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Bruton Tyrosine Kinase Inhibitor Monotherapy for the Treatment of High-Risk Patients With Previously Untreated Chronic Lymphocytic Leukemia: A Systematic Literature Review

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INTRODUCTION

- Chronic lymphocytic leukemia (CLL) is a common form of leukemia, with an annual incidence of 4.2 per 100,000 individuals in Europe[1]
- CLL is associated with a range of debilitating symptoms and detrimental effects on quality of life[2]
- The course of CLL is heterogeneous and driven by cytogenetic factors, which can be used to predict poor prognosis. Specifically, the presence of tumor protein 53 (*TP53*) mutation or 17p deletion (del[17p]) has been shown to impact treatment response. Patients with these factors are classified as being high risk[3]
- Bruton tyrosine kinase inhibitor (BTKi) monotherapies (zanubrutinib, acalabrutinib, and ibrutinib) are mainstay treatment options for high-risk patients, as highlighted in the European Society for Medical Oncology clinical practice guidelines[1]
- In this analysis, a clinical systematic literature review (SLR) was conducted to assess trials that have measured treatment efficacy of BTKis in patients with CLL; a key goal of the review was to characterize the efficacy evidence supporting the use of BTKi monotherapy in previously untreated high-risk patients with CLL

METHODS

- On July 1, 2022, searches were conducted in the Embase, MEDLINE (EMBASE interface), and Central Register of Controlled Trials (Cochrane Library) databases for studies published ≤15 years before the search date
- The PICOS criteria for the high-risk review question are presented in **Table 1**
- Database searches were supplemented with gray literature of relevant conference proceedings published within 2 years of the search date
- Once duplicates were removed, the abstracts (first pass) and full-text publications (second pass) were screened by 2 independent reviewers, followed by arbitration of disagreements by a third independent reviewer
- One reviewer extracted accepted studies into a predefined extraction grid, and a second reviewer performed quality assessment

Table 1. PICOS Criteria (Specific to the TN Review Question)

Category	Inclusion Criteria	Exclusion Criteria
Population	Patients with CLL classified as high risk (*TP53* mutation or del[17p])[a]	Studies that do not include patients of interest. Studies with a mixed patient population that do not present outcomes separately for patients of interest, with only a minority being of interest
Intervention/comparators	BTKis (zanubrutinib, acalabrutinib, and ibrutinib)[a]	No intervention/comparators of interest
Outcomes	Efficacy	No reported outcomes of interest (ie, only reporting pharmacodynamics; pharmacokinetics; genetic, cellular, or molecular outcomes)
Study type	RCTs, non-RCTs, observational studies (including patient registries)	Cross-sectional studies, animal studies, in vitro/ex vivo studies, individual case study reports
Publication type	Articles, conference abstracts, conference papers, articles in press	Short surveys, reviews, letters, comment articles

[a] The selection criteria for the full systematic literature review were broader than those for this specific review question.
BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; PICOS, population intervention, comparator, outcomes, study type; RCT, randomized controlled trial; *TP53*, tumor protein 53.

RESULTS

- **Figure 1** presents the PRISMA diagram for the full clinical SLR. Five randomized controlled trials were identified (33 associated publications) that evaluated BTKi monotherapy in patients with previously untreated CLL, including patients with high-risk factors.[4-8] **Table 2** presents a summary of the identified trials; all had a similar study design. **Table 3** presents key subgroup results from the latest identified efficacy data
  - SEQUOIA was the only study with a prospectively defined high-risk cohort of patients (cohort 2; n=111 patients with del(17p) treated with zanubrutinib). Outcomes in cohort 2 were similar to those in patients without del(17p) treated with zanubrutinib (cohort 1; n=241)[4]
  - The other 4 trials (CLL12, RESONATE-2, ALLIANCE, ELEVATE-TN) included mixed populations. Prespecified subgroup analyses demonstrated comparable outcomes in patients with and without high-risk factors in these trials, although high-risk patient numbers were small

Table 2. Summary of Studies Identified in the SLR

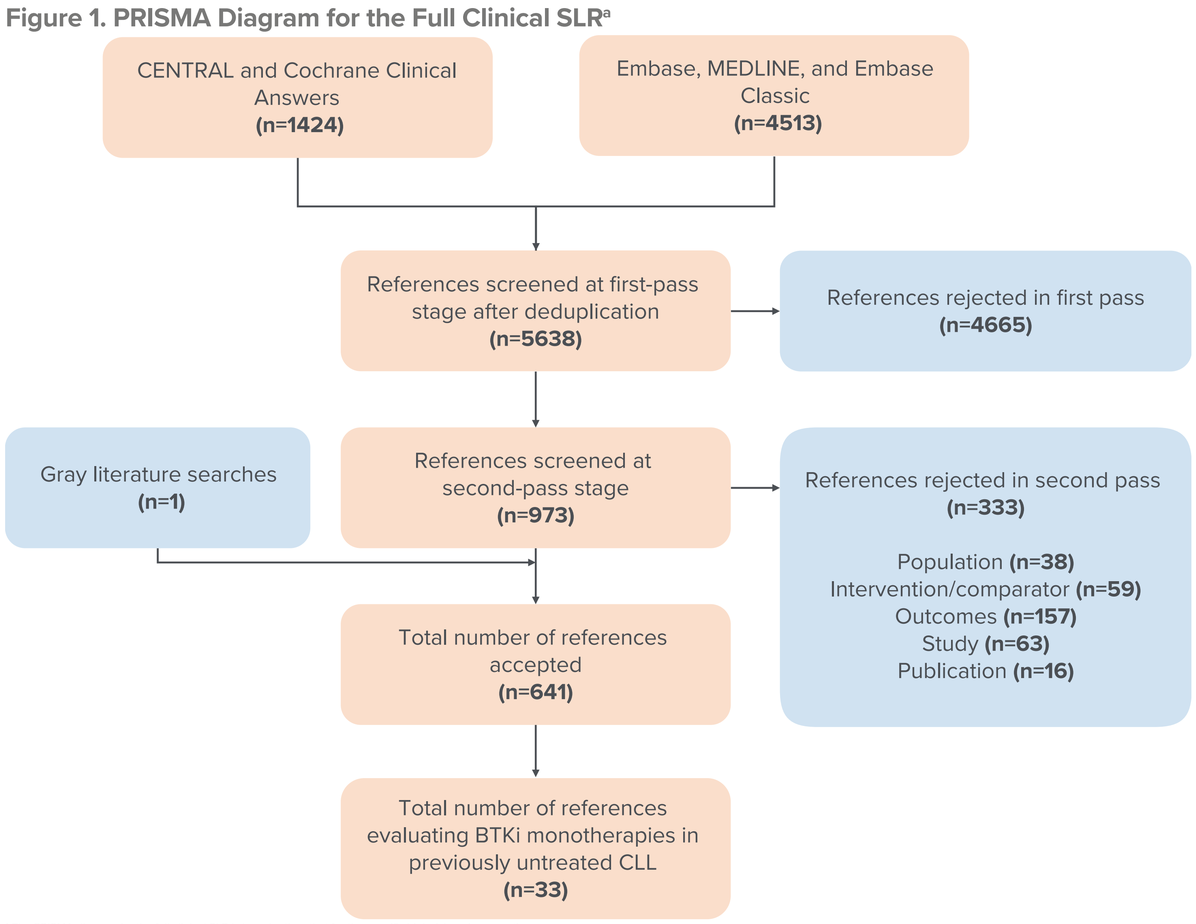
Trial	Study Design	Treatment Arms	Proportion of Patients With High-Risk Factor (BTKi Monotherapy Arm Only), n (%)	
			del(17p)	*TP53* Mutation
SEQUOIA (NCT03336333)[4]	Cohort 1: phase 3, open label, RCT Cohort 2: single arm, open label	Zanubrutinib cohort 1 (n=241) BR cohort 1 (n=238) Zanubrutinib cohort 2 (n=111)	Zanubrutinib cohort 1: 2 (1) Zanubrutinib cohort 2: 110 (99)	Zanubrutinib cohort 1: 15 (6) Zanubrutinib cohort 2: 47 (43)
CLL12 (NCT02863718)[5]	Phase 3, double blind, RCT	Ibrutinib (n=182) Placebo (n=181)	Ibrutinib: 6 (3)	Ibrutinib: 14 (8)
RESONATE-2 (NCT01724346)[6]	Phase 3, open label, RCT	Ibrutinib (n=136) Chlorambucil (n=133)	Ibrutinib: 0 (0)	Ibrutinib: 11 (9)
ALLIANCE (NCT01886872)[7]	Phase 3, open label, RCT	BR (n=183) Ibrutinib (n=182) IR (n=182)	Ibrutinib: 9 (5)	Ibrutinib: 15 (9)
ELEVATE-TN (NCT02475681)[8]	Phase 3, open label, RCT	AO (n=179) Acalabrutinib (n=179) CO (n=177)	Acalabrutinib: 16 (9)	Acalabrutinib: 19 (11)

AO, acalabrutinib with obinutuzumab; BR, bendamustine with rituximab; BTKi, Bruton tyrosine kinase inhibitor; CO, obinutuzumab and chlorambucil; IR, ibrutinib with rituximab; RCT, randomized controlled trial; SLR, systematic literature review; *TP53*, tumor protein 53.

CONCLUSIONS

- There is limited clinical evidence of efficacy of BTKi treatments in patients with CLL with high-risk factors. Most of the identified trials reported subgroup analyses that demonstrated comparable outcomes in patients with and without high-risk factors
- However, high-risk patient numbers were small. This can lead to difficulties in health technology assessment (HTA) appraisal of treatments, which requires comparative evidence vs BTKis in this key patient subgroup
- Due to the high unmet need in these patients, ibrutinib and acalabrutinib were licensed for use in these patient populations despite the small high-risk subgroups
- **SEQUOIA** (cohort 2) presents the largest prospective body of evidence in previously untreated high-risk patients with CLL treated with BTKi monotherapy. The availability of this evidence will allow for treatment comparisons vs BTKi monotherapy in high-risk patients to support future HTA submissions

Figure 1. PRISMA Diagram for the Full Clinical SLR[a]



[a] The PRISMA diagram for the full clinical SLR is broader than that for the specific high-risk review question.
BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Table 3. Summary of Studies Identified in the SLR (Specific to the TN Review Question)

Trial	Subgroup Definition and Sample Size		EFS/PFS Rate	HR (95% CI)
SEQUOIA (NCT03336333)[4]	del(17p)	Zanubrutinib (n=111)	24-month PFS (IRC): 88.9%	N/A
CLL12 (NCT02863718)[5]	del(17p)	Ibrutinib (n=6) Placebo (n=7)	24-month EFS: Ibrutinib: 83.3%; Placebo: 0%	EFS: 0.19 (0.02-1.77)
	TP53 mut	Ibrutinib (n=14) Placebo (n=13)	NR	NR
RESONATE-2 (NCT01724346)[6]	*TP53* mut, del(11q), and/or unmut IGHV	Ibrutinib (n=73) BR (n=69)	NR	PFS: 0.098 (0.060-0.161)
ALLIANCE (NCT01886872)[7]	del(17p) or del(11q)	Ibrutinib (n=9) BR (n=15)	NR	PFS: 0.26 (0.12-0.56)
ELEVATE-TN (NCT02475681)[8]	del(17p) and/or *TP53* mut	Acalabrutinib (n=23) CO (n=25)	NR	PFS: 0.23 (0.09-0.61)

BR, bendamustine plus rituximab; CO, obinutuzumab and chlorambucil; EFS, event-free survival; HR, hazard ratio; IGHV, immunoglobulin heavy-chain variable region; IRC, independent review committee; mut, mutation; N/A, not applicable; NR, not reported; PFS, progression-free survival; *TP53*, tumor protein 53; unmut, unmutated.

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DISCLOSURES

LM, KY, RO: Employment: BeiGene. **LW, SU, AM:** Employment: FIECON, which received consulting fees from BeiGene for this project.

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