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Venetoclax retreatment after MRD-guided Venetoclax +/- Ibrutinib: the IMPROVE study cohort

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BACKGROUND AND OBJECTIVES:

- **Venetoclax** is an effective therapy for chronic lymphocytic leukemia (CLL) with the potential to induce **deep remissions**, especially when administered in **fixed-duration combinations**.
- Information on the efficacy and tolerability of venetoclax retreatment in **patients with CLL relapsing after venetoclax-based fixed-duration regimens** is limited. Data collected in small cohorts suggest that venetoclax retreatment **can be effective and well tolerated**, so it is important to analyze venetoclax retreatment in additional cohorts of well-characterized CLL patients.
- We analyzed the efficacy and safety of venetoclax retreatment in patients with relapsed/refractory CLL enrolled in our **clinical trial IMPROVE (NCT04754035).**

METHODS:

IMPROVE trial is a phase 2 multicenter Italian study where ibrutinib is added to venetoclax, based on a MRD-driven strategy.
BTK- and BCL2-inhibitor naïve pts enrolled into the study were treated **with venetoclax single-agent for 12 months**:

- *Patients with undetectable measurable residual disease (uMRD)* → stopped therapy
- *Patients with detectable MRD* → added ibrutinib and continued venetoclax until uMRD, toxicity or for up to 12 months
- *Patients with detectable MRD at the end the combination therapy* → stopped venetoclax and continued with ibrutinib only

In **patients who relapsed due to confirmed progression (PD), venetoclax was restarted** according to the standard schedule with an initial 5-week dose escalation ramp-up and continued until PD or unacceptable toxicity *(Figure 1)*.

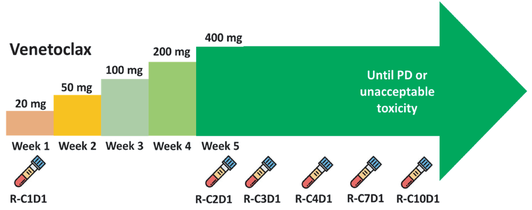

Figure 1. Dosing Schedule of Venetoclax and timepoints of MRD assessments

MRD was tested every 3 months in peripheral blood using the 8-color flow cytometry panel validated by ERIC *(Figure 2)*.

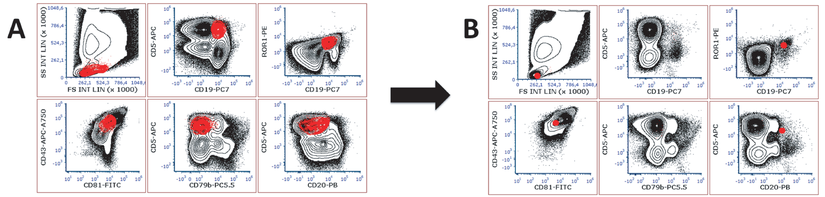

Figure 2. Flow cytometry contour plot analysis of MRD in patient responding to venetoclax reintroduction.
A. before treatment initiation and **B.** at Cycle 4 Day 1. The CLL cells (red lines) are typically CD5 positive, CD19 positive, ROR1 positive, CD43 positive, CD81 weak, CD79b weak, and CD20 weak.

RESULTS:

At the time of data-cut (10Feb2023), after a **median follow-up of 54 months** (5-62) from C1D1, **17/38 (44.5%)** patients experienced **PD** requiring treatment after discontinuing therapy, including:

- 16 upon reaching confirmed uMRD (9 treated with venetoclax single-agent, 8 with the combination of venetoclax + ibrutinib),
- 1 who discontinued both venetoclax and ibrutinib in response with detectable MRD due to an unrelated adverse event (AE).

Two out of 17 had Richter transformation (RT), 2 developed autoimmune hemolytic anemia, and all 4 went off study. The remaining **13 patients** (6 who previously achieved uMRD with venetoclax monotherapy, 6 uMRD who were treated with the combination of venetoclax and ibrutinib, 1 MRD+ discontinuing ibrutinib + venetoclax due to an intercurrent AE) received **venetoclax retreatment** at a median of 32 months (12-41) after the end of initial therapy (*Table 1*).

- ✓ 12 uMRD subjects out of 13 retreated patients experienced **MRD relapse at a median of 5 months** (0-41) after stopping treatment, **27 (0-37) months before disease progression requiring therapy**.
- ✓ Among those evaluable for response (n=10), **best overall response was partial response n=8 (80%), and 2 stable disease.**
- ✓ With a median time on treatment of 9.5 months, **2 pts achieved uMRD after 3 and 6 months**, the first one tested only once after starting retreatment, **the second one maintaining uMRD for 6 months** and then becoming MRD positive again (*Figure 3*).
- ✓ **Four out of 13 pts progressed after 7, 12 (n=2), and 14 months on VEN retreatment**, 3/4 received next-line treatment with ibrutinib and achieved a partial response.
- ✓ At last follow-up 11/13 patients undergoing venetoclax retreatment were alive (1 death due to RT on IBR, 1 due to CLL progression on non-covalent BTK inhibitor).
- ✓ Progression-free survival **(PFS) from venetoclax restart to PD on venetoclax retreatment**, last follow-up or death was **14 months** (0-23) (*Figure 4*).
- ✓ **Venetoclax retreatment** was very **well tolerated** (Table 2) with no patients experiencing TLS, 5/13 having grade 3-4 neutropenia, 3/13 infections (2 grade 3, 1 grade 2).

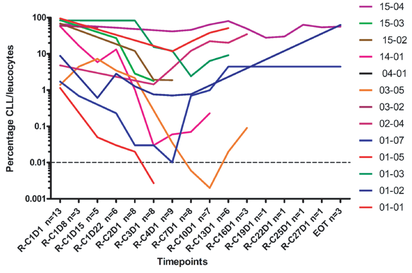

Figure 3. Measurable residual disease (MRD) kinetics in PB during venetoclax retreatment (n=13).

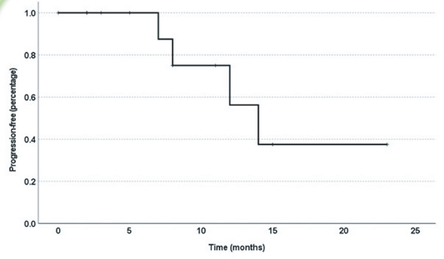

Figure 4. Median PFS on venetoclax retreatment (n=8).

Table 1. Baseline characteristics at baseline and at the time of venetoclax retreatment.

Characteristic	Venetoclax +/-ibrutinib (n=38)	Venetoclax retreatment (n=13)
Age at treatment initiation (median, range)	64 (47-81)	65 (51-82)
Male gender no./total (%)	25/38 (66)	8/13 (62)
Prior lines of therapy (median, range)	1 (1-7)	2 (1-7)
del(17p) no./total (%)	7/33 (21)	1/11 (9)
TP53 mutation no./total (%)	9/31 (29)	3/11 (27)
Unmutated IGHV no./total (%)	27/34 (79)	10/12 (83)
Venetoclax mono	-	6
Venetoclax + ibrutinib	-	7
TLS risk before venetoclax no./total (%)		
High	14/38 (37)	6
Medium	18/38 (47)	3
Low	6/38 (16)	4
Best overall response rate no./total (%)	36/38 (95)	8/10 (80)
Best PR	10/38 (26)	8 (80)
Best CR	26/38 (68)	0 (0)
Stable disease	0	2
PD	1	0

Table 2. Major adverse events during venetoclax retreatment.

Adverse event	Grade (all)	Grade 3-4
Tumor lysis syndrome	0	0
Neutropenia	9	5
Infections	3	2

CONCLUSIONS:

- ✓ **Venetoclax retreatment** was **effective** in patients previously exposed to venetoclax-based time-limited therapies. Nearly 80% of patients in our cohort achieved at least a partial response with venetoclax retreatment and 20% of patients achieved uMRD.
- ✓ **PFS from venetoclax restart to PD on venetoclax retreatment**, last follow-up or death was **14 months.**
- ✓ **MRD relapse after** time-limited treatment with **venetoclax +/- ibrutinib in patients with relapsed/refractory CLL** occurred at a median of **about 2 years** before **clinical progression** requiring treatment.
- ✓ **Venetoclax retreatment** was **well-tolerated** in our cohort of patients.

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