Comparing the Efficacy and Safety of First-Line Treatments for Chronic Lymphocytic Leukemia: A Network Meta-Analysis

Tingyu Wen MD[1,2]*, Guangyi Sun MD[3]*, Wenxin Jiang MD[2], Kat Steiner MSc[3], Suzannah Bridge MA[3], Peng Liu MD[2]

[1] National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, Tianjin's Clinical Research Center for Cancer, Tianjin, 300060, China.

2 Department of Medical Oncology and Radiation Oncology, National Cancer Center / National Clinical Research Center for Cancer / Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China.

3 Bodleian Health Care Libraries, University of Oxford, UK

*Authors contributed equally to this work.

Correspondence to: P Liu liupeng@cicams.ac.cn; Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China.

Abstract

Background The Chronic Lymphocytic Leukemia (CLL) treatment strategies have transitioned from chemotherapy and chemoimmunotherapy to chemo-free regimens. Frequentist network meta-analysis allows for both direct and indirect comparisons between different treatments.

Methods Randomized controlled trials assessing first-line treatments were included. Outcomes were progression-free survival (PFS), overall survival, undetectable minimal residual disease (MRD), objective response rate, and adverse events. Studies with comparable characteristics also underwent subgroup analysis, stratifying by age, comorbidities, IGHV status, and cytogenetic abnormalities.

Results 30 eligible trials involved 12,818 patients and 30 treatments were included. Acalabrutinib demonstrated a PFS advantage over ibrutinib and obinutuzumab-venetoclax (OV) in patients over 65 years old or with unmutated IGHV. In younger patients with comorbidities, Acalabrutinib-Obinutuzumab (AO) had superior PFS compared to Ibrutinib-Obinutuzumab (IO), Ibrutinib-Venetoclax (IV), and OV. For older patients with comorbidities, Acalabrutinib and AO both outperformed OV without significant difference between them. MRD-guided IV surpassed OV in patients without comorbidities. IO exhibited extended PFS benefits compared to OV in patients with mutated IGHV or with del(17p) and/or TP53 mutations. IV and IO have lower neutropenia rates than OV. IV have fewer infections than Acalabrutinib and AO. AO causes less diarrhea than IV but more headaches than IO and OV. OV has lower hypertension rates than IO. IV has fewer arthralgia than AO. For any grade secondary primary neoplasms, IV and OV is less than AO.

Conclusion Tailored chemo-free regimens can be selected based on age, comorbidities, IGHV status, and cytogenetic abnormalities to optimize treatment outcomes while considering different response spectra**.**

Introduction

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (CLL/SLL) is the most common leukemia in the US, around 200,000 individuals are affected, with 2023 estimates indicating 18,740 new cases and 4,490 deaths[1]. The median age at diagnosed is 70. The 5-year survival rate for CLL/SLL is about 90%, with a 10-year rate of approximately 82%. Initially, 70%-80% of patients require no treatment until they have evidence for progressive or symptomatic disease [2]. The unique characteristics of CLL/SLL, its chronic nature, and its high incidence rate warrant extensive attention.

In December 2015, the first-in-class drug Ibrutinib (Ibru) creates possibilities for an era of chemotherapy-free management of CLL/SLL. The treatment landscape for CLL/SLL is currently undergoing a significant transformation, moving away from traditional chemotherapy and chemoimmunotherapy (CIT) to embrace chemo-free approaches. The first-line treatment options for CLL/SLL that have been explored in clinical trials include Bruton's Tyrosine Kinase (BTK), B-cell lymphoma (BCL2) proapoptotic inhibitor, monoclonal Anti-CD20 Antibodies, and chemotherapies. Recent maturation and publication of trial data for chemo-free regimens have revealed notable efficacy disparities between chemo-free approaches and conventional CIT, yet direct comparisons among chemo-free regimens remain scarce. This evolution poses a challenge for clinicians in selecting the optimal initial treatment strategy, given the broad range of options. The latest NCCN guidelines for naïve CLL/SLL, without delineating a prioritized treatment hierarchy, but recommend Acalabrutinib ± Obinutuzumab (Acala/AO), Venetoclax-Obinutuzumab (OV), and Zanubrutinib (Zanu), suitable for patients with or without TP53 mutation/del(17p). The ESMO guidelines, last

updated in 2021[3], lack recent data on chemo-free regimens, showing a requirement for the most recent information in this rapidly evolving treatment landscape.

The application of network meta-analysis has provided a strategic approach for addressing clinical dilemmas. The choice of CLL/SLL as the research subject is feasible and has profound clinical significance. CLL/SLL, being the most common B-cell malignancy, boasts a notably high clinical trial success rate (7.3% from phase I to FDA approval), surpassing the rates observed in solid tumors (5.7%)[4]. This abundance of data makes CLL/SLL an ideal candidate for network meta-analysis. The market for CLL/SLL, now exceeding ten billion dollars, has undergone a revolutionary transformation with the introduction of target inhibitors, marking a paradigm shift towards chemotherapy-free regimens. Through network meta-analysis, this study quantitatively compares the clinical efficacy and toxicity of different regimens in CLL/SLL patients. It not only offers new insights for future clinical trials but also provides strategic positioning to address unmet clinical needs in the billion-dollar market.

Our study thoroughly assesses both the efficacy, characterized by progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and undetectable minimal residual disease rate (uMRD), and safety, defined by the incidence of 30 selected adverse event (AE) terms. It encompasses an analysis of 30 trials, comparing the outcomes of 30 distinct treatments among 12,818 treatment naïve CLL/SLL patients. Notably, the study delves into identifying optimal treatment regimens, providing precise recommendations tailored to disease characteristics, risk factors, and comorbid conditions, thereby refining treatment strategies for CLL/SLL. This research significantly contributes to key debates in CLL/SLL first-line

treatment by 1) deepening insights into the role of CIT in the chemo-free era, 2) identifying the preferred BTK inhibitor for initial treatments rather than second-line therapy, and 3) evaluating BTK-based combinations versus BTK monotherapy. The study also 4) contrasts continuous BTK-based combinations with time-limited Venetoclax therapies, and 5) investigates distribution differences in adverse events across various treatment regimens, 6) exclude weaker treatment options from preferred regimens in guidelines, considering different age groups, comorbidities, and molecular genetic profiles, aiding in the selection of the optimal therapy option.

Methods

This network meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. This systematic review has been registered in PROSPERO (CRD42023445683).

Search strategy

Systematic literature searches were conducted separately on Medline (via Ovid), Embase (via Ovid), Cochrane Central Register of Controlled Trials (via Wiley), and ClinicalTrials.gov (classic version), and WHO ICTRP on 2nd August 2023. The search strategy (Supplementary Table 1) consisted of subject headings and keyword terms for the concepts of CLL/SLL; treatment-naive, first line, or untreated; and drugs recommended for first-line therapy, taken from British and US Guidelines[1, 5]. The terms for CLL and SLL were adapted from Kreuzberger et al[6]. In Medline, the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

was used. In Embase, the CENTRAL RCT filter was used. Embase searches were limited to conference abstracts published from 2020 onwards. In ClinicalTrials.gov, results were limited to studies with results. No other limits or filters were used. Reference lists of relevant articles were scrutinized. To include complete and updated outcomes, abstracts of ongoing randomized controlled trials from several of the most important international conferences (American Society of Clinical Oncology, European Society of Medical Oncology, American Society of Hematology, and European Society of Hematology). During the peer-review period, we also conducted manual literature searches and updates, up to February 2024. The results underwent deduplication in EndNote. Trial registrations without results from Cochrane CENTRAL, WHO ICTRP and ClinicalTrials.gov were manually removed before screening.

Eligibility criteria and selection process

Included studies were: 1) Trials enrolling patients with documented CLL/SLL requiring treatment based on iwCLL criteria[2]. 2) Trials comparing two or more different first-line treatments. 3) Trials reporting on at least one of the following clinical outcomes: PFS, OS, ORR, uMRD. Response assessments conformed to iwCLL guidelines[1, 2]. Safety adverse events were defined and graded according to the National Cancer Institute's common terminology criteria for adverse events (NCI-CTCAE) and classified using the Medical Dictionary for Regulatory Activities classification system (MedDRA). 4) Phase II/III randomized controlled trials.

Exclusion criteria involved: 1) The study subjects includes both treatment-naïve individuals and those with relapsed/refractory conditions, which may introduce potential biases. 2)

Treatments used for maintenance, consolidation, or investigating dosage and sequence. 3) Small samples less than 20.

All study periods and follow-up durations were considered, including updated data from mature or long-term follow-ups. Titles and abstracts were screened, and the full text of potentially eligible articles were assessed for final inclusion by two independent reviewers.

Data collection

Data regarding trial details (e.g., study ID, first author, publication year, patient numbers and characteristics), treatments, outcomes, and adverse events were extracted into a spreadsheet by two independent reviewers. Preference was given to survival data assessed by an independent review facility to mitigate assessment bias. Treatment-related adverse events were prioritized, and if unspecified, all adverse events were considered. ClinicalTrials.gov and other sources were evaluated for recent and complete data. We reached out to study authors and pharmaceutical companies for clarification or unreported crucial data.

Study risk of bias assessment

Two reviewers utilized the Cochrane Risk of Bias Tool to evaluate biases within individual studies, focusing on factors like random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other possible biases. Ultimately, each study was scored for risk of bias as low, high, or unclear.

Data synthesis and statistical analysis

Before conducting comparisons, we performed similarity matching based on the clinical trial patient characteristics to ensure comparability among the included studies and to mitigate biases in the meta-analysis. We reported hazard ratios (HR) for survival outcomes such as PFS and OS, and odds ratios (OR) for binary outcomes including ORR, uMRD, and adverse events (AE), along with their corresponding 95% confidence intervals (CI). Empirical and simulation studies suggest that both frequentist and Bayesian approaches in network meta-analysis often yield overlapping results. Therefore, we opted for a frequentist network meta-analysis in this study. Network plots were produced for each outcome to visualize network geometry and node connectivity. We estimated effect sizes for categorical and survival outcomes using the Mantel-Haenszel method for ORs and either fixed or random effects models for HRs based on heterogeneity, with 95% confidence intervals calculated using the DerSimonian-Laird method. Missing information was imputed using approximate or exact adjustment methods as described by Gerta et al[7]. The frequentist method uses P-scores to rank treatments, which measure the certainty that one treatment is better than another treatment, averaged over all competing treatments, using the Netmeta R package[8, 9]. Heterogeneity between studies was assessed using the Q test and I^2 statistic, with statistical significance set at a P value of 0.05. Heterogeneity was classified as low, moderate, or high for estimated I^2 values under 25%, between 25% and 50%, and over 50%, respectively. Fixed-effects models were used when heterogeneity was low to moderate, while random-effects models were employed otherwise. We employed the Separate Indirect from Direct Evidence method to detect inconsistencies between direct and indirect evidence in the network meta-analysis. This method utilizes a back-calculation approach, incorporating the proportion of direct evidence in the computation

of indirect evidence, as described by König et al[10]. Additionally, transitivity was assessed using descriptive statistics for study types and demographic characteristics.

Subgroup analysis

To enhance the comparability of enrollment criteria among the studies and to ascertain the optimal efficacy of various treatment regimens within precision subjects, subgroup analyses were performed, stratifying patients according to age, comorbidities, IGHV mutational status, and cytogenetic abnormalities. Those over 65 years old are defined as elderly, while those under 65 are considered young, as defined in most studies. Unfit is defined as being over 65 years old or having comorbidities. Cytogenetic abnormalities at diagnosis considered include deletion 17p (del(17p)) and/or *TP53* mutation, deletion 11q (del(11q)), deletion 13q (del(13q)), and complex karyotype. The complex karyotype is defined by the presence of three or more distinct chromosomal abnormalities. Notably, del(17p), del(11q), *TP53* mutations, unmutated IGHV, and complex karyotype are identified as unfavorable prognostic factors in CLL/ SLL. Conversely, del(13q) and mutated IGHV are considered favorable factors. These features provide critical prognostic insights regarding survival and time to progression in patients undergoing chemoimmunotherapy-based treatments. The impact of these prognostic variables in patients receiving targeted therapies remains less clearly defined.

The study aims to thoroughly evaluate a wide range of AEs, categorizing them into treatment discontinuation, dose reductions exceeding 20%, and adverse events of any grade or those grade 3 or higher. AEs includes neutropenia, infections, hypertension, skin disorders, tumor

lysis syndrome, secondary primary neoplasms, atrial fibrillation, bleeding events, arthralgia, diarrhea, anemia, headaches, infusion-related reactions, and thrombocytopenia.

Sensitivity analysis, reporting bias assessment and evidence confidence assessment

For the sensitivity analysis, the robustness of the conclusions was evaluated by altering the effect size models (for instance, switching from fixed-effect to random-effects models), and considering the removal of studies identified as having a high risk of bias. The evaluation of publication bias will entail scrutinizing funnel plots for asymmetries potentially arising from variations in study size or other influences, suggesting the presence of publication bias. When the number of included studies exceeds 10, statistical approaches will incorporate Egger's regression test and Begg's rank correlation test, which are tools capable of quantifying the magnitude of bias and determining its statistical significance. The certainty of evidence across six key domains—within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and inconsistency—is assessed employing the CINeMA framework.

Result

Study selection and characteristics

A total of 33 randomized controlled clinical trials were identified as eligible for inclusion (Figure 1, Table 1). However, due to the inability of three studies to form a network within the closed loop, the network meta-analysis ultimately included 30 eligible trials, involving 12,818 patients, and encompassing 30 different treatments. Bias risk assessments indicate that most studies are at low risk (Supplementary Figure 1). The majority of trials included were published in prestigious journals such as The Lancet, NEJM, Lancet Oncology, and the Journal

of Clinical Oncology with high quality. This research revealed over 500 new positive results comparing the efficacy and safety of 30 regimens in different subgroup analysis, previously unreported by any head-to-head clinical trials (Figure2-3, Supplementary Figures 31, Supplementary Table 59-61).

Chemotherapy regimens include FC (Fludarabine, Cyclophosphamide), F (Fludarabine), Clb (Chlorambucil), CC (Cladribine, Cyclophosphamide), B (Bendamustine), CMC (Cladribine, Mitoxantrone, Cyclophosphamide), and 2-CdA (Cladribine). Targeted therapy encompasses OIV (Obinutuzumab, Ibrutinib, Venetoclax), Zanu, RV (Rituximab, Venetoclax), R (Rituximab), OV, Len (Lenalidomide), IV (Ibrutinib, Venetoclax), IV MRD (MRD-guided IV), IR (Ibrutinib, Rituximab), IO (Ibrutinib, Obinutuzumab), Ibru, AO, Alemtuzumab, and Acala. BTK inhibitors include Ibru, Acala, and Zanu. Chemoimmunotherapy options include R-Clb (Rituximab, Chlorambucil), O-Clb (Obinutuzumab, Chlorambucil), FR (Fludarabine, Rituximab), FCR, FCM-R (Fludarabine, Cyclophosphamide, Mitoxantrone, Rituximab 500mg), FCM-miniR (Fludarabine, Cyclophosphamide, Mitoxantrone, Rituximab 100mg), FC plus alemtuzumab, BR (Bendamustine, Rituximab), CIT (age less than 65 years received FCR, others received BR), and Ofa-Clb (Ofatumumab, Chlorambucil).

UK FLAIR is a phase 3 adaptive trial. Initially, it compared IR and FCR in CLL. However, in 2017, the trial was amended to include two additional groups: Ibru and IV-MRD. Since there was no direct comparison between IV-MRD and IR, we divided UK FLAIR into two separate studies for clarity in our presentation.

Network meta-analysis in the overall subjects

The PFS of AO in the overall subjects significantly superior to all chemo-free regimens and CITs, except the MRD-guided IV and IV regimens (AO vs Ibru, HR 0.19, 95%CI 0.12-0.32; AO vs Zanu, HR 0.23, 95%CI 0.13-0.43; AO vs OV, HR 0.34, 95%CI 0.22-0.53; AO vs IO, HR 0.56, 95%CI 0.32-0.98). The monotherapy of Acala also provides PFS benefit compared to Zanu (HR 0.4, 95%CI 0.22-0.72), Ibru (HR 0.33, 95%CI 0.2-0.53), and OV (HR 0.59, 95%CI 0.39-0.88). AO vs. IO involved only one node transmission. The PFS of IV (HR 0.53, 95%CI 0.32-0.87) and IV-MRD (HR 0.43, 95%CI 0.22-0.85) were superior to OV. For OS, AO (HR 0.44, 95%CI 0.23-0.87), and IV (HR 0.35, 95%CI 0.16-0.78) were comparable to FCR, and IV-MRD (HR 0.32, 95%CI 0.12-0.87) were comparable to Zanu, in providing OS benefit. The OS data of AO, IV, and Zanu come from patients with comorbidities, and the OS data of IV-MRD and FCR come from patients younger than 75 years old without comorbidities, which may present certain heterogeneity. The uMRD of Ibru monotherapy was lower than AO, IO, IV-MRD, and OV (Supplementary Table 3-6, Supplementary Figure 2).

Network meta-analysis in old patients or with severe comorbidities

The SEQUOIA, ELEVATE-TN, CLL14, Glow, iLLUMINATE, CLL11, and Complement1 trials exclusively enrolled patients with comorbidities, with no age restrictions. The A041202, CLL5, RESONATE, and ORIGIN trials only included elderly patients aged over 65. Other studies had enrollment criteria of no comorbidities but may allow patients over 65 years of age; if so, we aggregated the subgroup data of patients older than 65 from these studies (Supplementary Table 2,7-19, Supplementary Figure 3-9).

In patients older than 65 years or with severe comorbidities, the PFS of Acala was superior to that of Ibru (HR 0.32, 95%CI 0.19-0.53), OV (HR 0.64, 95%CI 0.42-0.97), and Zanu (HR 0.43, 95%CI 0.22-0.83). The PFS of AO was superior to IO (HR 0.56, 95%CI 0.32-0.98), OV (HR 0.37, 95%CI 0.24-0.58), and Zanu (HR 0.25, 95%CI 0.13-0.49). Additionally, the PFS of IV was superior to OV (HR 0.57, 0.34-0.96) and Zanu (HR 0.38, 95%CI 0.19-0.79). The direct (HR 1.72, 95%CI 1.16-2.56) and pooled estimates (HR 1.72, 95%CI 1.16-2.55) of PFS for Acala vs. AO were consistent. The pooled HR for overall OS among Acalabrutinib vs. AO was HR 1.44 (95%CI 0.92-2.27), consistent with the direct comparison results (HR 1.45, 95%CI 0.92-2.28).

To further compare the applicability of various regimens in patients with severe comorbidities, we divided this subject into younger and older groups, using 65 years as the threshold. The PFS of AO was always greater than OV (any age: HR 0.4, 95%CI 0.25-0.63; younger: HR 0.08, 95%CI 0.02-0.31; older: HR 0.3, 95%CI 0.13-0.68). In younger patients, the PFS of AO showed a benefit compared to IO (HR 0.08, 95%CI 0.02-0.34) and IV (HR 0.08, 95%CI 0.01-0.49). In older patients, the PFS of Acalabrutinib also showed a benefit compared to OV (HR 0.45, 95%CI 0.21-0.97).

Network meta-analysis in patients without severe comorbidities

After excluding studies that only enrolled patients with severe comorbidities, we categorized the population into any age, younger than 65 years, and older than 65 years. IV-MRD provided superior PFS (HR 0.31, 95% CI 0.15-0.66) but ORR (OR 0.34, 95% CI 0.14-0.82) and uMRD (OR 0.41, 95% CI 0.23-0.73) compared to OV. Chemo-free regimens, including Ibrutinib (HR

0.52, 95%CI 0.32-0.84), OIV (HR 0.3, 95%CI 0.13-0.69), and OV (HR 0.4, 95%CI 0.19-0.83), showed superior PFS benefit compared to chemoimmunotherapy FCR in patients older than 65 years without severe comorbidities (Supplementary Table7-12, Supplementary Figure 3-9).

Network meta-analysis in patients with mutated IGHV

BTK-CD20 combination AO (HR 0.23, 95%CI 0.06-0.84) and IO (HR 0.18, 95%CI 0.04-0.75) were comparable to Ibru in providing PFS benefits. The PFS of IO, rather than AO, was superior to both IV (HR 0.28, 95%CI 0.08-0.95) and OV (HR 0.27, 95%CI 0.07-0.99). Compared to FCR, the PFS of AO (HR 0.18, 95%CI 0.05-0.65) and IO (HR 0.14, 95%CI 0.03-0.58) demonstrated a significant PFS advantage (Supplementary Figure 10, Supplementary Table 20-21).

Network meta-analysis in patients with unmutated IGHV

Both monotherapy Acala and combination AO provide PFS benefit compared to Ibru, IV, IR, OV, and Zanu. While no difference between Acala and AO from the direct (HR 1.59, 95% CI 0.99-2.55) and pooled estimate (HR 1.54, 95% CI 0.96-2.48). Compared to FCR, both Acala (HR 0.15, 95%CI 0.08-0.27) and Ibru (HR 0.5, 95%CI 0.3-0.83) provide benefit PFS (Supplementary Figure 10, Supplementary Table 22-23).

Network meta-analysis in patients with del (17p) and/or *TP53* mutation

Due to many trials excluding this high-risk subject, only a limited number of patients were included. A notable positive finding in our research is that the PFS of IO was superior to OV (HR 0.23, 95%CI 0.05-0.97) (Supplementary Figure 11, Supplementary Table 26).

Network meta-analysis in patients with del (11q)

The OIV demonstrated a significant PFS advantage over Zanu (HR 0.2, 95%CI 0.05-0.81). Acala showed superiority over FCR (HR 0.14, 95%CI 0.02-0.97) (Supplementary Figure 11, Supplementary Table 24).

Network meta-analysis in patients with del (13q) or complex karyotype

IV-MRD showed PFS benefit compared to BR in patients with no obvious significant PFS benefit among in patients with complex karyotype, despite the P-score of AO rank the first. IV-MRD demonstrated a PFS benefit compared to BR in patients with del(13q). Among patients with a complex karyotype, no clear significant PFS benefit was observed among Acala, AO, OV, Zanu, and OIV, even though the P-score of Acala/AO ranked the highest Supplementary Figure 11, Supplementary Table 25-27).

Adverse events (Supplementary Table 28-57, Supplementary Figure 12-26)

The incidence of grade 3 or higher adverse events for Zanu is significantly lower than that for Acala, AO, IO, IV, and OV. The incidence of grade 3 or higher adverse events for Acala is also lower than that for IO, IV, and OV. The OIV regimen was associated with increased occurrences of dose reductions exceeding 20% and treatment discontinuations due to AEs relative to Zanubrutinib.

In terms of neutropenia across all grades and specifically for grade 3 or higher, Zanu demonstrated lower incidence rates in comparison to Acala, Ibru, IO, IV, AO, and OV. The

incidence of neutropenia with IV was inferior to that observed with OV (Any grade: OR 0.5, 95% CI 0.26-0.98; Grade ⩾3: OR 0.5, 95%CI 0.26-0.97). For any grade or Grade ⩾3, the incidences of thrombocytopenia in Zanu were lower than IO, OV, and AO. For any grade infections, the incidence was higher in Acala/AO compared to Zanu, Ibru, IV, and IR. The incidence rate of Ibru was lower than that of IO (OR 0.24, 95%CI 0.08-0.69) and OV (OR 95%CI 0.38,0.21-0.7).

The IV regimen exhibited a higher incidence of Grade ≥3 diarrhea compared to Acala, I, AO, and OV, with OV showing a greater incidence than both Ibru and Zanu. Acala/AO recorded a higher frequency of headaches than IO and OV. Furthermore, Grade ≥3 hypertension was less common in Acala/AO than in Ibru, with Ibru monotherapy presenting a higher incidence than both IO and OV. Arthralgia of any grade was more prevalent in AO than in IV. Additionally, IV demonstrated a lower occurrence of any grade secondary primary neoplasms relative to Acala/AO.

Regarding infusion-related reactions of any grade, IV had a lower incidence compared to IO and OV, with IO in turn registering fewer instances than OV. Lastly, the incidence of Grade ≥3 rash was notably higher in Ibru than in OV and RV, delineating a distinct profile of adverse effects across the treatment regimens.

Heterogeneity Assessment and Publication Bias

Our assessment indicated low to moderate heterogeneity in over half of the comparisons (31/48) across various outcomes. The consistency model fit was similar to the inconsistency model

(Supplementary Table 58). Funnel plot analysis and Egger's test suggested no evident publication bias across various outcomes(Supplementary Figure 27-30). After the removal of high-risk trials, the robustness of results was also detected in the comparisons of the remaining treatments.

Discussion

To our knowledge, this network meta-analysis includes the largest number of naive CLL/SLL patients, incorporating 30 eligible trials and a total of 12,818 patients across 30 different treatments. Studies with comparable characteristic were subject to further subgroup analysis. This research revealed over 500 new positive results comparing the efficacy and safety of 30 regimens in different subgroups, previously unreported by any head-to-head clinical trials (Supplementary Figure 31).

There are some network meta-analyses focused on CLL published before. Yin and Liu et al. [11, 12] focused solely on treatments involving BTK inhibitors and didn't make a distinction between treatments for newly diagnosed patients and those already treated, which might lead to bias. Rizzuto et al. [13] aimed to analyze first-line treatments through a Molecular-Biology-Driven approach. They combined IR and IO into one group, but we found efficacy differences between these two CD20 antibodies. Their research was also limited by its scope, covering only 9 studies and 11 treatments, and offered a limited comparison of side effects. Our study adds comparisons of new regimens IV, MRD-guided IV, RV, and Zanu. Moreover, many network analyses published before 2021 lacked updates on new regimens [14-17], especially

those including BCL2 and BTK inhibitors, which have been published mostly in the last two years and represent significant progress, like the GAIA-CLL13[18], NCRI FLAIR[19], and UK FLAIR[20] studies. Acalabrutinib or Zanubrutinib are non-inferior or superior to ibrutinib in R/R CLL/SLL based on PFS [21, 22], with lower toxicity and no significant OS difference, but there are no head-to-head studies comparing different BTK inhibitors in the first-line setting. Additionally, most of these studies focused on specific groups of patients or single classes of treatments, missing a broader and more systematic review of treatments for newly diagnosed CLL/SLL patients. This gap highlights the need for a more up-to-date and comprehensive study that looks at a wider range of treatments and their outcomes.

Generally, the NCCN, ESMO, and BSH guidelines recommend Acala/AO/OV/Zanu/Ibru/FCR, without providing a specific ranking. Our study has undertaken a detailed exploration and identified new insights. Patients over 65 years and/or with comorbidities might benefit more from Acala and IV, as the PFS are superior to OV/Zanu/Ibru, with no significant difference in PFS and OS between Acala and AO. IO demonstrated a PFS benefit compared to IR in patients older than 65 years, indicating differences among CD20 antibodies—a novel finding of our study.

For patients under 65 years with comorbidities, our findings indicate that the PFS for AO exceeds that of IO, IV, and OV. Direct comparisons from ELEVATE-TN have shown that the PFS associated with Acala is inferior to that of Acala with AO. The uMRD of Acala is also inferior to AO. Given that the SEQUOIA study has not yet reported the efficacy of Zanu in

the subgroup of patients younger than 65, we have justification to recommend AO over Acala, IO, IV, and OV, with Zanu also being a viable option.

For patients without comorbidities, we found that the PFS of IV-MRD was superior to OV. Since the ELEVATE-TN and SEQUOIA studies only included subjects with comorbidities, there are no comparable data for Acala, AO, or Zanu. Based on these findings, we believe it is reasonable to recommend IV-MRD, and consider Acala, Zanu, and AO regimens as viable options.

For patients with mIGHV, our findings indicate that the PFS of AO and IO is greater than that of Ibru and FCR, with IO also surpassing IV and OV. Direct comparisons from ELEVATE-TN suggest no significant difference in PFS between Acala and AO. Therefore, Ibru/IV/OV are not prioritized treatment options.

For patients with umIGHV, we discovered that the PFS of Acala and AO is superior to Ibru, IV, IR, OV, and Zanu. Similar to mIGHV, there is a lack of OS data for comparison among these treatments. Both direct comparisons from ELEVATE-TN and estimates from network meta-analyses indicate no significant difference in PFS between Acala and AO. Thus, Acala and AO are good options.

Patients with del(17p)/TP53 mutations, known for their poor prognosis and lower response rates, are often excluded from direct comparative studies. Our results demonstrate promising efficacy of IO compared to OV; a finding not explicitly recommended in current guidelines.

There is a lack of comparable data for IV. Del(17p)/*TP53* mutations impair the sensitivity to drugs that depend on functional p53. Results from phase I clinical trials have shown that, compared to patients without del(17p), those with del(17p) have a shorter PFS when treated with Venetoclax[23]. Although Anderson et al. found that Venetoclax potently induces rapid onset apoptosis of CLL cells in vitro and in vivo, independent of TP53 function[24], the preferential use of BCL2 inhibitors in such high-risk groups still warrants further validation in the future. We would not prioritize recommending the OV regimen. Due to the small samples in this subgroup, a further large cohort for validation is warranted for this heavily worse prognosis subjects.

Regarding the efficacy comparison among the three BTK inhibitors, Zanu vs. Ibru and Acala vs. Ibru involved a two-node transmission, whereas the comparison of Acala vs. Zanu necessitated navigating through a four-node transmission. The comparison between AO and IO required only a single node transmission. The baseline data from ELEVATE-TN, SEQUOIA, Resonate-2, A041202, and CLL11 are comparable for these comparisons. We classify the evidence level for Acala vs. Ibru and Zanu vs. Ibru as moderate, while the evidence level for Zanu vs. Acala is considered low. Acala is shown to offer superior progression-free survival (PFS) over Ibru in patients with comorbidities, especially in older patients, and those with unmutated IGHV.

The spectrum of AE varies markedly among different treatment regimens. This meta-analysis facilitates a comprehensive factorial analysis of the AE profiles related to both monotherapy and combination therapies. The Acala/AO regimens are associated with higher incidences of

headaches, arthralgia, and secondary primary malignancies, with the addition of Obinutuzumab further increasing the risk of thrombocytopenia and infections. Ibru presents a higher risk of bleeding, hypertension, and rash, and its combination with Obinutuzumab also elevates the risk of thrombocytopenia and infections. Zanu is characterized by lower rates of anemia, neutropenia, thrombocytopenia, infections, and diarrhea but a higher incidence of hypertension. IV, being an all-oral treatment regimen, offers easier administration compared to OV, with diarrhea being its most significant toxicity. OV is associated with higher occurrences of neutropenia, thrombocytopenia, infusion-related reactions, and tumor lysis syndrome. When selecting treatments, it is imperative to consider comorbidities, concurrent medications, and the spectrum of AE to prevent overlapping toxicities.

Continuous BTK inhibitor-base combinations or time-limited Venetoclax containing therapy, which is preferable? Fixed-duration regimens include OV, IV, and VR, with OV and VR lasting one year, and IV for 15 months. The continuous treatment regimens include AO, IO, and various BTK monotherapies. Prior to our network meta-analysis, there was no compelling data comparing IV to OV and IV to VR. IV represents an all-oral treatment regimen, while Obinutuzumab is an intravenous drug. The OV regimen is associated with a high incidence of adverse reactions related to intravenous infusion, making IV a simpler practical option. This article provides new evidence elevating IV/IV-MRD as preferred treatment options, especially in patients without severe comorbidities and those with IGHV-unmutated status.

Owing to numerous studies excluding patients with del17p deletion or TP53 mutation, the cohort size available for analysis within this high-risk subgroup remains constrained.

Furthermore, not all therapeutic regimens are represented in each subgroup analysis. Occasionally, even when data exist, they form isolated nodes that preclude network formation for comparative purposes. Consequently, achieving a comprehensive ranking within each subgroup analysis is unfeasible. All analyzed data derive from published clinical trials, rather than individual patient-level data. We conducted pairing based on the baseline characteristics of each study, allowing only matched studies to proceed to further subgroup analysis. The corroborative analysis of both the overall subjects and various subgroups reinforced the stability of the results.

Tailored chemo-free regimens can be selected based on age, comorbidities, IGHV status, and cytogenetic abnormalities to optimize treatment outcomes while considering different response spectra. In the absence of extensive direct evidence from randomized clinical trials for most chemo-free regimens, this study uses matched indirect comparisons and network estimates to evaluate the efficacy and safety of various treatments. It significantly contributes by addressing key questions in CLL/SLL therapy, providing high-level, evidence-based recommendations for clinical practice, and highlighting the evolving landscape of cancer therapy relevant to various tumor types. The research exemplifies factorial analysis applied to multi-drug combinations and emphasizes the urgent need for future direct head-to-head trials to confirm these findings in well-defined precision subjects.

Data availability: Supplementary figures and Tables online available.

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References:

[1]. Shadman, M., Diagnosis and Treatment of Chronic Lymphocytic Leukemia. JAMA, 2023. 329(11): p. 918.

[2]. Hallek, M., et al., iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood, 2018. 131(25): p. 2745-2760.

[3]. Eichhorst, B., et al., Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 2021. 32(1): p. 23-33.

[4]. Wen, T., et al., Inhibitors targeting Bruton's tyrosine kinase in cancers: drug development advances. Leukemia, 2021. 35(2): p. 312-332.

[5]. Walewska, R., et al., Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology, 2022. 197(5): p. 544-557.

[6]. Kreuzberger, N., et al., Prognostic models for newly-diagnosed chronic lymphocytic leukaemia in adults: a systematic review and meta-analysis. Cochrane Database Syst Rev, 2020. 7(7): p. CD012022.

[7]. Rucker, G., C.J. Cates and G. Schwarzer, Methods for including information from multi-arm trials in pairwise meta-analysis. Res Synth Methods, 2017. 8(4): p. 392-403.

[8]. Rucker, G. and G. Schwarzer, Resolve conflicting rankings of outcomes in network meta-analysis: Partial ordering of treatments. Res Synth Methods, 2017. 8(4): p. 526-536.

[9]. Rucker, G., Network meta-analysis, electrical networks and graph theory. Res Synth Methods, 2012. 3(4): p. 312-24.

[10]. Konig, J., U. Krahn and H. Binder, Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. Stat Med, 2013. 32(30): p. 5414-29.

[11]. Yin, S., et al., Efficacy and safety of new-generation Bruton tyrosine kinase inhibitors in chronic lymphocytic leukemia/small lymphocytic lymphoma: a systematic review and meta-analysis. Annals of Hematology, 2023.

[12]. Liu, X., et al., Evaluation of Bruton tyrosine kinase inhibitors monotherapy and combination therapy in lymphocytic leukemia. Clin Exp Med, 2023. 23(8): p. 4237-4248.

[13]. Rizzuto, A., et al., Molecular-Biology-Driven Frontline Treatment for Chronic Lymphocytic Leukemia: A Network Meta-Analysis of Randomized Clinical Trials. International Journal of Molecular Sciences, 2023. 24(12): p. 9930.

[14]. Alrawashdh, N., et al., Comparative Efficacy of First-Line Treatments of Chronic Lymphocytic Leukemia: Network Meta-Analyses of Survival Curves. Clinical Lymphoma Myeloma and Leukemia, 2021. 21(11): p. e820-e831.

[15]. Davids, M.S., et al., Comparative Efficacy of Acalabrutinib in Frontline Treatment of Chronic Lymphocytic Leukemia: A

Systematic Review and Network Meta-analysis. Clinical Therapeutics, 2020. 42(10): p. 1955-1974.e15.
[16]. Xu, Y., et al., Front-line treatment of patients with chronic lymphocytic leukemia: a systematic review and network meta-analysis. Journal of Comparative Effectiveness Research, 2018. 7(5): p. 421-441.
[17]. Ladyzynski, P., M. Molik and P. Foltynski, A network meta-analysis of progression free survival and overall survival in first-line treatment of chronic lymphocytic leukemia. Cancer Treatment Reviews, 2015. 41(2): p. 77-93.
[18]. Eichhorst, B., et al., First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. New England Journal of Medicine, 2023. 388(19): p. 1739-1754.
[19]. Hillmen, P., et al., Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI FLAIR Study. Blood, 2023. 142(Supplement 1): p. 631-631.
[20]. Hillmen, P., et al., Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukaemia (FLAIR): interim analysis of a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol, 2023. 24(5): p. 535-552.
[21]. Byrd, J.C., et al., Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. J Clin Oncol, 2021. 39(31): p. 3441-3452.
[22]. Brown, J.R., et al., Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med, 2023. 388(4): p. 319-332.
[23]. Roberts, A.W., et al., Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med, 2016. 374(4): p. 311-22.
[24]. Anderson, M.A., et al., The BCL2 selective inhibitor venetoclax induces rapid onset apoptosis of CLL cells in patients via a TP53-independent mechanism. Blood, 2016. 127(25): p. 3215-24.
[25]. Shanafelt, T.D., et al., Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. Blood, 2022. 140(2): p. 112-120.
[26]. Sharman, J.P., et al., Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. Leukemia, 2022. 36(4): p. 1171-1175.
[27]. Sharman, J.P., et al., Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Five-year follow-up of ELEVATE-TN. Journal of Clinical Oncology, 2022. 40(16_suppl): p. 7539-7539.
[28]. Munir, T., et al., Chronic Lymphocytic Leukemia Therapy Guided by Measurable Residual Disease. N Engl J Med, 2023.
[29]. Eichhorst, B., et al., First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. The Lancet Oncology, 2016. 17(7): p. 928-942.
[30]. Kutsch, N., et al., Long Term Follow-up Data and Health-Related Quality of Life in Frontline Therapy of Fit Patients Treated With FCR Versus BR (CLL10 Trial of the GCLLSG). HemaSphere, 2020. 4(1): p. e336-1-15.
[31]. Michallet, A., et al., Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. Haematologica, 2018. 103(4): p. 698-706.
[32]. Munir, T., et al., Results of the randomized phase IIB ADMIRE trial of FCR with or without mitoxantrone in previously untreated CLL. Leukemia, 2017. 31(10): p. 2085-2093.
[33]. Howard, D.R., et al., Results of the randomized phase IIB ARCTIC trial of low-dose rituximab in previously untreated CLL. Leukemia, 2017. 31(11): p. 2416-2425.
[34]. Knauf, W.U., et al., Phase III Randomized Study of Bendamustine Compared With Chlorambucil in Previously Untreated Patients With Chronic Lymphocytic Leukemia. Journal of Clinical Oncology, 2009. 27(26): p. 4378-4384.
[35]. Knauf, W.U., et al., Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. British Journal of Haematology, 2012. 159(1): p. 67-77.
[36]. Hillmen, P., et al., Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol, 2007. 25(35): p. 5616-23.
[37]. Byrd, J.C., et al., Lenalidomide consolidation benefits patients with CLL receiving chemoimmunotherapy: results for CALGB

10404 (Alliance). Blood Advances, 2018. 2(14): p. 1705-1718.
[38]. Robak, T., et al., Comparison of Cladribine Plus Cyclophosphamide With Fludarabine Plus Cyclophosphamide As First-Line Therapy for Chronic Lymphocytic Leukemia: A Phase III Randomized Study by the Polish Adult Leukemia Group (PALG-CLL3 Study). Journal of Clinical Oncology, 2010. 28(11): p. 1863-1869.
[39]. Fischer, K., et al., Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood, 2016. 127(2): p. 208-215.
[40]. Hallek, M., et al., Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. The Lancet, 2010. 376(9747): p. 1164-1174.
[41]. Stilgenbauer, S., et al., Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood, 2014. 123(21): p. 3247-3254.
[42]. Geisler, C.H., et al., Frontline low-dose alemtuzumab with fludarabine and cyclophosphamide prolongs progression-free survival in high-risk CLL. Blood, 2014. 123(21): p. 3255-62.
[43]. Rai, K.R., et al., Fludarabine Compared with Chlorambucil as Primary Therapy for Chronic Lymphocytic Leukemia. New England Journal of Medicine, 2000. 343(24): p. 1750-1757.
[44]. Lepretre, S., et al., Excess mortality after treatment with fludarabine and cyclophosphamide in combination with alemtuzumab in previously untreated patients with chronic lymphocytic leukemia in a randomized phase 3 trial. Blood, 2012. 119(22): p. 5104-5110.
[45]. Flinn, I.W., et al., Phase III Trial of Fludarabine Plus Cyclophosphamide Compared With Fludarabine for Patients With Previously Untreated Chronic Lymphocytic Leukemia: US Intergroup Trial E2997. Journal of Clinical Oncology, 2007. 25(7): p. 793-798.
[46]. Eichhorst, B.F., Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood, 2005. 107(3): p. 885-891.
[47]. Robak, T., Cladribine alone and in combination with cyclophosphamide or cyclophosphamide plus mitoxantrone in the treatment of progressive chronic lymphocytic leukemia: report of a prospective, multicenter, randomized trial of the Polish Adult Leukemia Group (PALG CLL2). Blood, 2006. 108(2): p. 473-479.
[48]. Gonzalez, D., et al., Mutational status of the TP53 gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. J Clin Oncol, 2011. 29(16): p. 2223-9.
[49]. Munir, T., et al., ZANUBRUTINIB (ZANU) VS BENDAMUSTINE + RITUXIMAB (BR) IN PATIENTS (PTS) WITH TREATMENT-NAÏVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL): EXTENDED FOLLOW-UP OF THE SEQUOIA STUDY. HemaSphere, 2023. 7(S3): p. e15364af.
[50]. Tam, C.S., et al., Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. The lancet oncology, 2022. 23(8): p. 1031-1043.
[51]. Ramakrishnan, V., et al., Broad Superiority of Zanubrutinib (Zanu) Over Bendamustine + Rituximab (BR) Across Multiple High-Risk Factors: Biomarker Subgroup Analysis in the Phase 3 SEQUOIA Study in Patients With Treatment-Naive (TN) Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) without del(17p). Blood, 2023. 142(Supplement 1): p. 1902-1902.
[52]. Sharman, J.P., et al., Acalabrutinib ± Obinutuzumab Vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of Elevate-TN. Blood, 2023. 142(Supplement 1): p. 636-636.
[53]. Sharman, J.P., et al., Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial. The Lancet, 2020. 395(10232): p. 1278-1291.
[54]. Al-Sawaf, O., et al., Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol, 2020. 21(9): p. 1188-1200.
[55]. Al-Sawaf, O., et al., Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. Nature Communications, 2023. 14(1): p. 2147.

[56]. Al-Sawaf, O., et al., Minimal Residual Disease Dynamics after Venetoclax-Obinutuzumab Treatment: Extended Off-Treatment Follow-up From the Randomized CLL14 Study. Journal of Clinical Oncology, 2021. 39(36): p. 4049-4060.
[57]. Tausch, E., et al., Prognostic and predictive impact of genetic markers in patients with CLL treated with obinutuzumab and venetoclax. Blood, 2020. 135(26): p. 2402-2412.
[58]. Kater, A.P., et al., Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. NEJM Evidence, 2022. 1(7).
[59]. Niemann, C.U., et al., Fixed-duration ibrutinib – venetoclax versus chlorambucil – obinutuzumab in previously untreated chronic lymphocytic leukaemia (GLOW): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology, 2023. 24(12): p. 1423-1433.
[60]. Moreno, C., et al., Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol, 2019. 20(1): p. 43-56.
[61]. Moreno, C., et al., First-line treatment of chronic lymphocytic leukemia with ibrutinib plus obinutuzumab *versus* chlorambucil plus obinutuzumab: final analysis of the randomized, phase III iLLUMINATE trial. Haematologica, 2022. 107(9): p. 2108-2120.
[62]. Goede, V., et al., Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. Leukemia, 2015. 29(7): p. 1602-4.
[63]. Goede, V., et al., Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions. New England Journal of Medicine, 2014. 370(12): p. 1101-1110.
[64]. Offner, F., et al., A five - year follow - up of untreated patients with chronic lymphocytic leukaemia treated with ofatumumab and chlorambucil: final analysis of the Complement 1 phase 3 trial. British Journal of Haematology, 2020. 190(5): p. 736-740.
[65]. Hillmen, P., et al., Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. The Lancet, 2015. 385(9980): p. 1873-1883.
[66]. Woyach, J.A., et al., Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med, 2018. 379(26): p. 2517-2528.
[67]. Woyach, J.A., et al., Long-term Follow-up from A041202 Shows Continued Efficacy of Ibrutinib Regimens for Older Adults with CLL. Blood, 2024.
[68]. Eichhorst, B.F., et al., First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood, 2009. 114(16): p. 3382-3391.
[69]. Barr, P.M., et al., Up to seven years of follow-up in the RESONATE-2 study of first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Journal of Clinical Oncology, 2021. 39(15_suppl): p. 7523-7523.
[70]. Barr, P.M., et al., Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. Haematologica, 2018. 103(9): p. 1502-1510.
[71]. Burger, J.A., et al., Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia, 2020. 34(3): p. 787-798.
[72]. Burger, J.A., et al., Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. New England Journal of Medicine, 2015. 373(25): p. 2425-2437.
[73]. Chanan-Khan, A., et al., Randomized phase 3 study of lenalidomide versus chlorambucil as first-line therapy for older patients with chronic lymphocytic leukemia (the ORIGIN trial). Leukemia, 2017. 31(5): p. 1240-1243.

Figure 1: Workflow for Study Search and Selection. The process of literature screening, inclusion, and exclusion followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Figure 2: Forest plot comparing efficacy among chemo-free regimens with significant clinical significance. Only data meeting all three criteria were included: high-quality and moderate-quality new insights from our meta-analysis, not previously reported by any head-to-head clinical trial, and the comparative group remains relevant and continues to be considered one of the standard treatment regimens. Additional data were accessible for supplementary materials.

Figure 3: Forest plot comparing safety among chemo-free regimens with significant clinical significance. Only data meeting all three criteria were included: high-quality and moderate-quality new insights from our meta-analysis, not previously reported by any head-to-head clinical trial, and the comparative group remains relevant and continues to be considered one of the standard treatment regimens. Additional data were accessible for supplementary materials.

Table 1 | Baseline characteristics of studies included in the network meta-analysis.

Study	Intervention	Comparison	Sample size (No)	Median age	del 17p%, del 11q%, del 13q%,	IGHV Mutation %; Unmutated	TP53 mutated	Comorbidities
GAIA-CLL13 [18]	1. OIV 2.OV 3.VR	CIT (FCR/BR)	231 vs 229 vs 237 vs 229 (150/79)	60 vs 62 vs 62 vs 61	0 vs 0 vs 0 vs 0; 13.9 vs 19.2 vs 19 vs 17.9; 45.5 vs 41 vs 47.7 vs 44.1	43.7 vs 39 vs 40.1 vs 41.5; 53.2 vs 57 vs 56.5 vs 57.2	0 vs 0 vs 0 vs 0	No
E1912 [25-27]	IR	FCR	354 vs 175	58 vs 57	0.6 vs 0; 22.2 vs 22.3; 34.2 vs 33.1	25 vs 38.3; NA	91 vs 97	NA
NCRI FLAIR [20, 28]	IV MRD	FCR	260 vs 263	62	No; 20.6; 31.4	37.6; 56.9	NA	No
FLAIR [20]	IR	FCR	386 vs 385	63 vs 62	No; NA; 36 vs 34	38 vs 38; 50 vs 50	1 vs 1	No
CLL10 [29, 30]	BR	FCR	279 vs 282	61.0 vs 62.1	NA; 23 vs 24; 53 vs 55	32.2 vs 44.7； 67.8 vs 55.3	NA	No
ADMIRE [31, 32]	FCM-R	FCR	108 vs 107	63 vs 61	4.6 vs 8.4; 18.5 vs 16.8; NA	38 vs 30.8	NA	No
ARCTIC [33]	FCM-miniR	FCR	100 vs 100	63 vs 63	3 vs 4; 20 vs 10; 31 vs 30	31 vs 30	NA	No
Knauf et al [34, 35]	B	Clb	162 vs 157	63.0 vs 63.6	NA	NA	NA	No
CAM307 [36]	Alemtuzumab	Clb	149 vs 148	59.0 vs 60.0	7.7 vs 7.2; 16.1 vs 22.3; 23.1 vs 24.5	NA	NA	No
CALGB 10404 [37]	FCR	FR	110 vs 123	60 vs 61	90 vs 89; 94 vs 93; 50 vs 50	NA	NA	No
CLL3 [38]	CC	FC	211 vs 212	58 vs 59	15 vs 19; 25 vs 19; 24 vs 25	NA	NA	No
CLL8 [39-41]	FCR	FC	408 vs 409	61 vs 61	7 vs 10; 27 vs 22;54 vs 60	37 vs 37; 63 vs 63	72 vs 62	No
HOVON68 [42]	FC-alemtuzumab	FC	133 vs 139	42.8	11 vs 13; 23 vs 27; 18 vs 9	17 vs 6;78 vs 81	NA	No
CALGB9011 [43]	F	Clb	179 vs 193	64 vs 62	NA	NA	NA	No

CLL2007FMP [44]	FC- alemtuzumab	FCR	83 vs 82	57 vs 57	0 vs 0; 20.48 vs 19.51; NA	39.76 vs 45.12; 60.24 vs 54.88	NA	No
E2997 [45]	FC	F	141 vs 137	61 vs 61	10 vs 9; 24 vs 16; 43vs 38	0 vs 1.8	NA	No
Eichhorst [46]	FC	F	180 vs 182	58 vs 59	NA	NA	NA	No
CLL2 [47]	2-CdA	1. CC 2. CMC	166 vs 162 vs 151	61 vs 63 vs 59	NA	NA	NA	No No
CLL4 [48]	FC	1. F 2. Clb	196 vs 194 vs 387	65 vs 64 vs 65	NA	NA	12 vs 9 vs 19	No No
SEQUOIA [49-51]	Zanubrutinib	BR	241 vs 238	70 vs 70	1 vs 0; 18 vs 19; 56 vs 54	NA; 53 vs 52	6 vs 6	Yes
ELEVATE-TN [26, 52, 53]	1. AO 2.A	O-Clb	179 vs 179 vs 177	70 vs 70 vs 71	9.5 vs 8.9 vs 9; 17.3 vs 17.3 vs 18.6	57.5 vs 66.5 vs 65.5; NA	11.7 vs 10.6 vs 11.9	Yes
CLL14 [54-57]	OV	O-Clb	216 vs 216	71 vs 72	6.7 vs 8.1; 18.3 vs 17.1; NA	39.9 vs 38; 59.1 vs 60.5	9 vs 10.9	Yes
GLOW [58, 59]	IV	O-Clb	106 vs 105	71 vs 71	No; 18.9 vs 17.1; NA	25.5 vs 25.7; 51.9 vs 51.4	7 vs 2	Yes
iLLUMINATE [60, 61]	IO	O-Clb	113 vs 116	70 vs 72	12 vs 16; 12 vs 19; NA	38 vs 47;62 vs 53	12 vs 15	Yes
CLL11 [62, 63]	1. O-Clb 2. R-Clb	Clb	333 vs330 vs 118	74 vs 73 vs 72	8 vs 5 vs 10; 16 vs 14 vs 15; 29 vs 33 vs 28	36 vs 34 vs 36	NA	Yes
Complement 1 [64, 65]	Ofa-Clb	Clb	221 vs 226	69 vs 70	5 vs 8；19 vs 11；57 vs 51	43 vs 44；57 vs 56	NA	Yes
A041202 [66, 67]	1. I 2. IR	BR	182 vs 182 vs 183	71 vs 71 vs 70	8 vs 5 vs 6；18 vs 19 vs 21; 36 vs 36 vs 36	58 vs 63 vs 61；42 vs 37 vs 39	16/174 vs 15/168 vs 20/168	No
CLL5 [68]	F	Clb	93 vs 100	71 vs 70	7 vs 6; 19 vs 10; undefined	33 vs 41; 67 vs 59	NA	No
RESONATE-2 [69-72]	Ibrutinib	Clb	136 vs 133	73 vs 72	No; 22 vs 21; 22 vs 30	33 vs 33; 48 vs 47	12 vs 3	No

ORIGIN [73]	Len	Clb	225 vs 225	72	8.4 vs 7.1; 19.1 vs 18.7; 55.1 vs 55.1	39.6 vs 35.1; 54.7 vs 57.8	NA	No

Abbreviations: Chemotherapy regimens include FC (Fludarabine, Cyclophosphamide), F (Fludarabine), Clb (Chlorambucil), CC (Cladribine, Cyclophosphamide), B (Bendamustine), CMC (Cladribine, Mitoxantrone, Cyclophosphamide), and 2-CdA (Cladribine). Targeted therapy encompasses OIV (Obinutuzumab, Ibrutinib, Venetoclax), Zanu (Zanubrutinib), RV (Rituximab, Venetoclax), R (Rituximab), OV (Obinutuzumab, Venetoclax), Len (Lenalidomide), IV (Ibrutinib, Venetoclax), IR (Ibrutinib, Rituximab), IO (Ibrutinib, Obinutuzumab), I (Ibrutinib), AO (Acalabrutinib, Obinutuzumab), Alemtuzumab, and A (Acalabrutinib). Chemoimmunotherapy options include R-Clb (Rituximab, Chlorambucil), O-Clb (Obinutuzumab, Chlorambucil), FR (Fludarabine, Rituximab), FCR (Fludarabine, Cyclophosphamide, Rituximab), FCM-R (Fludarabine, Cyclophosphamide, Mitoxantrone, Rituximab 500mg), FCM-miniR (Fludarabine, Cyclophosphamide, Mitoxantrone, Rituximab 100mg), FC plus alemtuzumab, CIT (age less than 65 years received FCR, others received BR), BR (Bendamustine, Rituximab), and Ofa-Clb (Ofatumumab, Chlorambucil).

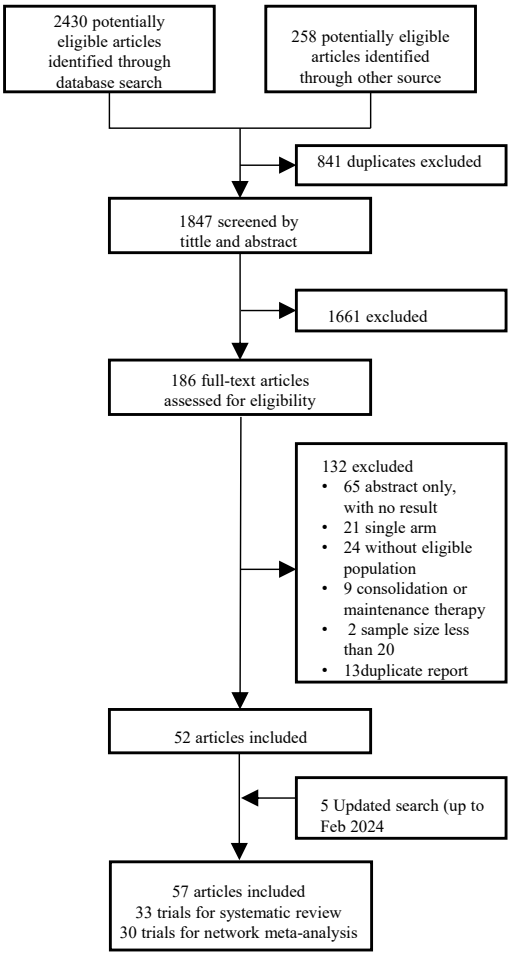
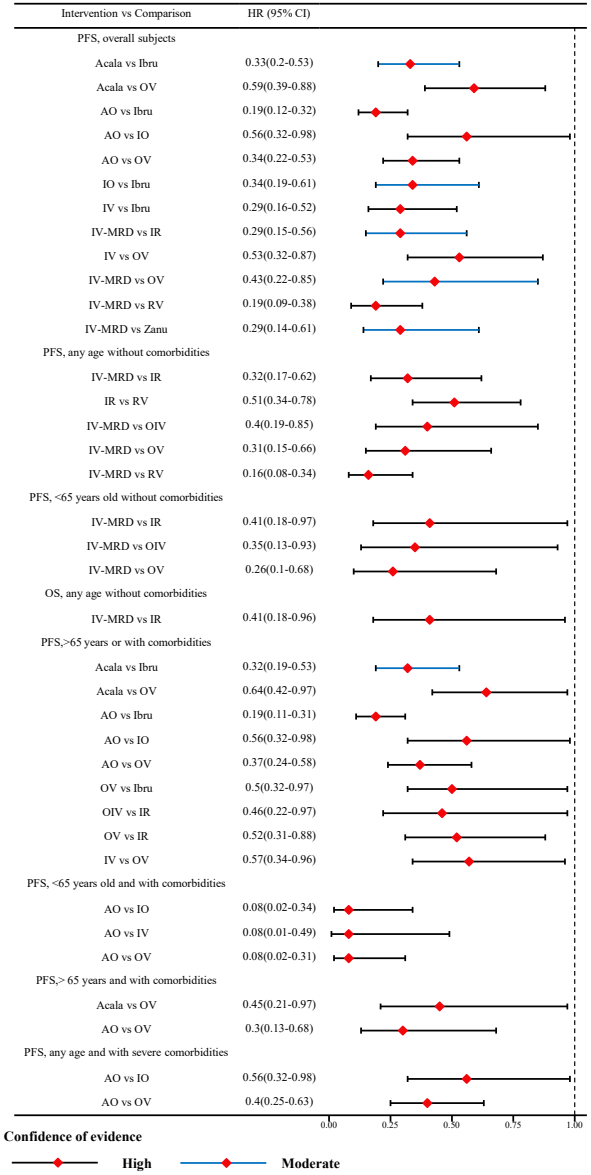
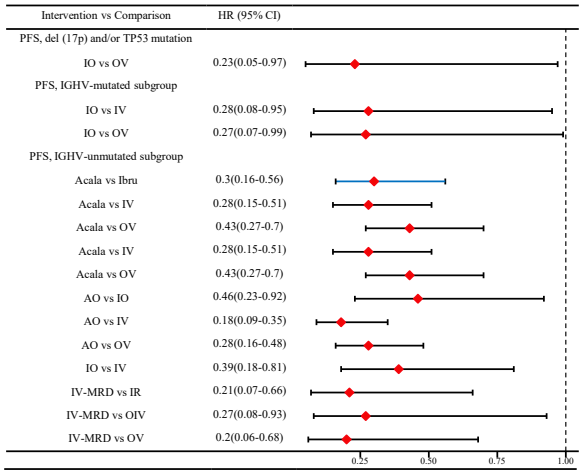
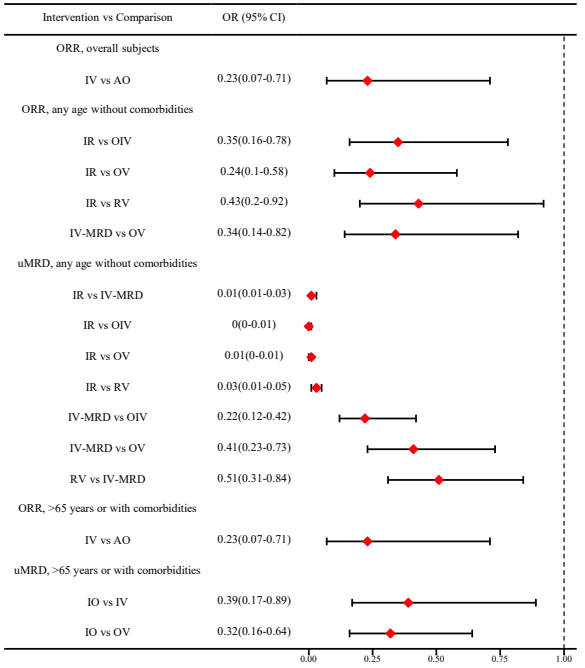


Figure2







Figure

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