Bruton Tyrosine Kinase Inhibitors in Relapsed/Refractory Patients with Richter's Transformation: A Systematic Review

C. D. DIRICAN[1], B. FERNANDES[1], A. AL MARDINI[1], W. AIMAN[2], M. A. ALI[3], and V. NOOKALA[1]

1. NYMC at St Mary's and St Clare's, Denville, NJ, USA
2. Department of Hematology and Oncology, Roswell Park Cancer Center, University of Buffalo, Buffalo, NY, USA
3. Department of Hematology and Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA, USA

NEW YORK MEDICAL COLLEGE
A MEMBER OF TOURO UNIVERSITY
School of Medicine

Introduction

- Richter transformation (RT) is the progression of chronic lymphocytic leukemia (CLL) to an aggressive lymphoma.
- Prognosis for relapsed/refractory (R/R) RT remains poor, and treatment is challenging.
- Bruton tyrosine kinase inhibitors (BTKis), both covalent and non-covalent, have demonstrated clinical activity in R/R disease.
- This systematic review evaluates the efficacy of BTKi-based regimens in patients with R/R RT.

Aim / objectives

To evaluate the efficacy and outcomes of BTKi, used alone or in combination, in patients with relapsed/refractory Richter's Transformation (RT), through a systematic review of current clinical trials.

Methods

Systematic literature search: PubMed, Embase, and ClinicalTrials.gov

Timeframe: 2015–2025

Keywords: "Richter's Transformation" and "Bruton's Tyrosine Kinase Inhibitors"

Guidelines: PRISMA

Inclusion Criteria:

- Clinical trials with BTKi monotherapy or combination regimens
- Studies reporting ORR, PFS, or OS

Exclusion Criteria:

- Case reports
- Non-English studies

Screening: 125 articles reviewed → 6 trials included (N=137)

Results

Six clinical trials with a total of 137 R/R RT were included

Pirtobrutinib (BRUIN trial, N=74)
- ORR: 48.6% (95% CI: 36.9–60.6)
- Median PFS: 3.6 months (95% CI: 2.4–4.6)
- Median OS: 11.8 months (95% CI: 6.9–19.5)

Tislelizumab + Zanubrutinib (RT1 trial, N=10)
- ORR: 60.0% (95% CI: 26.2–87.8)
- 12-month PFS rate: 60.0% (95% CI: 19.9–100.0)

Acalabrutinib (Eyre et al., N=14)
- ORR: 43% (95% CI: 17.7–71.1)
- Median PFS: 2.0 months (95% CI: 1.7–11.1)

Nivolumab + Ibrutinib (Jain et al., N=10)
- ORR: 30%
- Median OS: 9.1 months

Nivolumab + Ibrutinib (Younes et al., N=20)
- ORR: 65%
- Median PFS: 5 months
- Median OS: 10.3 months

Ibrutinib + Selinexor (Stephens et al., N=9)
- ORR: 11%
- Stable disease observed in 55% of patients

Summary

BTKi regimens, both as monotherapy and in combination, show variable efficacy in R/R RT.

Best response rates observed with tislelizumab-zanubrutinib and nivolumab-ibrutinib combinations.

Pirtobrutinib, a next-generation non-covalent BTKi, demonstrates encouraging survival outcomes.

Further research with randomized trials and biomarker-driven approaches is warranted to refine therapeutic strategies.

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Study	Regimen	N	ORR (%)	Median PFS (mo)	Median OS (mo)
BRUIN (Phase 1/2)	Pirtobrutinib	74	48.6 (36.9–60.6)	3.6 (2.4–4.6)	11.8 (6.9–19.5)
RT1	Tislelizumab + Zanubrutinib	10	60.0 (26.2–87.8)	— (12-mo PFS: 60%)	—
Eyre et al. (2021)	Acalabrutinib	14	43 (17.7–71.1)	2.0 (1.7–11.1)	—
Jain et al. (2022)	Nivolumab + Ibrutinib	10	30	—	9.1
Younes et al.	Nivolumab + Ibrutinib	20	65	5	10.3
Stephens et al. (2022)	Ibrutinib + Selinexor	9	11	—	—