CLL-471

Real-World Comparative Outcomes of First-Line (1L) Venetoclax + Obinutuzumab (VenO) versus Covalent Bruton's Tyrosine Kinase Inhibitors (BTKis) ± Anti-CD20 Therapy Among Patients with Chronic Lymphocytic Leukemia (CLL) in the United States (US)

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Summary

This was a real-world study using data from a de-identified database, comparing outcomes, including **time to next treatment or death (TTNT-D)**, in patients receiving 1L treatment for CLL

1L **VenO** was associated with a **significantly longer TTNT-D** versus 1L covalent BTKis (cBTKis)

Although real-world treatment patterns may differ, patients receiving fixed-duration **VenO may experience the benefit of time off treatment** until progression, while those on cBTKis ± anti-CD20 therapy receive treatment continuously, according to their respective Food & Drug Administration (FDA) labels

For patients receiving VenO versus cBTKis + anti-CD20, **median TTNT-D was not reached** for either treatment, and this difference was not significant

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Background

- Currently, there are limited data comparing the outcomes between continuous cBTKis, such as ibrutinib and acalabrutinib, with or without anti-CD20 therapy, and fixed-duration therapy with B-cell lymphoma 2 inhibitors, such as VenO, in patients with CLL in the 1L setting.[1] The highly anticipated results from the ongoing CLL17 trial (NCT04608318) may inform us on survival outcomes of iburitinib monotherapy versus VenO and ibrutinib plus venetoclax.
- This was a real-world study using data from the Flatiron Health database to assess comparative outcomes in patients with 1L CLL, specifically TTNT-D.
- A secondary outcomes analysis was conducted (time to next alternative regimen) to account for patients switching from a 1L cBTKi to an alternative cBTKi for treatment in the second-line (2L) setting
  - **Rationale for secondary outcomes analysis**: As the treatment landscape for cBTKis has evolved from first-generation cBTKis, such as ibrutinib, to second-generation cBTKis, such as acalabrutinib, patients who discontinue cBTKis for reasons such as toxicity, rather than disease progression, may switch to an alternative cBTKi treatment.[2–4]

Methods

Study design and data source

- This was a retrospective, observational study conducted using the nationwide Flatiron Health electronic health record-derived database – a longitudinal database, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction,[5,6] originating from ~280 US cancer clinics (~800 sites of care); the majority of patients in the database originated from community oncology settings.
- Patients with CLL/small lymphocytic lymphoma (SLL), who initiated VenO, cBTKi, or cBTKi + anti-CD20 regimens (acalabrutinib/ibrutinib + obinutuzumab or ibrutinib + rituximab) in the 1L setting between January 2019 and December 2021 were included; patients were followed-up until August 2023.
- Patient attrition and study eligibility criteria are described in **Table 1**.

Table 1. Patient attrition and eligibility criteria.

	Total number of patients	Percentage of previous step
Included in the Flatiron Health database for CLL (August 2023)	17,160	–
Diagnosed with CLL/SLL between January 1, 2016 and December 31, 2021	5,104	30
Initiated 1L treatment between January 1, 2019 and December 31, 2021	2,697	53
Aged ≥18 years at index (defined as the date of first treatment)	2,697	100
Had ≥1 visit within 90 days of CLL diagnosis	2,294	85
Did not participate in a clinical trial in any LOT	2,212	96
Received VenO, cBTKis, or cBTKis + anti-CD20 therapy as 1L CLL treatment	1,477	67
Did not have a documented LOT switch to the same cBTKis ± anti-CD20 therapy	1,471	100
1L treatment aligned with FDA approval dates	1,418	96
Did not receive the same cBTKi for 1L and 2L treatment	1,417	100
Did not receive 2L treatment for non-CLL diagnosis	1,373	97

LOT, line of therapy.

Study outcomes

- The primary outcome was TTNT-D, defined as the time from index date of initiation with 1L treatment until the start of subsequent treatment (regardless of reason) or death.
- The secondary outcome was time to next alternative regimen, defined as:
  - Time from date of initiation with 1L cBTKi until the start of subsequent treatment that was not a cBTKi (different mechanism of action) or death (patients that received a cBTKi as 1L treatment and were then treated with a different cBTKi for 2L therapy were not included as an event)
  - Time from date of initiation with 1L VenO until the start of subsequent treatment or death (no change from TTNT-D).

Statistical analysis

- Patient characteristics and treatment patterns were reported using descriptive statistics.
- Propensity score matching was performed 2:1 for cBTKis (ibrutinib or acalabrutinib) to VenO, and 1:1 for cBTKis + anti-CD20 therapy to VenO
  - Exact matching variables included age category, sex, and race
  - Nearest neighbor matching variables included practice type, payer category, and socioeconomic status (SES) index.
- To account for potential bias due to residual covariate imbalance between treatment groups, an additional multivariable adjusted Cox proportional hazards model was applied post-matching; some variable categories were combined due to the small sample size to avoid non-convergence in the model.
- A time-to-event analysis was carried out using the Kaplan-Meier methodology.
- For patients with no recorded next LOT or death date, the censor date was the date of the last confirmed activity.

Results

- A total of 1,373 patients met the study eligibility criteria (**Table 2**).

Table 2. Regimens for first LOT.

n (%)	n=1,373
VenO*	232 (17)
cBTKi	1,001 (73)
Acalabrutinib	225 (16)
Ibrutinib	776 (57)
cBTKi + anti-CD20 therapy†	140 (10)
Acalabrutinib + obinutuzumab	64 (5)
Ibrutinib + obinutuzumab	29 (2)
Ibrutinib + rituximab	47 (3)

*Obinutuzumab was initiated within 35 days of index venetoclax; †Anti-CD20 therapy (obinutuzumab or rituximab) was initiated within 90 days of index cBTKi.

- A total of 438 patients receiving cBTKis as monotherapy were matched 2:1 to 219 patients receiving VenO
  - The majority of patients (77%; n=338) received ibrutinib, while the remainder of patients (23%; n=100) received acalabrutinib.
- A total of 120 patients receiving cBTKis + anti-CD20 therapy were matched 1:1 to 120 patients receiving VenO
  - Regimens included acalabrutinib + obinutuzumab (48%; n=58), ibrutinib + obinutuzumab (22%; n=26), and ibrutinib + rituximab (30%; n=36).
- Baseline demographics and clinical characteristics are shown in **Table 3**; mean age across the full study cohort was 68 years (standard deviation [SD]): 10).

Table 3. Baseline patient demographics and clinical characteristics.

	cBTKi monotherapy versus VenO (2:1)			cBTKi + anti-CD20 therapy versus VenO (1:1)		
	cBTKi (n=438)	VenO (n=219)	SMD	cBTKi + anti-CD20 (n=120)	VenO (n=120)	SMD
Age category (years), n (%)						
<54	42 (9)	21 (9)		13 (11)	13 (11)	
55–64	122 (28)	61 (28)	–	29 (24)	29 (24)	–
65–74	180 (41)	90 (41)		43 (36)	43 (36)	
75+	94 (21)	47 (21)		35 (29)	35 (29)	
Gender, n (%)						
Female	120 (27)	60 (27)	–	38 (32)	38 (32)	–
Male	318 (73)	159 (73)		82 (68)	82 (68)	
Race/ethnicity, n (%)						
White	274 (63)	137 (63)	–	62 (52)	62 (52)	–
Black	24 (6)	12 (6)		10 (8)	10 (8)	
Other*/Missing	140 (32)	70 (32)		48 (41)	48 (41)	
Practice type, n (%)						
Academic	68 (16)	27 (12)	–	9 (8)	9 (7)	–
Community	370 (84)	192 (88)		111 (92)	111 (93)	
Insurance at 1L initiation, n (%)						
Commercial	138 (32)	60 (27)	0.09	46 (38)	37 (31)	0.16
Medicare/Medicaid	180 (41)	76 (35)	0.13/0.03	35 (29)	43 (36)	0.13/0.10
Patient Assistance Program	9 (2)	35 (16)	0.38	6 (5)	12 (10)	0.19
Other	21 (5)	11 (5)	0.01	6 (5)	5 (4)	0.04
Missing	89 (20)	37 (17)	0.10	27 (22)	23 (19)	0.08
Region, n (%)						
Midwest	63 (14)	51 (23)		15 (12)	36 (30)	
Northeast	66 (15)	34 (16)		19 (16)	16 (13)	
South	172 (39)	80 (37)	–	54 (45)	47 (39)	–
West	63 (14)	23 (11)		22 (18)	11 (9)	
Unknown	74 (17)	31 (14)		10 (8)	10 (8)	
SES						
1 (lowest)	37 (8)	19 (9)	0.05	14 (12)	18 (15)	0.10
2	71 (16)	33 (15)	0.04	15 (12)	20 (17)	0.12
3	78 (18)	37 (17)	0.08	27 (22)	27 (22)	0.00
4	85 (19)	52 (24)	0.13	24 (20)	22 (18)	0.04
5 (highest)	126 (29)	59 (27)	0.04	32 (27)	25 (21)	0.13
Missing	41 (9)	19 (9)	0.02	8 (7)	8 (7)	0.00
Tested for IGHV mutation†	197 (45)	133 (61)	–	50 (42)	70 (58)	–
Unmutated IGHV†‡	118 (60)	75 (56)	–	23 (46)	43 (61)	–
Tested for 17p deletion†	325 (74)	179 (82)	–	92 (77)	99 (82)	–
Positive for 17p deletion†‡	41 (13)	20 (11)	–	16 (17)	12 (12)	–
Follow-up (years), mean (SD)	2.5 (1)	2.2 (1)	–	2.1 (1)	2.1 (1)	–

*Including Hispanic; †Cytogenetic testing was not included in the matched or adjusted analysis as testing was not performed for all patients; ‡Percentages calculated were among patients who underwent cytogenetic testing.
SMD, standardized mean difference.

Results

VenO versus cBTKis

- In the primary analysis, TTNT-D was significantly longer for patients receiving VenO versus cBTKis (**Figure 1**)
  - Median TTNT-D was not reached with VenO versus 48.8 months with cBTKis; this difference was statistically significant in the matched comparisons (p=0.0042)
  - After further adjustment for residual covariate imbalance across treatment groups from the matched comparisons, this difference remained significant with an adjusted hazard ratio (aHR) of 0.63 (95% confidence interval [CI]: 0.45–0.88; p=0.007).
- In the secondary analysis, time to next alternative regimen was significantly longer for VenO compared with cBTKis for the matched comparison, but this difference was not statistically significant after further adjustments (**Figure 2**)
  - Median time to next alternative regimen was not reached with VenO versus 49.3 months with cBTKis (p=0.044)
  - After further adjustment for residual covariate imbalance across treatment groups from the matched comparisons, this difference did not remain significant (aHR: 0.72 [95% CI: 0.52–1.01]; p=0.057).

Figure 1. TTNT-D with VenO versus cBTKis.

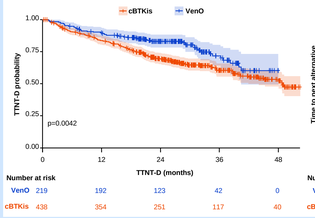
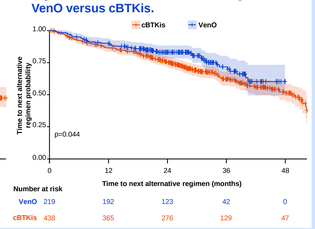


Figure 2. Time to next alternative regimen with VenO versus cBTKis.



VenO versus cBTKi + anti-CD20 therapy

- In the primary analysis, median TTNT-D was not significantly different between patients receiving VenO and cBTKis + anti-CD20 (**Figure 3**)
  - Median TTNT-D for VenO and cBTKi + anti-CD20 was not reached in the matched comparisons for either treatment (p=0.39)
  - After further adjustment for residual covariate imbalance across treatment groups from the matched comparisons, this difference remained non-significant (aHR: 0.80 [95% CI: 0.51–1.26]; p=0.30).
- In the secondary analysis, time to next alternative regimen was not significantly different between patients receiving VenO and cBTKis + anti-CD20 (**Figure 4**)
  - Median TTNT-D for VenO and cBTKi + anti-CD20 was not reached in the matched comparisons for either treatment (p=0.69)
  - After further adjustment for residual covariate imbalance across treatment groups from the matched comparisons, this difference remained non-significant (aHR: 0.88 [95% CI: 0.55–1.40]; p=0.60).

Figure 3. TTNT-D with VenO versus cBTKis + anti-CD20.

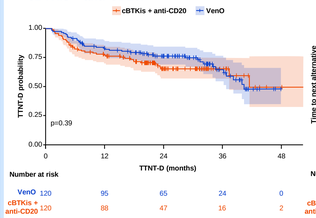
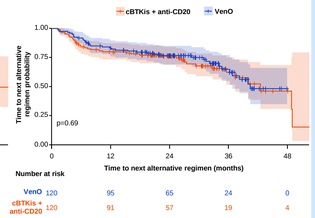


Figure 4. Time to next alternative regimen with VenO versus cBTKis + anti-CD20.



Conclusions

- 1L VenO was associated with a significantly longer TTNT-D versus 1L cBTKis; these differences were also observed with time to next alternative regimen, which is a more conservative approach to analyzing TTNT-D to account for treatment switches among the same drug class (e.g. ibrutinib to acalabrutinib)
  - While reasons for discontinuing cBTKis were not available in this database, prior studies have shown that patients may switch between cBTKis due to reasons such as toxicity.[2–4]
- Median TTNT-D was not reached between VenO and cBTKis + anti-CD20
  - While duration of treatment could not be confirmed in this database and real-world treatment patterns may differ, VenO is prescribed for ~12 months (12 cycles), which may allow patients to experience the benefit of time off treatment until progression, while cBTKis + anti-CD20 are prescribed as continuous treatments, according to their respective FDA labels.[7–9]

Presented at the 12th Annual Meeting of theSociety of Hematologic Oncology (SOHO 2024) | September 4–7, 2024

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Acknowledgments
This study was sponsored by Genentech, Inc. and AbbVie, Inc. Third-party editorial assistance, under the direction of Sophia Li, was provided by Vanessa Poon, MRes of Ashfield MedComms, an Inizio company, and was funded by Genentech, Inc., South San Francisco, CA, USA. The authors would like to thank Achal Patel for his assistance in providing technical review of this study and poster.

Disclosures
SL: current employment (Genentech, Inc.); stock ownership (Genentech, Inc.). **AR:** employee at the time of study (Genentech, Inc.); stock ownership (Genentech, Inc.). **RS:** current employment (Genentech, Inc.); stock ownership (Genentech, Inc., Medtronic); travel, accommodation, expenses (Roche/Genentech); **MS:** current employment (Genentech, Inc.); ended employment in the past 24 months (AstraZeneca); **MT:** consultancy (BeiGene, LOXO Oncology at Lilly, AstraZeneca, Janssen/Pharmacyclics, AbbVie, Inc., and Genentech, Inc.); honoraria: PeerView Medical Institute, MJH Life Sciences, Intellisphere LLC, DAVA Oncology, Phillips Group Oncology Communications, Brazilian Association of Hematology, Hemotherapy and Cellular Therapy, Massachusetts Medical Society, Curio Science, VJHemOnc, and Mashup Media); travel support for investigator meeting (Kura Therapeutics, Genmab, and DAVA Oncology).