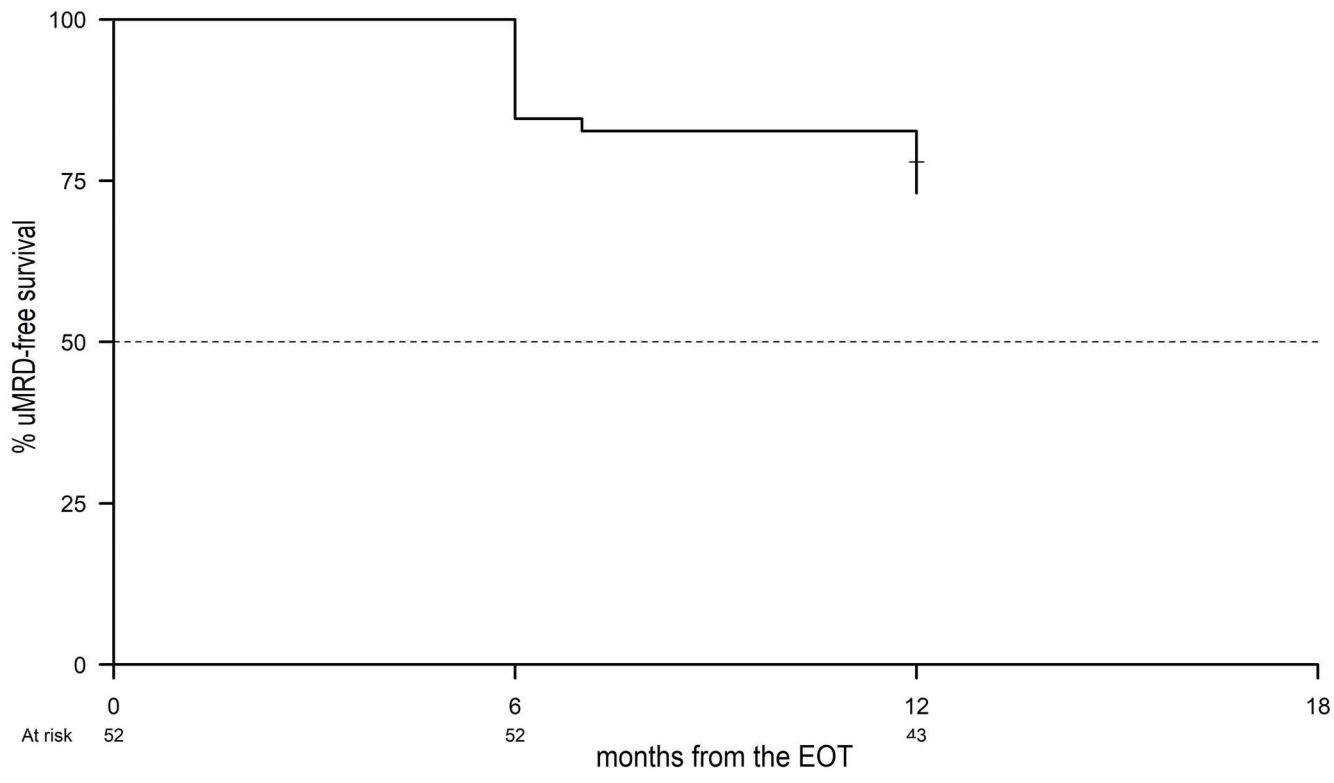

Figure 4. Undetectable minimal residual disease-free survival. uMRD: undetectable minimal residual disease; EOT: end of treatment.

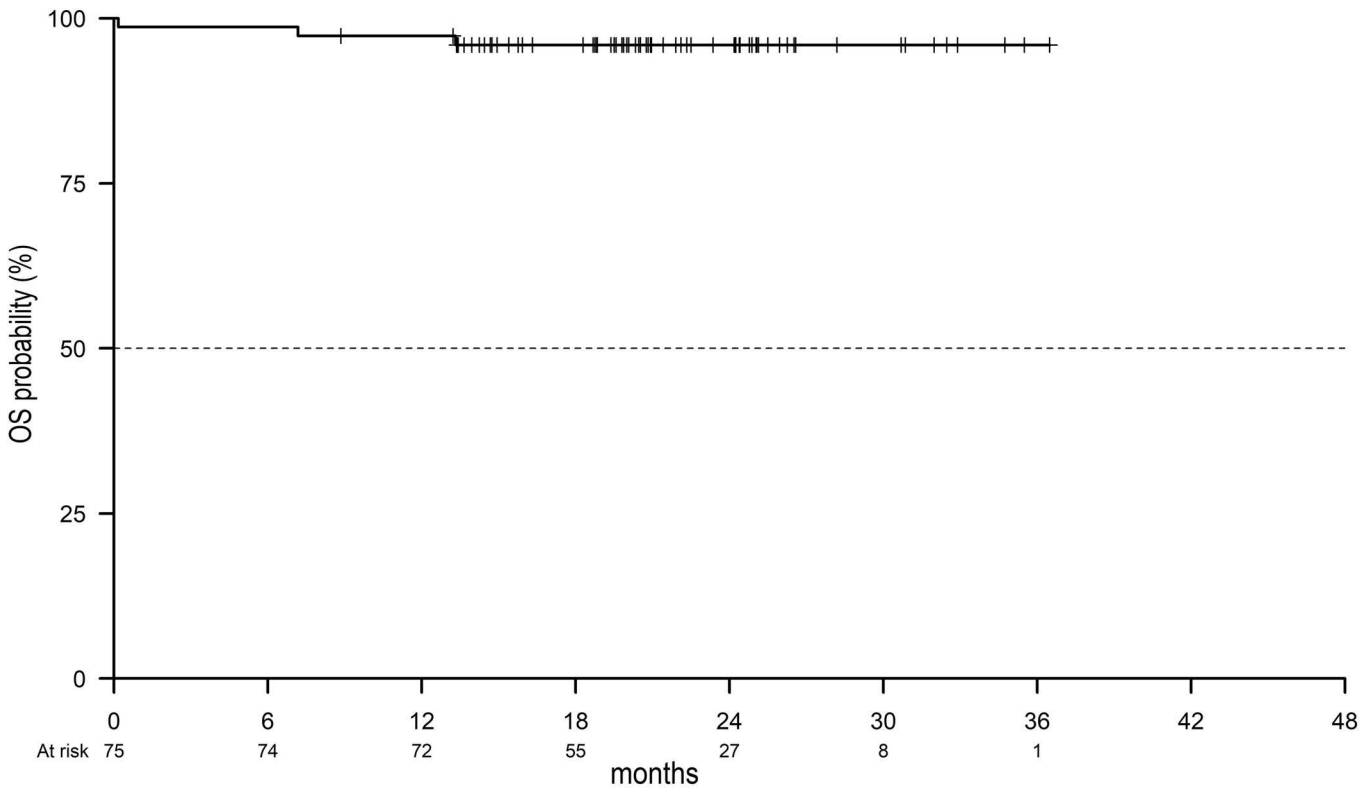

Figure 5. Overall survival of the whole cohort of 75 patients enrolled in the study. OS: overall survival.

purposes (more details on this clinical case are reported in the *Online Supplementary File*). One patient was diagnosed with follicular lymphoma 24 months after the start of treatment. No cases of Richter syndrome or non-hematologic cancers were recorded. Three patients died due to an adverse event, one with a clinical tumor lysis syndrome, and two 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 biological profile achieved a response with the VenR fixed-duration treatment. Moreover, no evidence of residual disease was detected in the peripheral blood of 69.3% of patients and in the bone marrow of 58.7%. After a median follow-up of 20.8 months, no cases of disease progression had occurred. These data confirm, in previously untreated patients, the efficacy of the VenR combination described in patients with relapsed/refractory CLL in the Murano trial.[24-26]

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

Our study included young (≤65 years), fit patients with a CIRS score of ≤6. The presence of comorbidities, even with a CIRS score <6, was associated with a lower complete response rate. Interestingly, in a real-world study, higher CIRS scores were 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 progression-free survival data are therefore premature. A valid surrogate of the efficacy of VenR is represented by the rate of patients with undetectable MRD in the peripheral blood, as determined by ASO-PCR in the CLL14 trial.[21] The 69.3% rate of responses with undetectable MRD in peripheral blood recorded in our study compares favorably with the rates of undetectable MRD observed with FCR in the CLL10 and ECOG1912 trials (49% and 59.2%, respectively).[9,36] In the CLL13 trial, which included patients with a more favorable genetic profile, a similar schedule produced responses with undetectable MRD in 57% of cases.[41]

Higher rates of responses with undetectable MRD in the peripheral blood were found in the CLL14 and CLL13 trials with the venetoclax and obinutuzumab combination (76% and 86.5%, respectively).[21,41] Obinutuzumab, a more potent CD20 monoclonal antibody with a greater capacity for direct killing of B cells and a glyco-engineered Fc-fragment for improved effector-cell recruitment, has shown an advantage over rituximab as a partner of venetoclax. Although in the CLL13 trial infusion-related reactions associated with obinutuzumab were more severe than those seen with rituximab, patients treated with venetoclax and obinutuzumab showed a higher rate of responses with undetectable MRD and more prolonged progression-free survival compared to those treated with VenR.[41]

In the Glow trial, which included elderly/unfit patients with CLL, the venetoclax plus ibrutinib combination resulted in 54.7% of patients having responses with undetectable MRD in the peripheral blood,[42] while higher rates were observed in the Flair trial (71.3%),[37] and in the MRD and fixed-duration cohorts of the Captivate study (75% and 77%, respectively).[38,39] In the CLL13 trial, the triplet combination of venetoclax, ibrutinib, and obinutuzumab was associated with the highest rate of responses with undetectable MRD in the peripheral blood (92.2%).[41] A comparison between the rates of undetectable MRD in the different studies is hampered by the technique used to measure residual disease, which was ASO-PCR in some studies,[21,42] like ours, and flow cytometry in others.[38-39;41] Although cross-trial comparisons 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 can benefit from different and more prolonged venetoclax-based treatments.

CD38 positivity, recorded in 51% of patients, emerged as the only factor with an unfavorable impact on the rate of undetectable MRD in the bone marrow. CD38, a multifunctional surface 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 venetoclax. In a study by Sargent *et al.*,[47] a significant inverse relationship was observed *in vitro* between the proportion of CD38-positive cells and the level of BCL2 expression. Based on this finding, we speculate that CD38-negative patients could express higher levels of the anti-apoptotic BCL2 protein, resulting in a more pronounced activity of venetoclax.

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.

The re-emergence of MRD after FCR treatment is more rapid in patients with unmutated IGHV than in those with mutated IGHV.[48] In our study, which included mainly patients with unmutated IGHV, 73% of patients who achieved a response with undetectable MRD maintained the status of undetectable MRD in the peripheral blood at 12 months after the EOT. Despite the unfavorable genetic characteristics of our study cohort, the MRD-free survival in our analysis is in line with that observed in unfit patients treated with venetoclax 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 adverse event was granulocytopenia, which was easily manageable with granulocyte growth factors. Unfortunately, our study was carried out during the outbreak of the SARS-CoV-2 pandemic before vaccines were introduced, and five of the nine grade ≥3 infections were due to SARS-CoV-2 infection. About half of the patients in this study had a high risk of tumor lysis syndrome. However, only one case of fatal clinical tumor lysis syndrome was observed in a patient who underwent the ramp-up phase of the treatment regimen while receiving a drug, for analgesic purposes, which may have interfered with the metabolism of venetoclax. One 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 VenR combination as front-line treatment is easily manageable, well-tolerated, and associated with high rates of complete responses and durable responses with undetectable MRD in younger patients with CLL and unfavorable genetic characteristics.

Disclosures

FRM reports advisory board and lecture fees from Abbvie, Janssen, AstraZeneca, BeiGene; and research funding from AbbVie and Takeda. MMar has received consulting fees from GILEAD. GMR has received payments or honoraria for lectures, presentations, speakers' bureau, manuscript writing or educational events from Astrazeneca, GILEAD, Janssen, Abbvie; has received support for attending meetings and/or travel from Janssen. IDG has received payments or honoraria for lectures, presentations, speakers' bureau, manuscript writing or educational events from Astrazeneca; has received support for attending meetings and/or travel from Roche, Janssen and Takeda; has sat on a Data Safety Monitoring Board or Advisory Board of Janssen; has held a leadership or fiduciary role in another board, society, committee or advocacy group, paid or unpaid of Fondazione Italiana Linfomi (FIL), Commissione studi biologici. RMu has received payments or honoraria for lectures, presentations, speakers' bureau, manuscript writing or educational events from Astrazeneca and Janssen; and has received support for attending meetings and/or travel from Abbvie, Astrazeneca and Janssen. RMa has received consulting fees from Abbvie and Jannsen; has received payments or honoraria for lectures, presentations, speakers' bureau, manuscript writing or educational events from Abbvie, Janssen and Astrazeneca; and has received support for attending meetings and/or travel from Abbvie and Astrazeneca. MT participated in an Advisory Board for Abbvie. PS has received grants or contracts from GILEAD, Novartis and Abbvie. AA has received payments or honoraria for lectures, presentations, speakers' bureau,manuscript writing or educational events from Janssen, Abbvie and Servier; and has received support for attending meetings and/or travel from Takeda and Janssen. AV has received support for attending meetings and/or travel from Abbvie, Janssen, and Beigene; and has sat on a Data Safety Monitoring Board or Advisory Board for Janssen, Abbvie, and Beigene. MV plays a consultant or advisory role or has participated in speakers' bureau for Amgen, Novartis, Mattioli srl, IQVIA and Dephaforum S.r.l. The other authors do not have any conflicts of interest to disclose.

Contributions

FRM, AC and RF developed the concept and design of the study, interpreted data and wrote the manuscript. MMes, VA, PF, MV, and AP managed the 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, RMa, RMu, LLa, FI, CS, DM, MMas, GMR, LS, MMar, LLe, MT, AA, GM, MD, PG, VBP, DG, AML, AG, MCM, DP, VM, AV, and CV managed patients and participated in the collection of clinical data. All authors critically revised the manuscript and reviewed and approved the final version.

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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 obtained from a.piciocchi@gimema.it.

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