Bruton Tyrosine Kinase Inhibitors for Treatment-Naïve Patients with Richter's Transformation: A Systematic Review

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Introduction

- Richter's Transformation (RT) is an aggressive lymphoma arising from Chronic Lymphocytic Leukemia (CLL), associated with poor prognosis.
- Bruton tyrosine kinase inhibitors (BTKi) have shown efficacy in CLL, but their role in treatment-naïve RT remains under investigation.
- Early trials of BTKi alone or with immune checkpoint inhibitors (ICIs) suggest possible therapeutic benefit.
- This review synthesizes current evidence to evaluate these regimens' effectiveness.

Aim / objectives

To evaluate the efficacy and outcomes of Bruton tyrosine kinase inhibitors (BTKi), used alone or in combination, in treatment-naïve patients with Richter's Transformation (RT), through a systematic review of current clinical trials.

Methods

- **Databases:** PubMed, EMBASE, ClinicalTrials.gov
- **Search Period:** Inception to January 2025
- **Guidelines Followed:** PRISMA
- **Inclusion Criteria:** Clinical trials of BTKi-based therapies in treatment-naïve RT
- **Exclusion:** Case reports, non-English publications
- **Primary Endpoints:**
  - Overall Response Rate (ORR)
  - Progression-Free Survival (PFS)
  - Overall Survival (OS)
- **Articles Reviewed:** 125 screened → 4 clinical trials included (N=71)

Results

Four clinical trials involving a total of 71 treatment-naïve RT patients were included.

Wierda et al. (2024)
- Treatment: Pirtobrutinib monotherapy (N=8)
- ORR: 62.5%
- Median PFS: 10.1 months (95% CI: 1.3–16.8)
- Median OS: 13.25 months (95% CI: 2.6–18.3)

Al-Sawaf et al.
- Treatment: Tislelizumab + Zanubrutinib(N=38)
- ORR: 57.9% (95% CI: 40.8–73.7)
- Median PFS: 10 months
- 12-month PFS rate: 43.5% (95% CI: 23.2–63.9)

Eyre et al. (2021)
- Treatment: Acalabrutinib (N=11)
- ORR: 36% (95% CI: 10.9–69.2)
- Median PFS: 3.2 months (95% CI: 1.6–3.7)

Jain et al. (2022)
- Treatment: Ibrutinib + Nivolumab (N=14)
- ORR: 50%
- Median OS: 24.1 months

Summary

BTKi-based therapies show varying degrees of effectiveness in treatment-naïve RT.

Highest ORR seen with pirtobrutinib (62.5%), followed by combinations with ICIs.

Median PFS ranged from 3.2 months (acalabrutinib) to 10.1 months (pirtobrutinib).

Combination regimens may enhance outcomes through synergistic effects.

Evidence remains limited due to small sample sizes and lack of randomized comparisons.

Discussion

BTKi and BTKi+ICI combinations show promise in treating treatment-naïve RT.

Next-generation BTKis like pirtobrutinib may offer better responses.

Future research should focus on randomized trials, biomarker-driven patient selection and long-term outcome data

References

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Study	Regimen	N	ORR (%)	Median PFS (mo)	Median OS (mo)
Wierda et al. (2024)	Pirtobrutinib	8	62.5	10.1 (CI 1.3–16.8)	13.25 (CI 2.6–18.3)
Al-Sawaf et al.	Tislelizumab + Zanubrutinib	38	57.9	10.0	— (12-mo PFS: 43.5%)
Eyre et al. (2021)	Acalabrutinib	11	36	3.2 (CI 1.6–3.7)	—
Jain et al. (2022)	Ibrutinib + Nivolumab	14	50	—	24.1