RWD128

Treatment Sequencing and Line-of-Therapy Patterns in the BTKi Era: Real-World Evidence from 24,410 Chronic Lymphocytic Leukemia (CLL) Patients Using NorstellaLinQ Electronic Health Records (EHR) and Claims

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Background

BTKi-based therapy has become the dominant first-line treatment for CLL,[2] yet real-world sequencing patterns across lines of therapy, including switching, rechallenging, and regimen diversity in later lines, remain poorly characterized at population scale. Understanding these patterns is essential for contextualizing treatment decisions and for evaluating the real-world role of emerging therapies as options expand.

NorstellaLinQ[6] links open claims, structured EHR, and human-in-the-loop LLM-extracted clinical notes, enabling LoT-level characterization including biomarker-stratified sequencing not achievable from structured data alone.

Objective

To characterize treatment sequencing transitions, regimen utilization across lines of therapy, BTKi rechallenging and switching patterns, and line-level treatment duration among patients with Chronic Lymphocytic Leukemia (CLL) using a large real-world linked dataset.

Methods

Data Sources	NorstellaLinQ: linked open claims (from 2017), structured EHR (from 2015), and human-in-the-loop LLM-extracted clinical notes. 50M+ US patients | 600+ hospitals | 36B+ clinical transactions. Data sources applied: Open Claims, Closed Claims, Structured EHR, Unstructured EHR.
Study Design	Retrospective descriptive cohort study. Study period: January 2019 to September 2025. Index date: date of incident CLL diagnosis.
Population	Incident CLL: ≥2 ICD-10-CM codes C83.0 or C91.1, ≥30 days apart, on or after January 1, 2019, with no prior CLL diagnosis in the full available data history (minimum 2-year lookback to confirm incident status). 204,756 incident CLL patients were identified. Patients initiating systemic treatment were included. 24,410 patients form the analytical cohort: those with sufficient claims data to complete line-of-therapy (LoT) assignment under NorstellaLinQ business rules. This is not all treated CLL patients; patients without adequate claims capture are excluded.
Line of Therapy Assignment	LoT construction applies a standardized four-step process: • Step 1. Claims/Encounters: raw drug claim records per patient (drug name, start/end date). • Step 2. Episodes: claims for same patient/drug stitched when overlapping or within 42 days; episodes <30 days removed. • Step 3. Regimens: concurrent episodes grouped into one regimen; subset regimens <30 days merged iteratively. • Step 4. Lines of Therapy: adjacent regimens merged (max gap 120 days) when identical, current is subset of previous, or previous is subset of current (<30 days). First-line priority: (1) first regimen after advanced/metastatic drug or 30d before metastatic Dx; (2) ≥60d after primary surgery; (3) ≥120d after Dx index.
Outcomes	Regimen utilization and average duration by line (LoT1–LoT4) | Most common sequencing transitions from LoT1 to LoT2 | BTKi switching and rechallenge rates | Regimen diversity across lines | Sequencing patterns stratified by biomarker status (TP53 mutation, del(17p)) via LLM extraction. All outcomes descriptively assessed.

Results

204,756 patients
Incident CLL patients identified
(2019-2025)

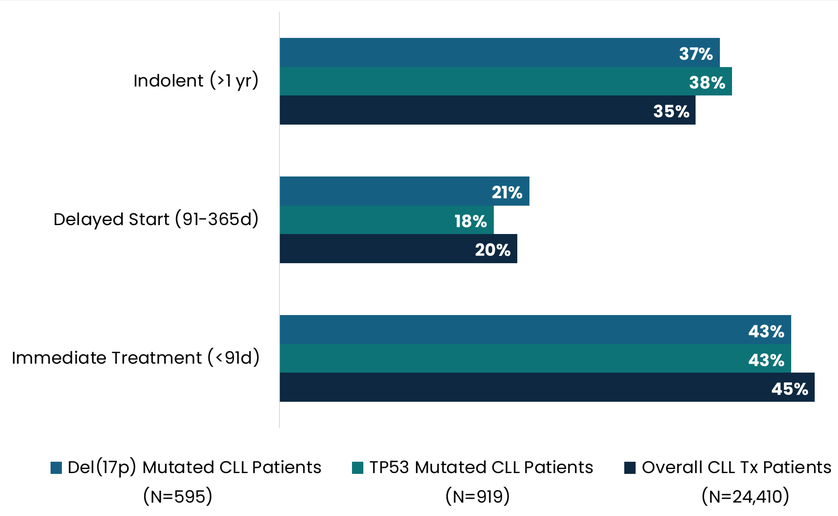
24,410 patients
Initiating systemic treatment
(LoT-eligible cohort)

41%
Of treated CLL patients initiate treatment on a BTKi monotherapy

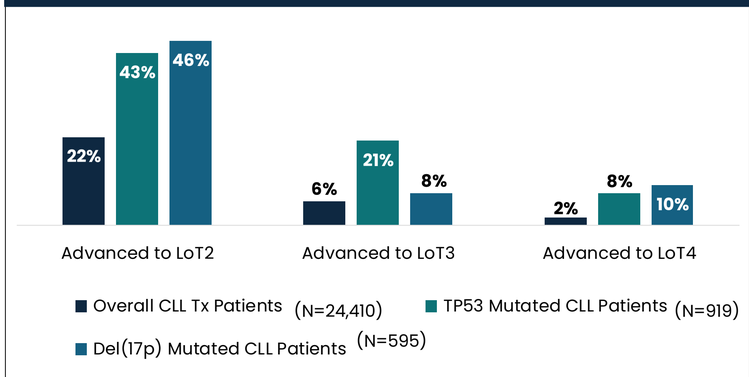
Baseline Demographics at Incident CLL Diagnosis

Metric		Overall CLL Population	TP53 Mutated CLL Population	Del(17p) Mutated CLL Population
N-Size		204,756	1,741	993
Gender	Male	58%	61%	62%
	Female	42%	39%	38%
Race	White	85%	92%	91%
	Black	7%	6%	6%
	Hispanic	5%	1%	1%
	Asian	3%	1%	2%
Age	>51	5%	6%	5%
	51-60	12%	15%	16%
	61-70	29%	32%	30%
	71-80	35%	33%	34%
	81+	19%	14%	15%

Time to First-Line Treatment Initiation by Biomarker Status

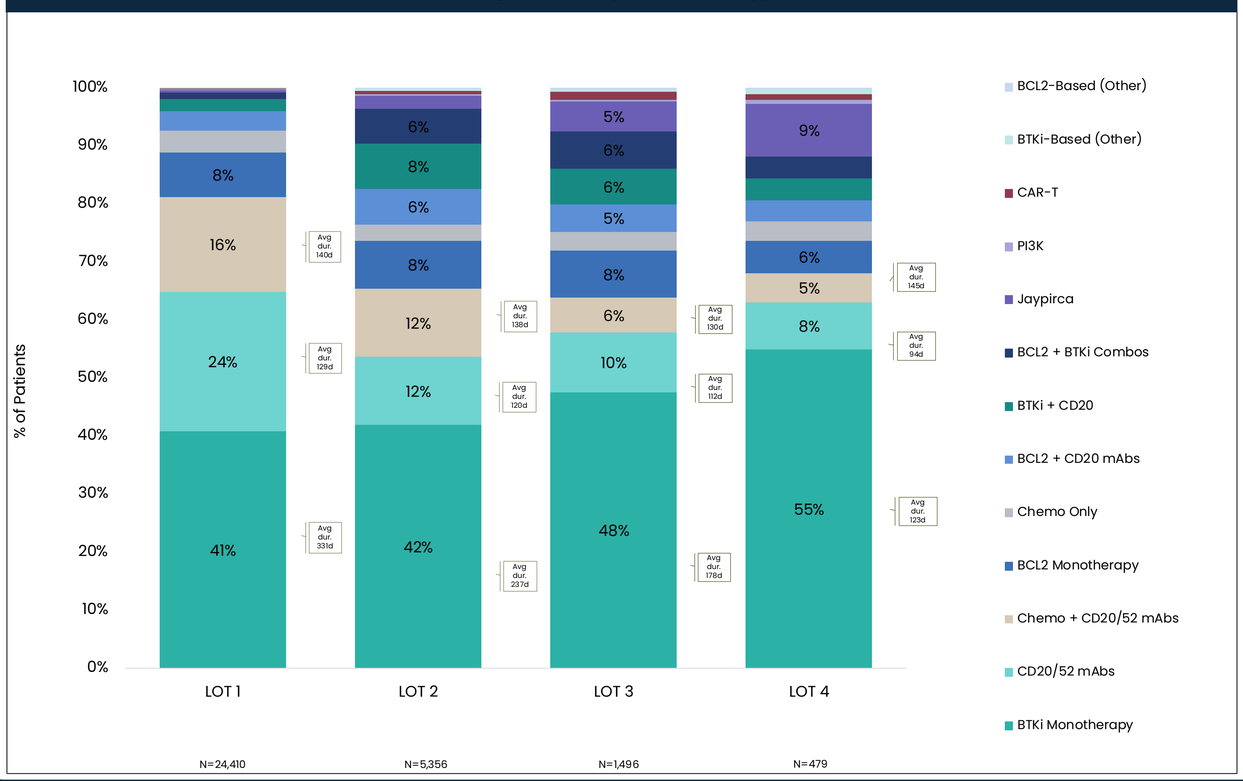


Line Advancement Rate by Biomarker Status

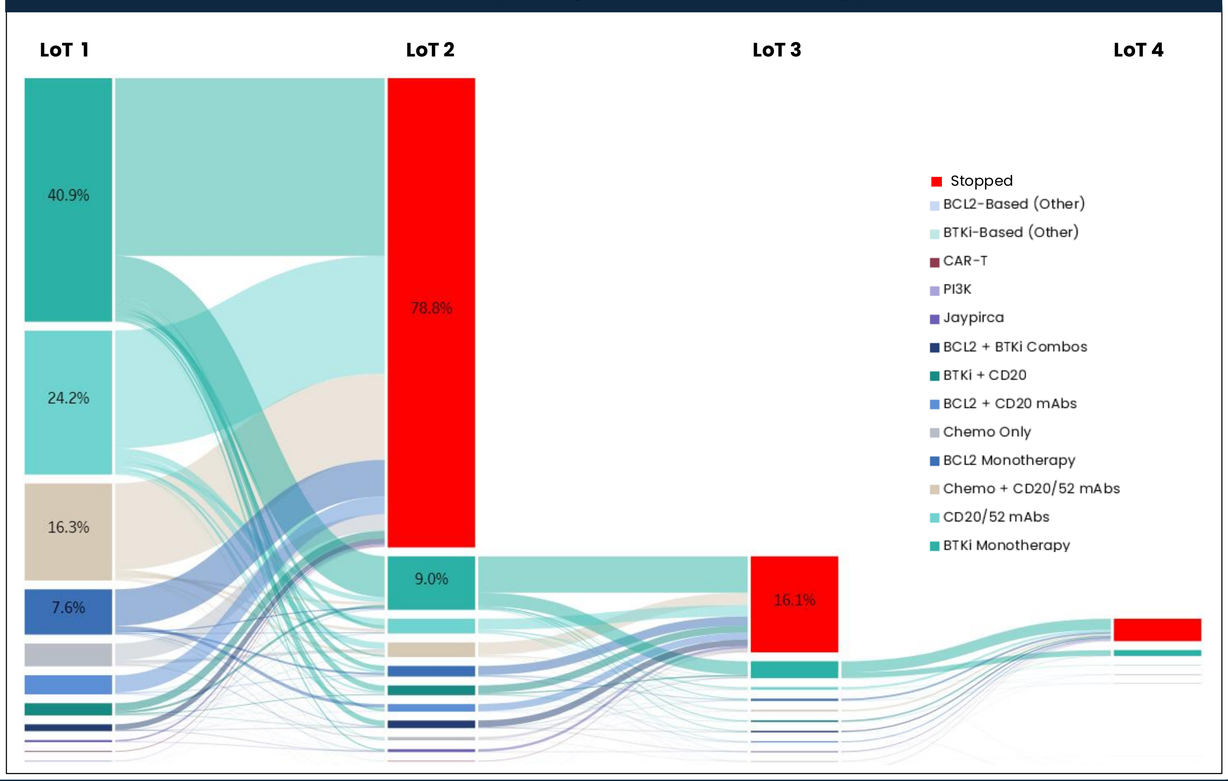


High-risk biomarker patients advance to later lines at dramatically higher rates than the overall cohort: del(17p)+ patients are the most aggressive (46% reach LoT2, 23% LoT3, 10% LoT4), followed by TP53+ (43% / 21% / 8%), versus overall (22% / 6% / 2%). This nearly 2–5x higher escalation rate validates LLM-extracted biomarker status as a clinically meaningful stratifier for predicting treatment intensity and sequencing complexity.[6]

Regimen Mix by Line of Therapy



Treatment Sequencing Flow Across Lines of Therapy



Conclusion

1. BTKi-based therapy remains the predominant treatment approach across all lines of therapy in real-world CLL practice. First-line management is relatively homogeneous (BTKi monotherapy dominant, 331-day average duration), but the treated population narrows substantially across lines (24,410 → 5,356 → 1,496 → 479), with 79.5% of patients never advancing beyond LoT1.[2]
2. Later-line treatment demonstrates increasing regimen diversity: BTKi-to-BCL-2 switching is the most common LoT2 transition, followed by within-class BTKi cycling. Regimen heterogeneity increases further in LoT3+, encompassing non-covalent BTKi (including pirtobrutinib), PI3K inhibitors, and cellular therapies, reflecting escalating therapeutic complexity.[1]
3. Among patients with LLM-extracted TP53 mutation or del(17p), earlier treatment initiation (43% within 90 days) and higher rates of later-line escalation were observed, highlighting the clinical utility of note-derived biomarker data for characterizing high-risk sequencing behavior in real-world CLL populations.[6]

Key Limitations

1.N=24,410 represents patients meeting LoT assignment criteria; this is not all treated CLL patients.
2.Regimen durations are algorithmic from claims data and should not be interpreted as clinical treatment persistence.
3.BTKi rechallenge and switching rates reflect claims-based patterns and may undercount transitions not captured in claims.
4.Biomarker status available only for patients with LLM-extractable clinical notes; N is not population-representative.
5.No clinical outcomes (response rates, survival, time to progression) are assessed.

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