Prior Covalent BTK Inhibitor Exposure Is Associated with Inferior Survival After DLBCL-Type Richter Transformation in CLL/SLL

Shorter Overall Survival Despite Numerically Similar Response Rates

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Introduction

- DLBCL-type RT is the most common histologic transformation of CLL/SLL and remains a high-risk disease with poor survival after conventional chemoimmunotherapy (1–3)
- Covalent BTK inhibitors are widely used in CLL/SLL. Although prior CLL-directed treatment has been associated with worse RT outcomes, the specific relationship between antecedent covalent BTKi exposure and post-RT outcomes remains unclear (1,2)
- We evaluated whether prior covalent BTKi exposure was associated with OS after DLBCL-type RT; PFS and best ORR to RT-directed therapy were secondary outcomes

Methods

- We conducted an IRB-approved, single-center retrospective cohort study of adults with documented CLL/SLL and biopsy-proven DLBCL-type RT; Hodgkin-variant RT was excluded
- Groups were defined by covalent BTKi exposure before RT diagnosis: prior BTKi exposure vs BTKi-naive
- The primary endpoint was OS from RT diagnosis. Secondary endpoints were PFS and best ORR to RT-directed therapy
- Survival was estimated by Kaplan-Meier and compared by log-rank test; HRs were calculated using the Mantel-Haenszel method

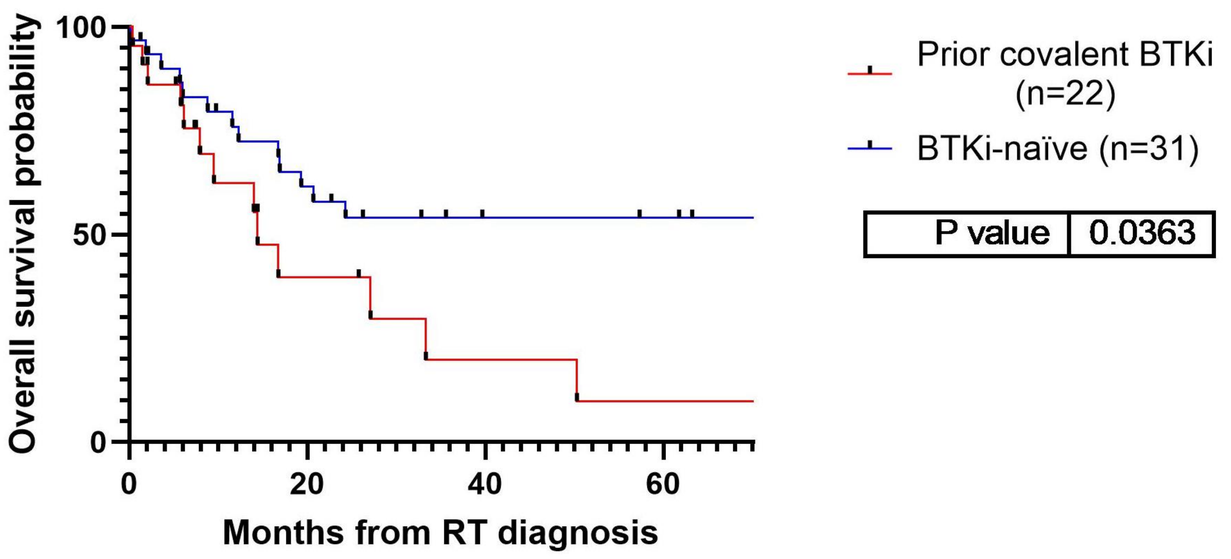
Results

- Fifty-three patients met inclusion criteria: 22 with prior covalent BTKi exposure and 31 BTKi-naive patients.
- Median follow-up for the overall cohort was 14.4 months.
- Median OS was significantly shorter after prior BTKi exposure: 14.4 vs 27.0 months (HR 2.46; 95% CI 1.06–5.71; p=0.036; Figure 1).
- Median PFS was 5.9 vs 9.9 months (HR 2.03; 95% CI 0.997–4.13; p=0.051); this trend did not meet conventional statistical significance (Figure 2).
- Best ORR was 41% (9/22) after prior BTKi exposure and 45% (14/31) among BTKi-naive patients; CR rates were 32% and 42%, respectively (Figure 3). No formal equivalence comparison was reported.

Conclusion

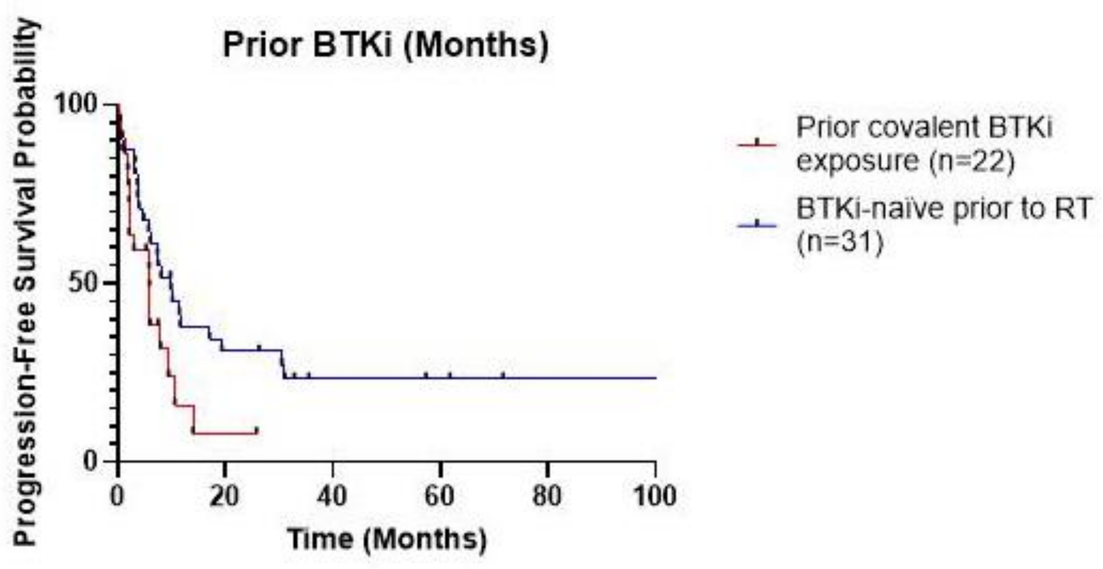
- Prior covalent BTKi exposure was associated with significantly shorter OS after DLBCL-type RT
- PFS showed a trend toward shorter duration but did not reach conventional statistical significance
- Numerically similar initial response rates alongside divergent survival may reflect differences in response durability, treatment history, disease biology, or other confounding factors; causality cannot be inferred
- Prior BTKi exposure may help identify a high-risk subgroup warranting improved therapeutic strategies and validation in larger, multicenter cohorts

Figure 1. Overall Survival



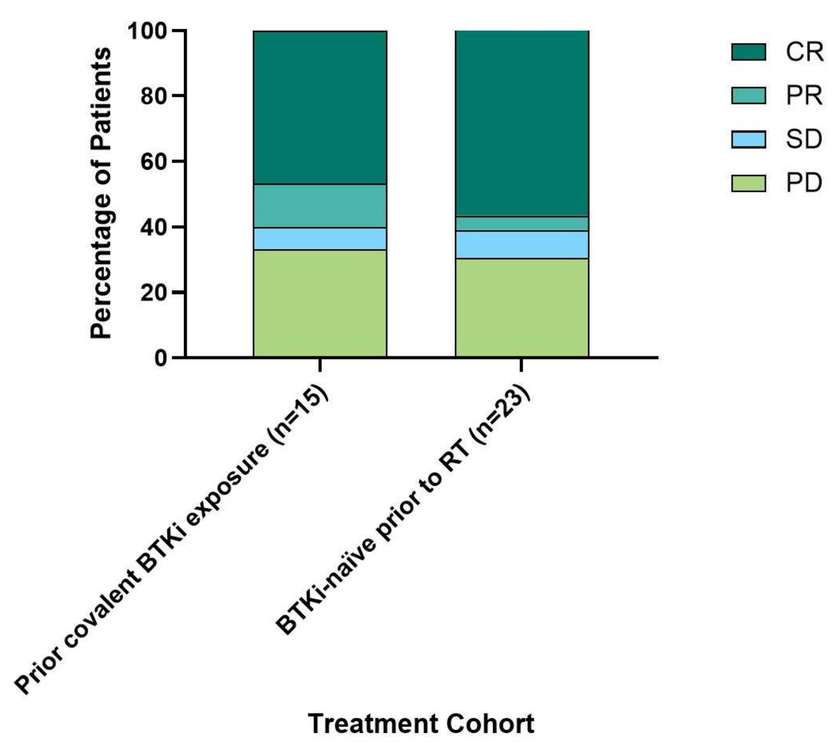
Kaplan-Meier estimates of OS from RT diagnosis by prior covalent BTKi exposure. Red indicates prior covalent BTKi exposure (n=22); blue indicates BTKi-naive patients (n=31). Median OS was 14.4 vs 27.0 months, respectively (HR 2.46; 95% CI 1.06–5.71; log-rank p=0.036). BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; OS, overall survival; RT, Richter transformation.

Figure 2. Progression-Free Survival



Kaplan-Meier estimates of PFS from RT diagnosis by prior covalent BTKi exposure. Red indicates prior covalent BTKi exposure (n=22); blue indicates BTKi-naive patients (n=31). Median PFS was 5.9 vs 9.9 months, respectively (HR 2.03; 95% CI 0.997–4.13; log-rank p=0.051); the difference did not meet conventional statistical significance. BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; RT, Richter transformation.

Figure 3. Best Response Among Response-Evaluable Patients



Stacked bars show best response among response-evaluable patients with prior covalent BTKi exposure (n=15) and BTKi-naive patients (n=23). Percentages are calculated within these response-evaluable subsets. In the full cohorts, best ORR was 41% (9/22) vs 45% (14/31), and CR rates were 32% vs 42%, respectively. Comparisons were descriptive; no formal equivalence test was reported. BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

References

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