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

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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

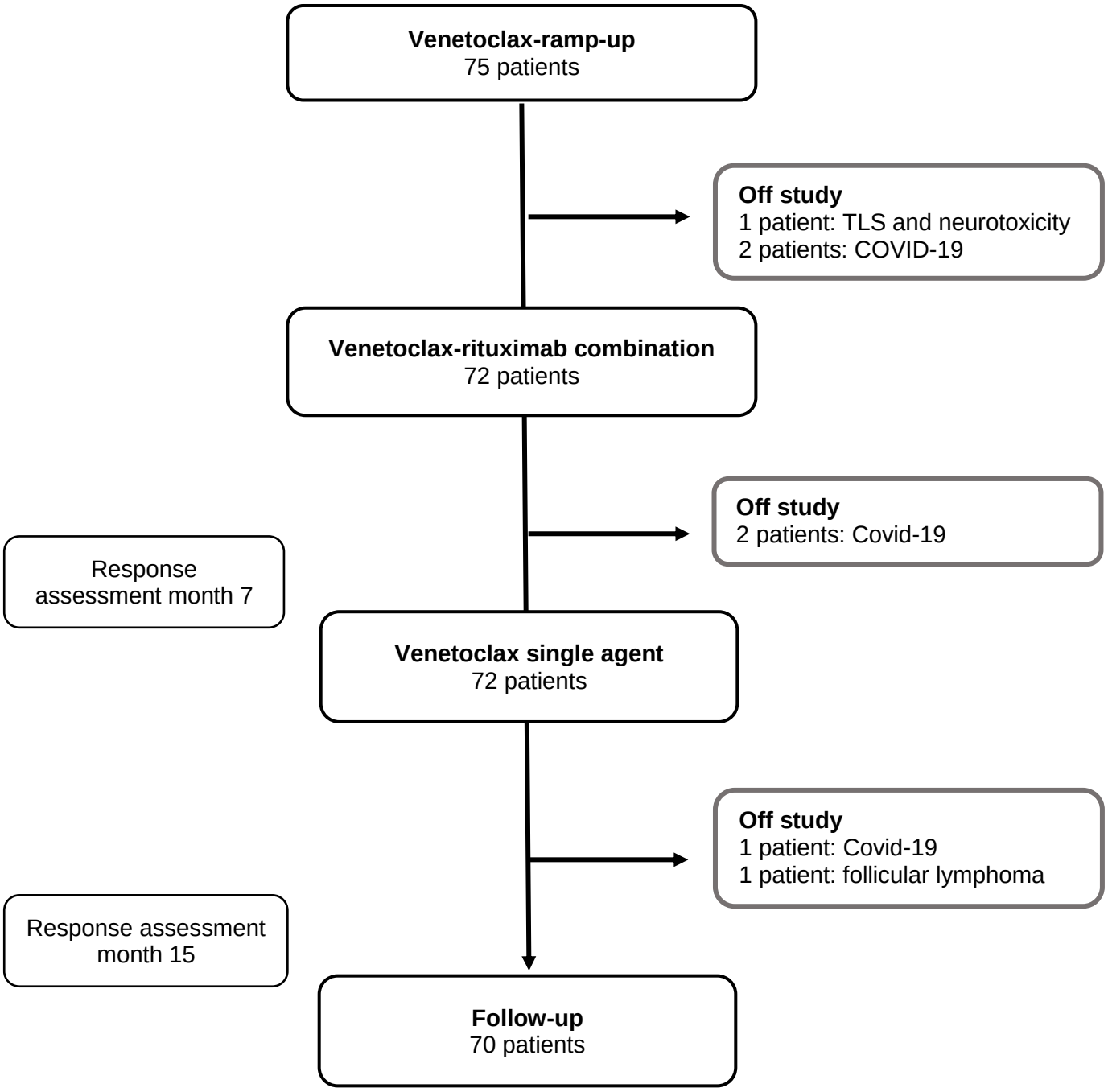
Patients' characteristics have been summarized using cross-tabulations for categorical variables or using quantiles for continuous variables. In univariate analysis, non-parametric tests were performed for comparisons between groups (Chi-Squared and Fisher Exact test in case of categorical variables 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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