Systematic literature review of treatments and outcomes in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma previously treated with Bruton tyrosine kinase inhibitors and venetoclax

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Introduction

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) is the most prevalent form of adult leukemia in Western countries, accounting for 25%–30%[1–3] of all leukemia types and occurring at a rate of 4.9 new diagnoses per 100,000 per year in the United Kingdom and United States (US)[3]
- Patients with relapsed or refractory (R/R) CLL/SLL require multiple lines of therapy, and outcomes are poor in these patients[4]
- The treatment landscape has evolved with the introduction of targeted agents such as Bruton tyrosine kinase inhibitors (BTKi), phosphatidylinositol 3-kinase inhibitors (PI3Ki), and the B-cell lymphoma 2 inhibitor (BCL2i) venetoclax[3]
- A systematic literature review (SLR) was conducted to understand the efficacy of treatments for patients with R/R CLL/SLL who have failed ≥ 2 prior lines of therapy (ie, third-line or later [3L+] R/R CLL/SLL), especially those previously treated with a BTKi and venetoclax

Methods

Study identification

Table 1. Data sources

	Sources	Time frame
Bibliographic databases	Embase, MEDLINE, MEDLINE In-Process, Cochrane Library	Inception–September 2022
Conference websites	EHA, ASCO, ISPOR, ESMO, ICML	2020–October 2022
	ASH	2020–February 2023
Trial registries	US National Institutes of Health Clinical Trial Registry, World Health Organization International Clinical Trials Registry Platform	Inception–October 2022
Regulatory agency websites	National Institute for Health and Care Excellence, US Food and Drug Administration, European Medicines Agency	Inception–October 2022
Hand searches	Relevant SLRs and meta-analyses were hand-searched	Inception–2022

ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; EHA, European Hematology Association; ESMO, European Society for Medical Oncology; ICML, International Conference on Malignant Lymphoma; ISPOR, International Society for Pharmacoeconomics and Outcomes Research.

- An SLR review was performed according to a prespecified protocol based on PRISMA-P guidelines, with data sources in **Table 1** and eligibility criteria in **Table 2**
- After completion of the search for this SLR, which focused on patients with 3L+ R/R CLL/SLL who were previously treated with a BTKi and venetoclax, additional studies (phase 2+ trials and observational studies) in patients with second-line or later (2L+)/3L+ R/R CLL/SLL who were previously treated with a BTKi and venetoclax became available and were added
- For included studies, the most recent publications after the initial search date were included

Table 2. Eligibility criteria (PICOS design framework)

	Criteria
Population	Adults (≥ 18 years of age) with R/R CLL/SLL • Data extraction: all patients who are 3L+ and previously treated with a BTKi and venetoclax
Intervention/Comparator	All pharmacological treatments available
Outcome	CR rate, ORR, PFS, OS, DOR, uMRD, TTD, TTNT
Study design	• Trials (phase 2+): RCT, nonrandomized, single arm • Observational studies: cohort, case control • SLRs and meta-analyses[a]
Language	• English

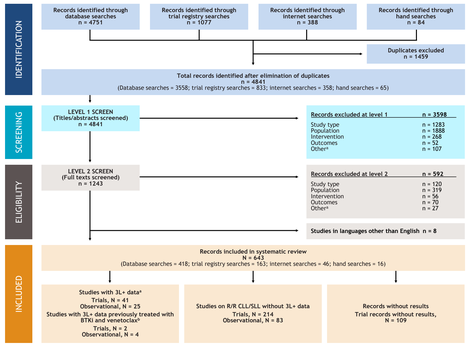
[a]Included for the perspective of identifying additional references.
CR, complete response; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PICOS, Population, Intervention, Comparator, Outcome, Study design; RCT, randomized controlled trial; TTD, time to treatment discontinuation; TTNT, time to next treatment; uMRD, undetectable minimal residual disease.

Data extraction

- Study design, treatment information, patient demographics and baseline characteristics, and efficacy outcomes were summarized
- Where available, efficacy outcomes were classified according to either individual pharmacologic classes or class groupings

Results

Figure 1. PRISMA diagram



[a]Outcome data for patients with 3L+ R/R CLL/SLL. *One trial and 4 observational studies in patients with 2L+/3L+ R/R CLL/SLL previously treated with a BTKi and venetoclax were added after the search completion.

- Three phase 2 trials investigated new therapies for R/R CLL/SLL previously treated with a BTKi and venetoclax (Table 3)
  - Two investigated noncovalent BTKis, nemtabrutinib and pirtobrutinib; one investigated the CD19 chimeric antigen receptor (CAR) T cell therapy, lisocabtagene maraleucel (liso-cel)
  - Patients in the liso-cel trial overall were more heavily treated than patients in the nemtabrutinib and pirtobrutinib trials (median prior lines of therapy [LOT]: 5 vs 4 and 3, respectively; prior BTKi and venetoclax: 82% vs 47% and 41%, respectively)
  - CR was achieved among 18% of patients receiving liso-cel after experiencing disease progression while on BTKi and venetoclax failure, whereas no CR was observed in patients receiving nemtabrutinib or pirtobrutinib after a prior BTKi and venetoclax

Table 3. Summary of trials in R/R CLL/SLL previously treated with a BTKi and venetoclax

Reference	Treatment (N)	Patients with a prior BTKi, %	Patients with a prior BTKi and ven, %	Population	Median (range) prior LOT	Median follow-up, months	CR rate, %	ORR, %	uMRD, %	Median (95% CI) DOR, months	Median (95% CI) PFS, months	Median (95% CI) OS, months
Eradat 2023[5] Woyach 2022[6]	Nemtabrutinib (57)	100	47	Overall	4 (2–18)	9.4	4	30	NA	26.0 (13.9–NR)	15.9 (9.9–NR)	NA
				Prior BTKi and ven	NA	4.8	0	25	NA	8.5 (2.7–NR)	10.1 (7.4–15.9)	NA
Mato 2023a[7]	Pirtobrutinib (247)	100	41	Overall	3 (1–11)	19.4	2	73	NA	NA	19.6 (16.9–22.1)	NR (33.9–NR)
				Prior BTKi and ven	5 (1–11)	18.2	0	70	NA	NA	16.8 (13.2–18.7)	NR
Siddiqi 2023[8]	Liso-cel (108)[a]	100	82	Overall	5 (3–7)	20.8	18	47	64 (53–74)	35.25 (19.78–NR)	17.97 (9.43–30.13)	43.17 (26.87–NR)
				Prior BTKi and ven	NA		NA	NA	NA	NA	NA	NA
				BTKi progression and ven failure[b]	5 (4–7)		18	43	63 (48–77)	35.25 (11.01–NR)	11.93 (5.72–26.18)	30.26 (11.24–NR)

Response was assessed according to the 2018 iwCLL response criteria. Partial response with lymphocytosis is not counted toward ORR.
[a]The number of patients treated with liso-cel at a target dose of 100 × 10^6 CAR$^+$ T cells (the recommended phase 2 dose); [b]A patient was included if they progressed on a BTK inhibitor and met 1 of the following criteria: discontinued venetoclax due to disease progression or intolerability and disease met indications for further therapy per 2018 iwCLL response criteria; or did not reach an objective response within 3 months of initiating therapy.
CI, confidence interval; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; NA, not available; NR, not reached; ven, venetoclax.

Table 4. Summary of observational studies in R/R CLL/SLL previously treated with a BTKi and venetoclax

Reference	Treatment received after a prior BTKi and ven (N)	Subgroup (n)	Median (range) prior LOT	Median follow-up, months	CR rate, %	ORR, %	uMRD, %	Median (95% CI) DOR, months	Median (95% CI) PFS, months	Median (95% CI) OS, months	Median (95% CI) TTD, months	Median (95% CI) TTNT, months
Awan 2022[9]	Conventional systemic therapies (57)	NA	3 (2–7)	11.1	NA	NA	NA	NA	NA	16.6 (11.0–27.5)	7.1 (5.0–11.8)	6.6 (3.6–10.1)
Lew 2021[4]	Conventional systemic therapies or ncBTKi (17)	NA	4 (2–8)	NA	NA	NA	NA	NA	NA	3.6 (2.0–11.0)	NA	NA
Thompson 2021[10]	Conventional systemic therapies, alloSCT, ncBTKi, or CAR T cell therapy (118)	CIT (23)	4 (2–12)	2	NA	31.8	NA	NA	3.0	NA	NA	NA
		PI3Ki (24)		4	NA	40.9	NA	NA	5.0	NA	NA	NA
		AlloSCT (17)		6.5	NA	76.5	NA	NA	11.0	NA	NA	NA
		ncBTKi (45)		9	NA	75.0	NA	NA	NR	NA	NA	NA
		CAR T (9)		3	NA	85.7	NA	NA	4.0	NA	NA	NA
Mato 2020[11]	Conventional systemic therapies, CAR T cell therapy (66)	BTKi (30)	5 (2–12)	3.5	10.0	36.7	NA	NA	12.0	NA	NA	NA
		PI3Ki (17)	5 (2–7)	5	5.9	41.1	NA	NA	5.0	NA	NA	NA
		CAR T (18)	5 (2–11)	2	33.3	66.6	NA	NA	9.0	NA	NA	NA
Eyre 2023[12]	Conventional systemic therapies and clinical trials (317)	NA	3 (1–6+)	NA	NA	34.4	NA	13.3 (10.6–19.5)	9.2 (7.0–10.6)	25.5 (20.1–40.7)	NA	NA
Mato 2023b[13]	Conventional systemic therapies (228)	NA	NA	NA	NA	NA	NA	NA	NA	NA	5.6 (4.3–6.0)	NA
Thompson 2022[14]	Ven monotherapy or combinations (18)	NA	NA	8	NA	56.3	NA	NA	15.0	NA	NA	NA
Hampel 2022[15,a]	Ibrutinib and ven combination (11)	NA	NA	NA	NA	NA	NA	NA	NA	27.0 (15.5–NR)	7.5 (4.3–NR)	11.2

Conventional systemic therapies include BTKi, BCL2i/venetoclax, PI3Ki, chemoimmunotherapy, or combinations of the aforementioned. Partial response with lymphocytosis is not counted toward ORR.
[a]Hampel 2022[15] reported clinical CR defined as meeting iwCLL 2018 CR criteria but without confirmatory bone marrow biopsy, and physical examination rather than imaging was used for response assessment.
AlloSCT, allogeneic stem cell transplantation; CAR T, chimeric antigen receptor T cell therapy; CIT, chemoimmunotherapy; ncBTKi, noncovalent Bruton tyrosine kinase inhibitor.

- Eight observational studies investigated existing therapies for R/R CLL/SLL previously treated with a BTKi and venetoclax (**Table 4**)
  - Investigated therapies included conventional systemic therapies (BTKi, BCL2i/venetoclax, PI3Ki, chemoimmunotherapy, or combinations of the aforementioned), alloSCT, noncovalent BTKi, and CAR T cell therapy
  - The median prior LOT ranged from 3 to 5
  - When reported as a miscellaneous group, conventional systemic therapies were associated with an ORR of 34%, median PFS of 9 months, and OS varying from 4 months for patients who developed progressive disease on both BTKi and venetoclax to 26 months for patients who had prior BTKi and venetoclax
  - When reported by pharmacologic class grouping, chemoimmunotherapy was associated with a 32% ORR, PI3Ki was associated with a 6% CR rate and a 41% ORR, BTKi was associated with a 10% CR rate and a 37% ORR, retreatment with venetoclax monotherapy or combinations was associated with a 56% ORR, noncovalent BTKi was associated with a 75% ORR, alloSCT was associated with a 77% ORR, and CAR T cell therapy was associated with a 33% CR rate and a 67%–86% ORR. The median PFS ranged from 3 months for chemoimmunotherapy to 15 months for retreatment with venetoclax monotherapy or combinations

Conclusions

- There remains a high unmet medical need for patients with R/R CLL/SLL previously treated with a BTKi and venetoclax, with poor outcomes associated with conventional systemic therapies
- Novel therapies such as CAR T cell therapy and noncovalent BTKi may provide better efficacy outcomes. CR was observed with CAR T cell therapy but not noncovalent BTKi in the included trials. A direct comparison of their survival benefits is not feasible, due to the absence of head-to-head trials
- CAR T cell therapy was associated with a higher CR rate and longer OS than that of conventional systemic therapies

References

1. Yao Y, et al. *Biomed Eng Online* 2022;21:4.
2. O'Reilly A, et al. *Clin Lymphoma Myeloma Leuk* 2018;18:249–256.
3. Milne K, et al. *Curr Oncol Rep* 2020;22:36.
4. Lew TE, et al. *Blood Adv* 2021;5:4054–4058.
5. Eradat H, et al. *Hematol Oncol* 2023;41(S2):565–567.
6. Woyach JA, et al. *Blood* 2022;140(suppl 1):7004–7006.
7. Mato AR, et al. *N Engl J Med* 2023;389:33–44.
8. Siddiqi T, et al. *Lancet* 2023;402:641–654.
9. Awan FT, et al. *Blood* 2022;140(suppl 1):7028–7029.
10. Thompson MC, et al. *Blood* 2021;138(suppl 1):2628.
11. Mato AR, et al. *Clin Cancer Res* 2020;26:3589–3596.
12. Eyre TA, et al. *Leuk Lymphoma* 2023;64:1005–1016.
13. Mato AR, et al. *Clin Lymphoma Myeloma Leuk* 2023;23:57–67.
14. Thompson MC, et al. *Blood Adv* 2022;6:4553–4557.
15. Hampel PJ, et al. *Br J Haematol* 2022;199:239–244.

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