Clinical Outcomes with Venetoclax-Based Treatment in Patients with Chronic Lymphocytic Leukemia (CLL)

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BACKGROUND

- Venetoclax-based therapy is a standard of care for previously untreated (Fischer et al. *NEJM* 2019) and relapsed (Seymour et al. *NEJM* 2018) chronic lymphocytic leukemia (CLL).

STUDY AIM:

- Identify factors that impact outcomes of venetoclax for patients with CLL treated in routine practice at a tertiary center across the most frequently encountered disease scenarios:
  - First-line
  - Relapsed/BTKi-naïve
  - Relapsed/BTKi-exposed

METHODS

- Identified patients who received venetoclax therapy for CLL (between 4/2012–4/2023) from the Mayo Clinic CLL Database.
- Overall survival (OS) was analyzed as the time from venetoclax start until date of death or last known to be alive.
- Treatment-free survival (TFS) after venetoclax was defined as the time from venetoclax start until the earliest date of next treatment, or death.
- Kaplan-Meier was used to display OS and TFS. Multivariable Cox proportional hazards regression models were used to estimate associations of factors with time-to-event outcomes.
- Undetectable measurable residual disease (uMRD) was defined as <1 CLL cell per 10,000 leukocytes using 8-color flow cytometry on peripheral blood (PB) or bone marrow (BM).
- Complex karyotype (CK) was defined as ≥3 aberrations on CpG stimulated karyotype.

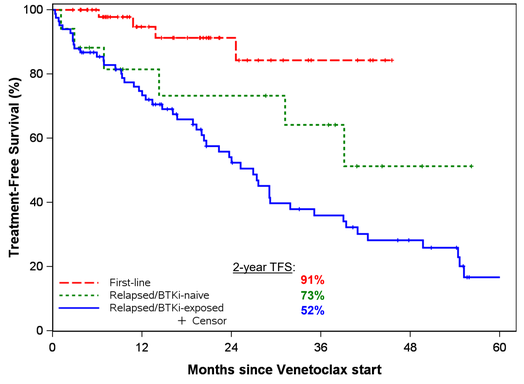
RESULTS

TABLE 1: Baseline characteristics at the time of venetoclax initiation

Parameter		Number (%) or Median [range]			
		All patients	Firstline	Relapsed/BTKi-naïve	Relapsed/BTKi-exposed
N		**155**	**55**	**17**	**83**
Age, years		66 [41-93]	65 [41-84]	67 [51-83]	68 [43-93]
Males		108 (70)	36 (66)	12 (71)	60 (72)
Prior lines of therapy		1 [0-11]	0	1 [1-6]	3 [1-11]
Combination with anti-CD20mAb	Rituximab	45 (29)	0 (0)	8 (47)	37 (45)
	Obinutuzumab	80 (52)	55 (100)	9 (53)	16 (19)
	None/Venetoclax Monotherapy	30 (19)	0 (0)	0 (0)	30 (36)
***IGHV* status*, n=129**	Unmutated	93 (72)	31 (61)	6 (43)	56 (88)
FISH*, n=134	None detected	20 (15)	11 (21)	4 (27)	5 (8)
	Other	5 (4)	0 (0)	0 (0)	5 (8)
	13q-	34 (25)	16 (30)	4 (27)	14 (21)
	Trisomy 12	23 (17)	11 (21)	2 (13)	10 (15)
	11q-	28 (21)	13 (25)	4 (27)	11 (17)
	17p-	24 (18)	2 (4)	1 (7)	21 (32)
Complex karyotype*, n=69	Complex (≥3 abnormalities)	27 (39)	3 (12)	3 (38)	21 (58)
***TP53* disruption*, n=136**	Present (Abnormal)	32 (24)	2 (4)	2 (13)	28 (41)

*Not available for all patients; missing data not shown

TREATMENT-FREE SURVIVAL



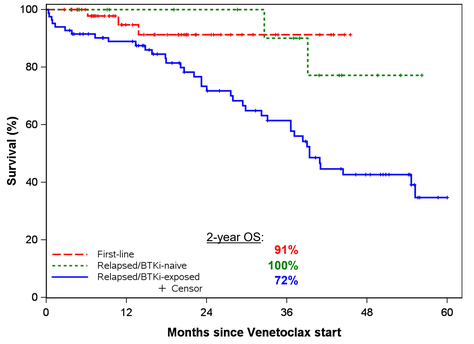
▶**Relapsed/BTKi-exposed (n=83)** median TFS with:

Prior disease progression on BTKi?
- Yes (n=55): **22.3 months**
- No (n=28): **42.3 months**

Anti-CD20 monoclonal antibody combination?
- Venetoclax monotherapy (n=30): **24.0 months**
- Venetoclax + rituximab (n=37): **26.9 months**
- Venetoclax + obinutuzumab (n=16): **39.0 months**

Prior receive of chemotherapy?
- Chemotherapy-naive (n=27): **29.1 months**
- Chemotherapy-exposed (n=56): **24.0 months**

OVERALL SURVIVAL



RISK FACTOR ANALYSES

Parameter	Cox Univariate HR (95% CI)	P-value
Treatment-Free Survival		
TP53 disruption	1.97 (1.07-3.61)	0.02
Unmutated *IGHV*	2.61 (1.10-6.19)	0.03
Older age at venetoclax start	1.03 (1.00-1.06)	0.03
Complex karyotype	5.26 (2.39-11.54)	<0.001
Disease progression on BTKi	3.26 (1.95-5.43)	<0.001
Overall Survival		
TP53 disruption	2.23 (1.14-3.37)	0.02
Older age at venetoclax start	1.03 (1.00-1.06)	0.04
Complex karyotype	4.76 (1.83-12.37)	0.001
Disease progression on BTKi	4.42 (2.30-8.49)	<0.001

Multivariable model (including only patients where all variables significant in the UVA were available):
- **TFS model** (n=53): only **CK** with HR 8.5 (2.5-29.1; P<0.001)
- **OS model** (n=65): only **CK** with HR 4.1 (1.2-14.0; P=0.03)

MRD ASSESSED IN LIMITED PATIENTS

	First-line	Relapse/BTKi-naïve	Relapsed/BTKi-exposed
Evaluated	**28**	**7**	**28**
uMRD	23 (82%)	7 (100%)	16 (57%)
PB only assessed	7	3	9
BM only assessed	2	2	2
PB & BM assessed	14	2	5
MRD+	3 (11%)	0	11 (39%)
Discordant	2 (7%)	0	1 (44%)
Median time to first uMRD	12.3 months	14.1 months	11.5 months

CONCLUSIONS

- In this study of CLL patients treated with a venetoclax-containing regimen in routine clinical practice, outcomes in the first-line and relapsed/BTKi-naïve settings were similar to those seen in published clinical trials (CLL14, MURANO).
- Patients with BTKi-exposed CLL, particularly those with prior disease progression on BTKi, had worse outcomes.
- Complex karyotype was an important baseline predictor of shorter treatment-free and overall survival in the total cohort.
  - **These findings support karyotype assessment for prognostication prior to venetoclax treatment.**
- The cohort size and retrospective design are limitations of this study.

FUTURE DIRECTIONS

- Validation of these findings in independent cohorts is required along with further evaluation of the impact of number of / specific chromosomal aberrations.
- Prospective study is required to determine an optimal venetoclax-based approach in the BTKi-refractory setting.

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