Targeted Treatments for Patients With Relapsed and/or Refractory Chronic Lymphocytic Leukemia: A Systematic Literature Review of Randomized Clinical Trials

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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]
- Historically, patients with CLL were treated with chemoimmunotherapy (CIT). However, the introduction of targeted therapies—namely, Bruton tyrosine kinase inhibitors (BTKis) and B-cell lymphoma 2 inhibitors—has greatly improved outcomes in CLL, reducing rates of both disease progression and mortality, and has led to a paradigm shift away from CIT[3]
- Following initial response, most patients will still experience relapse or become refractory to treatment. In addition, a proportion of patients have disease that is refractory to initial treatment[2]
- In this analysis, a clinical systematic literature review (SLR) was conducted to assess trials that have measured the efficacy of treatments in patients with CLL; a key goal of the review was to characterize the efficacy evidence supporting the use of BTKi monotherapy in relapsed and/or refractory (R/R) 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 R/R SLR 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 duplicate references 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 R/R Review Question)

Selection Criteria	Inclusion Criteria	Exclusion Criteria
Population	Patients with R/R CLL	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	Targeted therapies (BTKi and BCL2i)	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

BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; PICOS, population, intervention, comparator, outcomes, study type; RCT, randomized controlled trial; R/R, relapsed and/or refractory.

RESULTS

- Six randomized controlled trials (RCTs) (ALPINE, ELEVATE-RR, ASCEND, RESONATE, GENUINE, and NCT01973387) that evaluated BTKi monotherapy were identified for R/R CLL (67 associated publications). The trials were generally similar in design; however, the median prior lines of therapy varied (**Table 2**). Key efficacy results were extracted from the latest identified efficacy data cuts
- ALPINE and ELEVATE-RR provided the only head-to-head comparisons between BTKis:
  - ALPINE demonstrated superior efficacy of zanubrutinib vs ibrutinib. Progression-free survival (PFS) by investigator (INV) rates at 12 months were 94.9% with zanubrutinib compared with 84.0% with ibrutinib (hazard ratio [HR], 0.40; 95% CI, 0.23-0.69). OS rates at 12 months were 97.0% with zanubrutinib vs 92.7% with ibrutinib (HR, 0.54; 95% CI, 0.25-1.16)[4]
  - ELEVATE-RR demonstrated noninferior efficacy of acalabrutinib vs ibrutinib. Median independent review committee (IRC)–assessed PFS was 38.4 months in both arms (HR, 1.00; 95% CI, 0.79-1.27)[5]
- ASCEND, RESONATE, and NCT01973387 demonstrated superior outcomes with BTKi monotherapy compared with nontargeted treatment options:
  - In ASCEND, at a median follow-up of 36.0 months and 35.2 months for acalabrutinib and for rituximab plus idelalisib (IR)/bendamustine plus rituximab (BR), respectively, significantly prolonged IRC-assessed PFS with acalabrutinib vs IR/BR was observed (median, not reached vs 16.8 months; HR, 0.29; 95% CI, 0.21-0.41). PFS rates at 36 months were 63% and 21% with acalabrutinib and IR/BR, respectively[6]
  - In RESONATE, at a median follow-up of 44 months, PFS by IRC remained significantly longer with ibrutinib than with ofatumumab (HR, 0.133; 95% CI, 0.099-0.178). The 3-year PFS rate was 59% and 3% with ibrutinib and ofatumumab, respectively[7]
  - In NCT01973387, the 18-month INV-assessed PFS rate was 74.0% and 11.9% with ibrutinib and rituximab, respectively (HR, 0.18; 95% CI, 0.11-0.31)[8]
- GENUINE demonstrated improved response with ibrutinib plus ublituximab (IU) vs ibrutinib monotherapy. After a median follow-up of 41.6 months, median IRC-assessed PFS was not reached in the IU arm and 35.9 months in the ibrutinib arm after 25 PFS events (HR, 0.46; 95% CI, 0.24-0.87)[9]
- A further 3 RCTs assessed combination therapies: MURANO (NCT02005471), HELIOS (NCT01611090), and HOVON-141/VISION (NCT03226301):[10-12]
  - MURANO and HELIOS demonstrated improved outcomes with venetoclax plus rituximab and IR, respectively, vs BR
  - HOVON-141/VISION demonstrated comparable outcomes with ibrutinib monotherapy vs no treatment following initial ibrutinib plus venetoclax treatment

CONCLUSIONS

- According to treatment guidelines, a sequencing approach is adopted for patients with R/R CLL, which suggests that the optimal treatment following progression varies depending on the front-line therapy.[13] The treatment decision is often dependent on disease characteristics, patient characteristics and preference, and clinician decision
- However, this SLR highlighted a lack of head-to-head comparative data between targeted therapies, which poses a challenge in making informed and personalized treatment decisions
- All except 3 RCTs (ALPINE, ELEVATE-RR, GENUINE) compared targeted and nontargeted therapies
- **ALPINE** is the first and only RCT to demonstrate superior efficacy of zanubrutinib vs ibrutinib
- With increased use of targeted therapies, more head-to-head comparisons of targeted treatments are required to aid patient and clinician treatment decisions

Table 2. Summary of Studies Identified in the SLR (Specific to the R/R Review Question)

Trial	Study Design	Treatment Arms	Prior Lines of Therapy, Median (range)	>3 prior Lines, n (%)
BTKi monotherapy				
ALPINE (NCT03734016)[4]	Phase 3, open label, RCT	Zanubrutinib (n=207) Ibrutinib (n=208)	Zanubrutinib: 1 (1-6) Ibrutinib: 1 (1-8)	Zanubrutinib: 15 (7.3) Ibrutinib: 21 (10.1)
ELEVATE-RR (NCT02477696)[5]	Phase 3, open label, RCT	Acalabrutinib (n=268) Ibrutinib (n=265)	Acalabrutinib: 2 (1-9) Ibrutinib: 2 (1-12)	Acalabrutinib: 33 (12.3) Ibrutinib: 28 (10.6)
ASCEND (NCT02970318)[6]	Phase 3, open label, RCT	Acalabrutinib (n=155) IR (n=119) BR (n=36)	Acalabrutinib: 1 (1-8) IR/BR: 2 (1-10)	Acalabrutinib: 16 (10) IR/BR: 18 (12)
RESONATE (NCT01578707)[7]	Phase 3, open label, RCT	Ibrutinib (n=195) Ofatumumab (n=196)	Ibrutinib: 3 (1-12) Ofatumumab: 2 (1-13)	Ibrutinib: 103 (53)[b] Ofatumumab: 298 (46)[b]
NCT01973387[8]	Phase 3, open label, RCT	Ibrutinib (n=106) Rituximab (n=54)	Mean (SD) Ibrutinib: 2.0 (1.7) Rituximab: 2.2 (1.4)	Ibrutinib: 26 (24.8) Rituximab: 20 (37.0)
GENUINE (NCT02301156)[9]	Phase 3, open label, RCT	Ibrutinib (n=62) IU (n=64)	Ibrutinib: 1 (1-2) IU: 1 (1-2)	N/A
Other targeted therapies				
MURANO[10] (NCT02005471)	Phase 3, open label, RCT	VR (n=194) BR (n=195)	NR	VR: 4 (2.1) BR: 1 (0.5)
HELIOS[11]	Phase 3, open label, RCT	Ibrutinib + BR (n=289) Placebo + BR (n=289)	Mean (range) Ibrutinib + BR: 2 (1–11) Placebo + BR:2 (1–9)	Ibrutinib + BR: 77 (26.6)[b] Placebo + BR: 72 (25.0)[b]
HOVON-141/ VISION[12]	Phase 3, open label, RCT	Ibrutinib[a] (n=24) Treatment cessation[a] (n=48)	NR	NR

[a] Following initial treatment with I+V. [b] Inclusive of patients with 3 prior lines of therapy.
BR, bendamustine plus rituximab; BTKi, Bruton tyrosine kinase inhibitor; IR, rituximab plus idelalisib; IU, ibrutinib plus ublituximab; N/A, not applicable; NR, not reached; RCT, randomized controlled trial; R/R, relapsed and/or refractory; SLR, systematic literature review; VR, venetoclax plus rituximab.

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DISCLOSURES

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