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Comparison Between Efficacy Outcomes of Covalent Versus Non-Covalent Bruton Tyrosine Kinase (BTK) Inhibitor Treatments for Double-Exposed Chronic Lyhmpocitic Leukemia and Small Lymphocitic Lymphoma Patients: A Systematic Review

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ABSTRACT

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell malignancy. Covalent Bruton tyrosine kinase inhibitors (cBTKis), such as ibrutinib, acalabrutinib, and zanubrutinib, have improved clinical outcomes; however, their efficacy is limited by the emergence of resistance mutations at the BTK C481 binding site. Non-covalent BTK inhibitors (ncBTKis), including pirtobrutinib, were developed to overcome this resistance mechanism. This systematic review compares clinical outcomes between covalent and non-covalent BTK inhibitor treatments in patients with CLL/SLL. A systematic search of MEDLINE, CENTRAL, and EMBASE was conducted to identify studies published within the last 10 years that evaluated cBTKis and ncBTKis in CLL/SLL. Eligible studies reported efficacy outcomes, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Study quality was assessed using the Newcastle–Ottawa Scale. Four studies involving 137 patients met the inclusion criteria. Among ncBTKis, pirtobrutinib demonstrated a 70% PR rate and an 11% SD rate, whereas nemtabrutinib demonstrated a 25% PR rate without reported CRs. Covalent BTK inhibitor-based combinations achieved higher CR rates, including ibrutinib plus venetoclax (CR, 55%; PR, 45%) and acalabrutinib plus obinutuzumab (CR, 50%). PD rates were inconsistently reported across studies. Covalent BTK inhibitor-based combination therapies produced deeper responses than ncBTK inhibitor monotherapy, likely due to synergistic mechanisms of action and their use in earlier treatment settings. Non-covalent BTK inhibitors remain valuable therapeutic options for patients with cBTKi-resistant disease but demonstrate limited CR rates when used as monotherapy. Future clinical trials combining ncBTKis with B-cell lymphoma 2 (BCL-2) inhibitors or anti-CD20 monoclonal antibodies may further enhance remission depth and durability in patients with refractory CLL/SLL.

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INTRODUCTION

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell neoplasm characterized by the gradual accumulation of monoclonal B lymphocytes in the peripheral blood, bone marrow, and lymphoid tissues (Woyach et al., 2022). Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) represent the same disease entity and are classified as forms of mature B-cell non-Hodgkin lymphoma with distinct clinical presentations (Jahic & Custendil, 2017; Tees & Flinn, 2017; Wierda et al., 2020). The malignant cells in both CLL and SLL share identical pathological and immunophenotypic characteristics. The term CLL is used when the disease predominantly involves the peripheral blood and bone marrow, whereas SLL refers to cases in which the disease primarily affects lymph nodes and other lymphoid tissues (Mato et al., 2023).

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a relatively uncommon malignancy overall but represents the most common type of leukemia among adults. It accounts for less than 1% of all cancers and approximately 14% of all leukemias worldwide (Daltveit et al., 2025; Huang et al., 2022; Lin et al., 2021). CLL/SLL primarily affects older adults, with a median age at diagnosis of approximately 70 years, and demonstrates a slight male predominance, with a male-to-female ratio ranging from approximately 1.2:1 to 1.8:1 (Hampel et al., 2022; Woyach et al., 2022).

Bruton tyrosine kinase inhibitors (BTKis) and venetoclax are relatively novel therapeutic agents that have become key components in the management of both newly diagnosed and relapsed/refractory chronic lymphocytic leukemia (CLL) (Bennett & Seymour, 2024; Iskierka-Jażdżewska et al., 2022; Robak et al., 2024; Thompson & Burger, 2018). Although these therapies achieve favorable clinical outcomes in most patients, they are not curative, and disease progression may still occur (Mato et al., 2023).

With the introduction of first-in-class covalent Bruton tyrosine kinase inhibitors (cBTKis), the treatment landscape for chronic lymphocytic leukemia (CLL) has evolved rapidly, particularly over the past decade. Covalent Bruton tyrosine kinase inhibitors (cBTKis), including ibrutinib, acalabrutinib, and zanubrutinib, exert their antineoplastic activity through irreversible binding to the cysteine 481 (C481) residue within the active site of the BTK enzyme, thereby disrupting B-cell receptor signaling and promoting apoptosis in malignant B cells from patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) (Bagnara et al., 2022; Efremov et al., 2020; Patton & Woyach, 2024; Schmid & Hobeika, 2024). However, acquired resistance commonly develops through mutations at the BTK C481 site, which impair covalent drug binding. Non-covalent (reversible) BTK inhibitors (ncBTKis), such as pirtobrutinib, have been developed to overcome this limitation by binding to BTK independently of the C481 residue, thereby maintaining inhibitory activity in patients with disease refractory to covalent BTK inhibitors (Mato et al., 2023).

Venetoclax is an orally bioavailable small-molecule inhibitor that selectively targets the anti-apoptotic protein B-cell lymphoma 2 (BCL-2). It is approved for use in both frontline and relapsed/refractory settings, either as monotherapy or in combination with anti-CD20 monoclonal antibodies. Additionally, venetoclax is indicated for patients with del(17p13.1) CLL who have received at least one prior line of therapy (Mato et al., 2023). Patients who have been exposed to both a Bruton tyrosine kinase inhibitor (BTKi) and venetoclax, and who subsequently develop resistance to both therapeutic classes, are referred to as having "double-

refractory" CLL. Following discontinuation of covalent BTK inhibitor and venetoclax therapy, clinical outcomes in this population are extremely poor, with a median time to subsequent treatment failure or death of less than six months (Hampel et al., 2022).

This systematic review aims to synthesize evidence from clinical trials and real-world studies regarding available treatment options and their efficacy or effectiveness in patients with double-exposed chronic lymphocytic leukemia (CLL). This review is expected to provide evidence-based guidance for selecting optimal therapeutic strategies in double-exposed CLL/SLL patients, a population characterized by limited treatment options and poor prognosis, while clarifying whether non-covalent BTK inhibitors provide a meaningful therapeutic advantage over covalent agents or whether combination regimens remain necessary. The synthesized evidence will inform future clinical trial designs by identifying knowledge gaps related to treatment sequencing, combination strategies, and minimal residual disease (MRD)-driven approaches. Furthermore, the findings may support policymakers in evaluating cost-effectiveness considerations associated with these expensive novel agents. By consolidating heterogeneous evidence from small-scale studies, this review aims to generate comprehensive insights that individual studies alone cannot provide, ultimately contributing to improved therapeutic outcomes in this challenging patient population.

METHOD

Eligibility criteria

The inclusion criteria comprised studies comparing covalent and non-covalent BTK inhibitors (BTKis) that reported efficacy outcomes, including progressive disease, complete response, stable disease, and partial response, with full-text availability. The exclusion criteria included other study designs, such as letters, comments, case reports, reviews, animal studies, cadaveric studies, biomechanical studies, and study protocols; studies with abstracts only; and duplicate studies.

Search strategy

We searched systematically using the keywords Covalent Bruton tyrosine kinase inhibitor AND Non-Covalent Bruton tyrosine kinase inhibitor AND Anesthesia AND (Chronic Lymphocytic Leukemia OR Small Lymphocytic Lymphoma) in the MEDLINE, CENTRAL, and EMBASE databases to find prefered studies. Authors performed the study selection process to decrease possibility of discarding relevant studies. Duplicate studies were removed. Titles and abstracts were screened, and irrelevant studies were removed. Studies that passed the first screening were further evaluated for compliance with this review's inclusion and exclusion criteria. With 10 years limits regarding of publication. Articles were included if they reported data on clinical and functional outcomes and complications especially studies which compared Covalent and Non-Covalent BTKis outcome for treatment of CLL/SLL. Studies were evaluated for its quality before being included in the review, place and tools of research materials. Picture captions are placed as part of the picture title (figure caption) not part of the picture. The methods used in completing the research are listed in this section.

RESULT AND DISCUSSION

The results and discussion contain the results of research findings and scientific discussions. Write down scientific findings (scientific finding) obtained from the results of

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research that has been carried out but must be supported by adequate data. The scientific findings referred to here are not data obtained from research results. The scientific findings must be explained scientifically including: What are the scientific findings obtained? Why did that happen? Why such a variable trend? All these questions must be explained scientifically, not only descriptively, if necessary supported by adequate scientific basis phenomena. In addition, the comparison with the results of other researchers on the same topic should also be explained. Research results and findings must be able to answer the research hypothesis in the introduction.

Sub Point 1

Manuscripts can be written in Indonesian or English with a maximum number of 20 pages of figures and tables. Manuscripts must be written according to this article template in camera ready form. Articles must be written in A4 (210 x 297 mm) writing area and with the format left margin of 4 cm, right margin of 3 cm, bottom margin of 4 cm, and bottom margin of 3 cm. Manuscripts must be written in Times New Roman with a font size of 12 pt, one spaced apart, and in one column format (except for the article title, author's name and abstract). The distance between the columns is 1 cm.

Foreign words or terms are used in italic letters. It is better to avoid using foreign terms for articles in Indonesian. The new paragraph starts 1 cm from the left border, while there are no spaces between paragraphs.

Sub Point 2

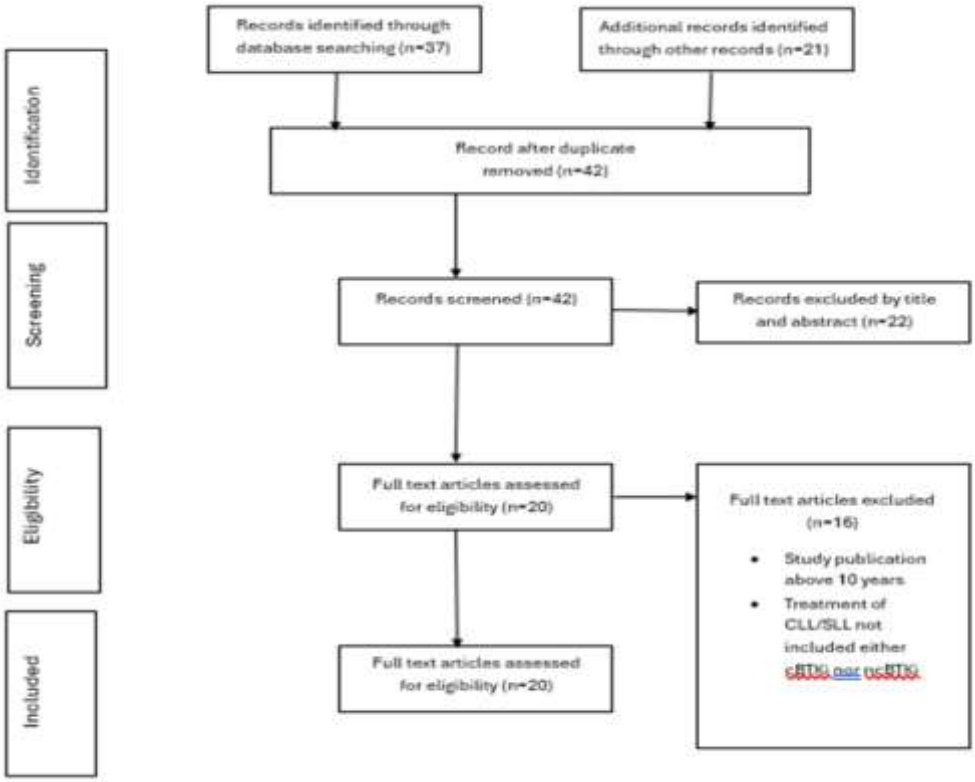

Figure 1. Flow diagram based on the PRISMA (Preferred Reporting Items for Systematic Meta-Analyses) guidelines

Source: Adapted from Page et al. (2021), PRISMA 2020 flow diagram for systematic reviews which included searches of databases and registers

Data items

Data items were author's name, treatment name, treatment class, number of patients, outcome including Complete Response, Partial Response, Stable Disease, Progressive Disease in percentage.

Table 1. Studies Outcomes

Study	Treatment Name	Treatment Class	Number of patient	Complete Response (%)	Partial Response (%)	Stable Disease (%)	Progressive Disease (%)
Mato et al, 2023	Pirtobrutinib	ncBTKi	100	0	70	11	-
Woyach et al, 2022	Nemtabrutinib	ncBTKi	24	0	25	-	-
Hampel et al, 2022	Ibrutinib+venetoclax	cBTKi	11	55	45	-	-
Din et al, 2023	Acalabrutinib + Obinutuzumab	cBTKi	2	50	-	-	-

Source: Outcome data for pirtobrutinib were reported in the BRUIN trial. Data for nemtabrutinib were derived from the BELLWAVE-001 study

Assessment of quality of study

Studies that met the inclusion and exclusion criteria were assessed for quality. The overall quality of evidence for the clinical trials studies was evaluated using the Newcastle-Ottawa Scale (NOS) guidelines. All four clinical trials studies were rated as having good quality based on the NOS, supporting the validity and reliability of their findings.

Assessment of study biases

Risk of bias was evaluated across all included studies using domains adapted from the Cochrane Risk of Bias tool and the Newcastle–Ottawa Scale (NOS). Overall, the methodological quality of the included studies was rated as moderate to good, but several potential sources of bias were identified

Selection:

All included studies were clinical trials enrolling patients with relapsed/refractory CLL/SLL, but sample sizes were small (ranging from 2 to 100 patients). This limited external validity and increased susceptibility to random variation. Additionally, inclusion criteria varied, with some trials enrolling heavily pretreated patients, potentially influencing treatment response rates.

Performance:

Most studies were open-label, introducing possible bias in clinical management and response assessment. Lack of blinding may have influenced investigator-reported outcomes, particularly in non-randomized or early-phase studies.

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Detection:

Response evaluation criteria were largely standardized (based on IWCLL guidelines); however, heterogeneity in imaging, laboratory follow-up intervals, and use of minimal residual disease (MRD) assessment could affect comparability across studies.

Attrition:

Follow-up durations differed substantially between studies, and outcome data for progressive disease (PD) were incomplete in some reports, potentially underestimating progression rates or overestimating response durability.

Reporting:

Two of the included studies were published as conference abstracts or early-phase reports with limited detail on safety and secondary outcomes. Selective reporting of favorable efficacy endpoints cannot be excluded.

Overall:

Despite the generally good methodological quality by NOS scoring, the limited sample size, heterogeneous patient populations, and incomplete outcome reporting introduce moderate overall risk of bias. Therefore, conclusions drawn from this review should be interpreted cautiously and validated by larger, randomized controlled studies.

Results and Discussion

Four studies comprising a total of 137 patients with CLL/SLL were included in the analysis, evaluating both covalent and non-covalent BTK inhibitor–based regimens. Among the non-covalent BTK inhibitors (ncBTKi), pirtobrutinib (Mato et al., 2023) demonstrated a partial response (PR) rate of 70% and stable disease (SD) in 11% of patients, with no complete responses (CR) reported. Similarly, nemtabrutinib (Woyach et al., 2022) yielded a PR rate of 25% without CRs. In contrast, covalent BTK inhibitor (cBTKi)–based combinations showed higher overall response rates. Ibrutinib plus venetoclax (Hampel et al., 2022) achieved a CR rate of 55% and PR rate of 45% among 11 patients. Acalabrutinib plus obinutuzumab (Din et al., 2023) reported CR in 50% of two treated patients. Progressive disease (PD) rates were not consistently reported across studies.

In this pooled analysis of 137 patients across four studies of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) treated with either covalent or non-covalent Bruton tyrosine kinase inhibitors (BTKis), some key observations emerge. The non-covalent BTKi regimens (namely Pirtobrutinib and Nemtabrutinib) yielded partial response rates of 70% and 25% respectively, with no complete responses reported in the cohorts included here. In contrast, the covalent BTKi combinations (Ibrutinib + Venetoclax and Acalabrutinib + Obinutuzumab) achieved substantially higher complete response (CR) rates (55% and 50%, respectively). These findings have several implications (Sharman et al., 2025; Woyach et al., 2025).

First, the superiority of covalent BTKi combinations in achieving CRs likely reflects both the mechanism of action and patient-selection factors. The covalent inhibitors irreversibly bind to BTK at the Cys-481 residue, resulting in profound B-cell receptor pathway suppression. Although not all studies report progressive disease (PD) rates, the higher CRs suggest deeper remissions. For example, Ibrutinib plus Venetoclax achieved CR in 55% of 11 patients in our data set, which is consistent with other literature showing high CR/undetectable minimal

residual disease (MRD) rates with this combination in relapsed/refractory (R/R) or even frontline CLL (Jones et al., 2019).

Second, the non-covalent BTKi data highlight a niche for patients with prior exposure or resistance to covalent BTKis. Pirtobrutinib has the advantage of being effective in the presence of BTK C481 mutations, which commonly confer resistance to covalent inhibitors. However, despite this mechanistic advantage, in our dataset the CR rate was zero and only 70% achieved a partial response. This suggests that although non-covalent BTKis provide a valuable therapeutic option post-covalent-BTKi failure, their ability to produce deep CRs may be more limited in the current care paradigm (Jones et al., 2019).

Third, the small patient numbers and heterogeneity of the dataset (e.g., different prior therapies, disease risk features, combination regimens) must temper the conclusions. The Acalabrutinib + Obinutuzumab combination had only 2 patients in our table (CR 50 %), thus interpretation is very limited. In addition, the absence of reported PD rates in several studies limits our ability to infer durability or failure patterns.

From a clinical perspective, these results support several points for discussion and further investigation:

Treatment sequencing and resistance: The emergence of C481 mutations under covalent BTKi pressure is well documented, and non-covalent BTKis like pirtobrutinib are purpose-built to overcome that resistance mechanism. Thus, integrating non-covalent BTKis earlier in appropriate patients may improve outcomes, but the limited CR rates indicate that monotherapy may not suffice for deep remission in many cases (Woyach et al., 2025).

Combination strategies: The higher CR rates seen with covalent BTKi combined with other targeted agents (e.g., venetoclax) suggest that combinations—rather than single agent BTKi—may be necessary to achieve deep and durable remissions. In particular, regimens that include BCL-2 inhibitors or anti-CD20 antibodies may deepen responses. For example, the Ibrutinib + Venetoclax study found 51% achieving CR in 53 patients in the CLARITY trial. Acalabrutinib plus Obinutuzumab also showed 32% CR in treatment-naïve patients in a phase Ib/II study. Thus, exploring non-covalent BTKi in combination (rather than monotherapy) is a logical next step (Hampel et al., 2022).

Depth of response and MRD: chieving CR or undetectable MRD has been associated with improved progression-free survival (PFS) and overall survival (OS) in CLL. The covalent BTKi-combination data suggest strong PFS benefits (e.g., 3-year PFS ~93% in Ibrutinib + Venetoclax frontline). Therefore, while non-covalent BTKi show efficacy, the ability to drive MRD negativity remains to be fully demonstrated, which may limit long-term benefit (Woyach et al., 2024).

Safety and tolerability: Although not captured in our summary table, safety profiles differ between agents and combinations, which affects tolerability and clinical choice. Highly selective BTKis (such as acalabrutinib) may have fewer off-target cardiovascular toxicities. Non-covalent BTKis may also offer safety advantages, but long-term safety data are still emerging (Sharman et al., 2023; Woyach et al., 2024).

CONCLUSION

In CLL/SLL treatment, covalent BTK inhibitor (cBTKi)-based combination regimens appeared to provide deeper responses, as reflected by higher complete response (CR) rates,

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compared with non-covalent BTK inhibitor (ncBTKi) monotherapy in the settings evaluated in this review. Non-covalent BTK inhibitors (ncBTKis) remain an important therapeutic option, particularly for patients with resistance to covalent BTK inhibitors; however, their full potential may be better realized through combination regimens and earlier lines of therapy. Future clinical trials should investigate ncBTKi-based combination approaches, head-to-head comparisons, and optimized sequencing strategies, with a specific focus on achieving deeper remissions, minimal residual disease (MRD) negativity, and improved long-term survival outcomes.

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