BTK Inhibitor Failure–Associated Richter Transformation: A Distinct Clinical and Molecular Phenotype from a Single-Center Real-World Series

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BACKGROUND

Richter transformation (RT) arising after Bruton tyrosine kinase inhibitor (BTKi) failure represents a growing clinical challenge in the modern CLL treatment era. Emerging evidence suggests that post-BTKi RT may demonstrate distinct biological characteristics and inferior outcomes compared with historical chemoimmunotherapy-era transformation.

OBJECTIVE

To characterize the clinical presentation, molecular features, and therapeutic outcomes of BTKi failure associated RT at our institution.

METHODS

- We retrospectively reviewed consecutive patients with biopsy-confirmed RT diagnosed between 2022–2025 following prior BTKi therapy.
- Clinical variables included demographics, prior lines of CLL therapy, duration of BTKi exposure, time from CLL diagnosis to transformation, Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase levels, and disease burden at transformation.
- Molecular profiling incorporated conventional cytogenetics and next-generation sequencing data, including *TP53* disruption and complex karyotype status.
- Treatment strategies, overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) were assessed using institutional follow-up data.

RESULTS: PATIENT & DISEASE CHARACTERISTICS

6 PATIENTS IDENTIFIED

67 MEDIAN AGE (YEARS) (RANGE 59–73)

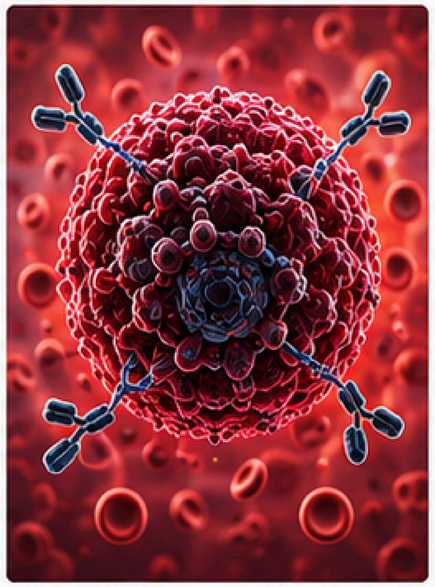
All had received prior BTKi therapy

Ibrutinib n=4
Acalabrutinib n=2

28 MEDIAN BTKi EXPOSURE (MONTHS) PRIOR TO TRANSFORMATION

4.6 MEDIAN TIME FROM CLL DIAGNOSIS TO RT (YEARS)

All presented with rapidly progressive lymphadenopathy and elevated LDH at transformation



CONCLUSION

BTKi failure–associated RT in this real-world series demonstrated aggressive clinical presentation, high prevalence of *TP53* disruption, and poor response to conventional chemoimmunotherapy. Compared with historical RT cohorts, outcomes remain poor, supporting the concept of a distinct post-BTKi transformation phenotype and underscoring the urgent need for novel targeted and cellular strategies.

RESULTS

MOLECULAR PROFILE
(Data available in five patients)

3/5 (60%) TP53 DISRUPTION

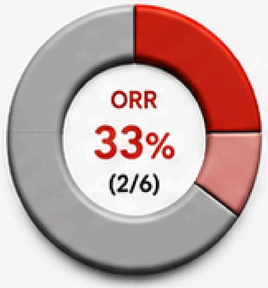
4/5 (67%) COMPLEX KARYOTYPE

Compared with historical institutional RT cases, BTKi-exposed patients demonstrated higher prevalence of adverse molecular features.

INITIAL THERAPY

Dose-adjusted R-EPOCH	n=3
R-CHOP	n=1
Venetoclax-based combinations	n=2

TREATMENT RESPONSE



- 1 Complete Remission
- 1 Partial Response
- 4 No Response

No objective responses were observed in patients with *TP53* disruption.

SURVIVAL OUTCOMES

MEDIAN PROGRESSION-FREE SURVIVAL (PFS)
3.9 MONTHS

MEDIAN OVERALL SURVIVAL (OS)
7.4 MONTHS

At a median follow-up of 10 months.

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None.

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REFERENCES

1. Dirican CD, Ajayi F, Al Mardini A, Crocete Aloysia Fernandes B, Sofia A, Gondhi V, Shaaban H, Maroules M. Efficacy and safety of BTK inhibitors in Richter's transformation: a systematic review of clinical evidence. Frontiers in Oncology. 2026 Jan 20;15;1681589.
2. Lin ZC, Chan MJ, Jaing TH, Lin TL, Hung YS, Su YJ. Richter transformation in chronic lymphocytic leukemia: current treatment challenges and evolving therapies. International Journal of Molecular Sciences. 2025 Sep 8;26(17):8747.