Sequencing Single Novel Agent-Based Therapy For Patients with CLL: A Retrospective Study of Patients Treated with Covalent Bruton Tyrosine Kinase Inhibitor (cBTKi) Followed by B-Cell Lymphoma 2 Inhibitor (BCL2i) versus BCL2i Followed by cBTKi

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DEFINITIONS

- **NA** Novel agent, e.g., cBTKi or BCL2i
- **NASeq** Novel agent sequence
  - **cBTKi → BCL2i**
  - **BCL2i → cBTKi**
- **TTNMD** Time to next mechanism of therapy or death

BACKGROUND

- NAs, including covalent Bruton tyrosine kinase inhibitors (cBTKi) and B-cell lymphoma 2 inhibitors (BCL2i) as monotherapies or in combination with anti-CD20 monoclonal antibodies (CD20mAb), are effective for the treatment of chronic lymphocytic leukemia (CLL) in both the frontline (1L) and relapsed/refractory (R/R) settings.
- Sequential single NA-based therapies allow for durable disease control in many patients with CLL, though whether cBTKi followed by BCL2i (**cBTKi → BCL2i**) or BCL2i followed by cBTKi (**BCL2i → cBTKi**) leads to a longer duration of disease control remains unknown.

METHODS

Single-center retrospective study

Inclusion Criteria:

- Received care at Mayo Clinic for CLL between 1/1/2012 and 4/1/2025
- Received sequential single NA-based therapies : cBTKi and BCL2i (+/- CD20mAB)
  - Administered first NA in 1L or R/R setting

Exclusion Criteria:

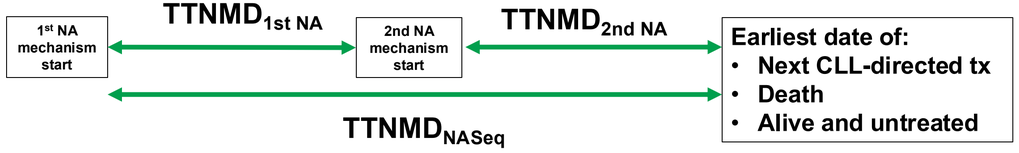
- Received a CLL-directed NA prior to NASeq
- Treated with at least one of the NAs in NASeq for Richter transformation
- Received any other CLL-directed therapy between the NAs in the sequence

Data Collection:

- Clinical and disease characteristics at first NA initiation
- Prior treatment history
- Duration of each single NA therapy and reasons for therapy discontinuation
- For patients who discontinued therapy due to intolerance or completion of planned therapy and subsequently received treatment within the same class of NA:
  - Entire duration of treatment with NA with the same mechansims and treatment-free observation were included in TTNMTD
  - Allowed for capturing the entire duration of disease control from each NA mechanism

Statistical Approach:

- Kaplan-Meier method used to estimate TTNMD and overall survival (OS)
- Multivariable Cox models used for outcome analysis with results reported as hazard ratios (HR) and 95% confidence intervals (95% CI)



PRIMARY OBJECTIVE

Compare $TTNMD_{NASeq}$ between cBTKi → BCL2i and BCL2i → cBTKi to determine which treatment sequence allowed for more durable disease control.

RESULTS

TABLE: Characteristics at Initiation of First NA in Sequence

	BCL2i → cBTKi (N=19)	cBTKi → BCL2i (N=149)	
	N with data n (%)	N with data n (%)	p value
Age at treatment initiation, median [range]	70.1 [37.0 – 85.6]	64.3 [39.5 – 85.9]	0.051
Sex	19	149	0.663
Female	6 (32)	40 (27)	
Male	13 (68)	109 (73)	
Rai Stage	14	112	0.712
0	2 (14)	15 (13)	
I / II	4 (29)	48 (43)	
III / IV	8 (57)	49 (44)	
IGHV Mutation Status	14	110	0.260
Mutated	4 (29)	18 (16)	
Unmutated	10 (71)	92 (84)	
FISH Results	13	95	0.478
Del(13q)	1 (8)	29 (31)	
Tri(12)	2 (15)	12 (13)	
Del(11q)	3 (23)	16 (17)	
Del(17p)	5 (39)	25 (26)	
Other	1 (8)	2 (2)	
Normal	1 (8)	11 (12)	
Complex Karyotype	6	20	0.105
No	2 (33)	14 (70)	
Yes	4 (67)	6 (30)	
TP53 Aberrant	15	108	0.599
No	10 (67)	79 (73)	
Yes	5 (33)	29 (27)	
Line of Therapy	19	149	0.364
First NA in R/R setting	14 (74)	94 (63)	
First NA in 1L setting	5 (26)	55 (37)	
Prior chemotherapy	19	149	0.370
No	11 (58)	70 (47)	
Yes	8 (42)	79 (53)	

FIGURE 1: TTNMD for A. First NA in the sequence; B. Second NA in the sequence

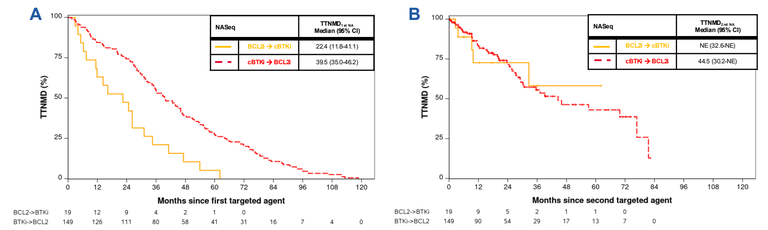
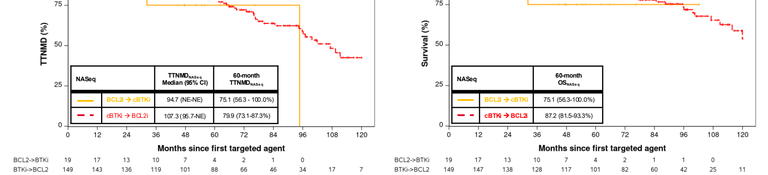


FIGURE 2: A. $TTNMD_{NASeq}$ by cohort; B. Overall survival by cohort



- There was no significant difference in $TTNMD_{NASeq}$ for patients treated with **cBTKi → BCL2i** vs **BCL2i → cBTKi** (HR 1.61, 95% CI 0.54, 4.81) after adjusting for TP53 aberration, prior chemoimmunotherapy exposure, and age.
- TP53 aberration was associated with inferior $TTNMD_{NASeq}$, regardless of NA treatment sequence (HR 3.15, 95% CI 1.64, 6.08).

CONCLUSIONS

- For patients who received sequential NA, either **cBTKi → BCL2i** or **BCL2i → cBTKi**, the overall duration of disease control achieved with these two classes was **not significantly different**.
- Future multicenter collaborations may allow for more power to observe differences between these NA sequences.
- These data support **basing treatment decisions on patient preference and comorbidities** for patients with CLL when selecting between cBTKi and BCL2i as the first NA-based therapy.