Real-world treatment usage of Venetoclax-rituximab in relapsed/refractory Chronic Lymphocytic Leukemia patients in Belgium – results of the AREVEDECY study

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OBJECTIVE

The AREVEDECY study was a retrospective chart review, set up in Belgium, to assess the real-world effectiveness of Venetoclax-rituximab (VenR) in patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL). Here, we present the reported usage (dosing, interruptions, discontinuation) of Venetoclax (Ven) in the study

CONCLUSIONS

Data from 117 patients across 9 centres could be included in the AREVEDECY study. Patients were slightly older than those in the MURANO trial and 43.6% were previously treated with a Bruton's tyrosine kinase inhibitor (BTKi)

Despite being reimbursed as VenR, 29.9% of patients did not receive concomitant treatment with rituximab, mostly due to COVID-19-related reasons

In a Belgian real-world setting, 79.5% of the patients reached 400mg at the end of the ramp-up. Ven (alone or in combination with rituximab) dosing intensity was 328.5mg and almost 50% of patients completed the normal Ven treatment duration. Non-tumor lysis syndrome (TLS)-related adverse events were the most cited as trigger for dosing reductions, treatment interruptions or discontinuations

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REFERENCES: 1. Kater AP, Harrup TJ, et al. MURANO: Final 7 year follow up and retreatment analysis in venetoclax-rituximab (VenR)-treated patients with relapsed/refractory chronic lymphocytic leukemia (R/R CLL). Hemasphere. 2023 Aug; 7(Suppl): e492813f.

ABBREVIATIONS: 2L: Second Line; **3L:** third Line; **4L+:** Fourth Line or More; **AE :** Adverse Event; **BTKI:** Bruton Tyrosine Kinase Inhibitors; **CLL:** Chronic Lymphocytic Leukemia; **EC:** Ethics Committee; **LFUS :** Long Follow-up analysis Set; **ORR:** Overall Response Rate; **OS:** Overall Survival; **PD:** Progressive Disease; **PFS:** Progression-Free Survival; **R/R CLL:** Relapsed/Refractory Chronic Lymphocytic Leukemia; **SD:** Stable Disease; **SD:** Standard Deviation; **TLS:** Tumor Lysis Syndrome; **UNK :** unknown; **VEN:** Venetoclax; **VenR:** Venetoclax-Rituximab.

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INTRODUCTION

- Real-world evidence is becoming increasingly important, as it provides valuable insights into the effectiveness and safety of medical interventions in real-world settings
- The MURANO trial showed positive outcomes in terms of best overall response rate (ORR), overall survival (OS), and progression-free survival (PFS) in R/R CLL patients treated with VenR,[1] yet results in a real-world setting are still limited
- In Belgium, the AREVEDECY study was set up to assess the real-world effectiveness of VenR, which has been reimbursed since 1st of September 2019
- The presented data focus on the reported usage (dosing, interruptions, discontinuation) of Ven in the study

METHODS

- AREVEDECY was a retrospective chart review on data from R/R CLL patients initiated with VenR in the period September 2019-July 2023
- Analyses, including treatment interruption, reductions and discontinuations were descriptively documented
- Kaplan-Meier (KM) curves were used to represent OS and PFS time-to-event data and time to discontinuation
- Ven dose intensity corresponded to the mean actual daily dose over the Ven treatment period
- Most analyses were performed on the full analysis set (FAS)
- Patients in the FAS who had a potential follow-up period of at least 24 months + 5 weeks (765 days) constituted the Long Follow-up analysis Set (LFUS)

Inclusion and exclusion criteria

Patient aged ≥ 18 years old
Patient with confirmed R/R CLL according to iwCLL 2008 criteria and assessment of the treating physician
Patient receiving/having received VenR as per Belgian reimbursement criteria and has received at least one prior therapy and has never received a reimbursement for venetoclax as a monotherapy
Patient starting VenR between 1st September 2019 and EC approval
Patients with confirmed R/R CLL who are receiving Ven as per intended monotherapy, i.e. Ven without (planned) fixed treatment duration
Patients without any post-baseline assessment
Patient who should not receive Ven-R according to Belgian reimbursement criteria

RESULTS

Baseline characteristics

- 117 patients from 9 hospitals were included
- Baseline patient and treatment characteristics are presented in **Table 1**
- Mean (SD) follow-up time in the study was 19.2 (10.5) months

Table 1. Patient and treatment characteristics at baseline

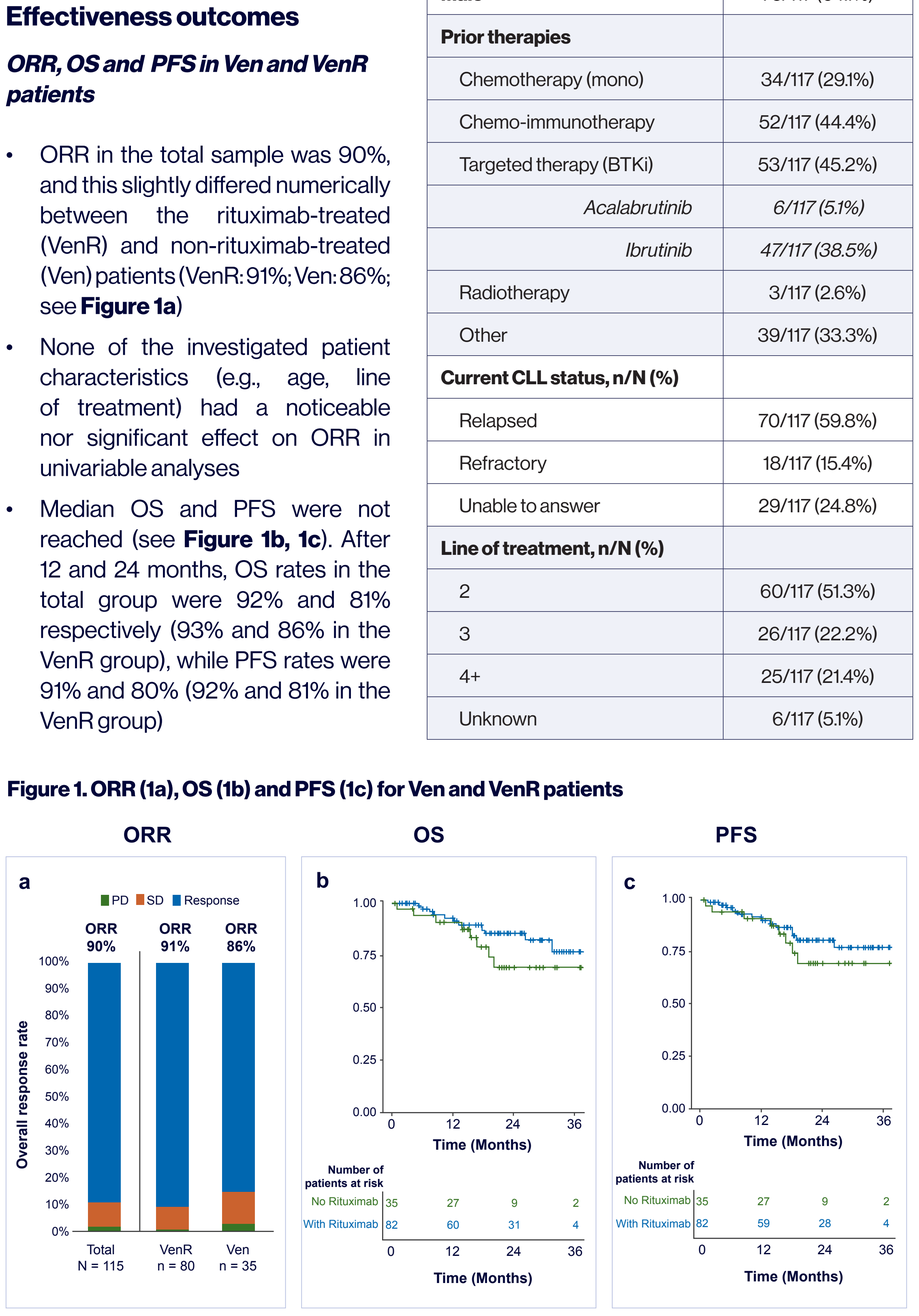
	Total, N = 117
Mean age at baseline (SD)	71.3 (10.1)
Mean age at CLL diagnosis (SD)	61.9 (11.0)
Male	75/117 (64.1%)
Prior therapies	
Chemotherapy (mono)	34/117 (29.1%)
Chemo-immunotherapy	52/117 (44.4%)
Targeted therapy (BTKi)	53/117 (45.2%)
Acalabrutinib	*6/117 (5.1%)*
Ibrutinib	*47/117 (38.5%)*
Radiotherapy	3/117 (2.6%)
Other	39/117 (33.3%)
Current CLL status, n/N (%)	
Relapsed	70/117 (59.8%)
Refractory	18/117 (15.4%)
Unable to answer	29/117 (24.8%)
Line of treatment, n/N (%)	
2	60/117 (51.3%)
3	26/117 (22.2%)
4+	25/117 (21.4%)
Unknown	6/117 (5.1%)

Effectiveness outcomes

ORR, OS and PFS in Ven and VenR patients

- ORR in the total sample was 90%, and this slightly differed numerically between the rituximab-treated (VenR) and non-rituximab-treated (Ven) patients (VenR: 91%; Ven: 86%; see **Figure 1a**)
- None of the investigated patient characteristics (e.g., age, line of treatment) had a noticeable nor significant effect on ORR in univariable analyses
- Median OS and PFS were not reached (see **Figure 1b, 1c**). After 12 and 24 months, OS rates in the total group were 92% and 81% respectively (93% and 86% in the VenR group), while PFS rates were 91% and 80% (92% and 81% in the VenR group)

Figure 1. ORR (1a), OS (1b) and PFS (1c) for Ven and VenR patients



Treatment characteristics

- 79% (N = 93) of the patients of the FAS reached the maximum 400 mg dose at the end of the ramp-up
- Fifty patients out of the FAS constituted the LFUS
- Of the LFUS patients (N = 50), 47% (95% CI 33%-62%) of the patients were reported to have completed the Ven-R treatment without progression up until 24 months+5weeks (Day 765)
- For those patients, part of the LFUS, the average time-on-treatment (without reported discontinuation or progression) was 20.13 months

Figure 2. Ven dosing and administration schedule (oral, 24 cycles)

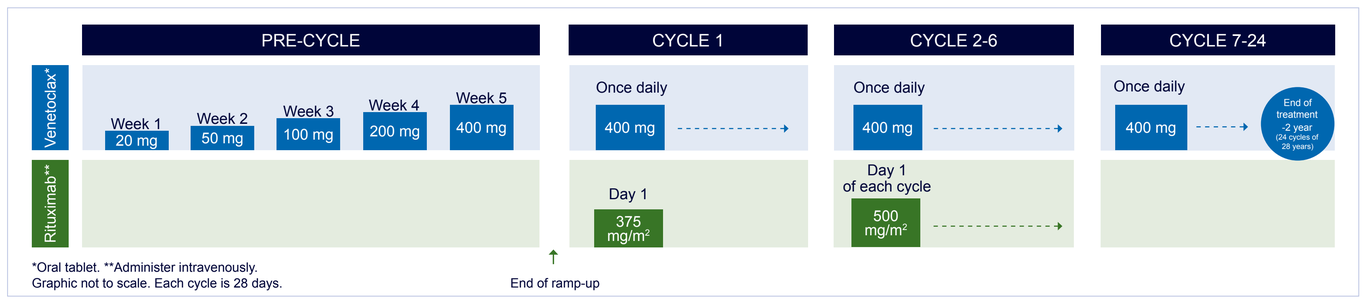


Figure 3. Maximum daily dose of Ven at the end of ramp-up

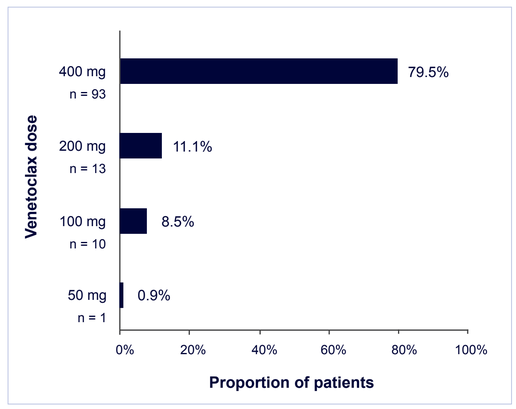


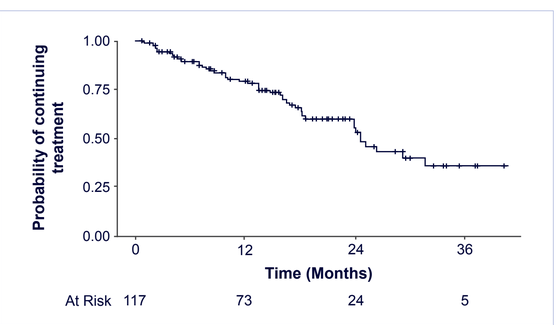
Table 2. Treatment interruptions, dose reductions & discontinuations during maintenance of Ven

Treatment interruptions	20/117 (17.1%)
Reasons for treatment interruption, n/N (%)	
AE - non TLS related	*12/20 (60%)*
AE - TLS related	*1/20 (5%)*
Tolerability	*5/20 (25%)*
UNK	*2/20 (10%)*
Median duration of interruption, days	**16 (IQR 7.8; 35 days)**
Mean duration of interruption, days (SD)	**72.3 (137.7)**
Dose reductions	**34/117 (29.1%)**
Treatment discontinuation	**46/117 (39%)**
Reasons for treatment discontinuation, n/N (%)	
AE - non TLS related	*22/46 (47.8%)*
AE - TLS related	*1/46 (2.2%)*
Progressive disease	*4/46 (8.7%)*
Other	*19/46 (41.3%)*
Median time-to-treatment discontinuation, months	**24.6**

Mean actual daily dose over treatment = 328.5 mg

- Twelve months after treatment start, 79% did not report yet discontinuation according to the KM estimate. After 18 months, this number dropped to 65%. The median time-to-treatment discontinuation was 24.6 months, suggesting around 50% of patients completed the normal Ven treatment duration (**Figure 4**)
- However, study results do seem to be under-documented in medical records and/or underreported in the study since the KM plot should drop to zero after 765 day-timepoint

Figure 4. Kaplan-Meier plot for time to treatment discontinuation in months



Adverse events leading to treatment interruptions and discontinuations

- Looking at treatment discontinuations, 22 patients (18.8%) stopped VenR/Ven-treatment due to adverse events of which 1 case was TLS-related
- Finally, 18 patients (15.4%) interrupted VenR/Ven-treatment due to adverse events of which 1 case was TLS-related