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Research Article

Venetoclax-Ibrutinib Combinations as First-Line Therapy in Chronic Lymphocytic Leukemia: A Meta-Analysis of Randomized Controlled Trials with GRADE Approach

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ABSTRACT

Objective: Chronic lymphocytic leukemia (CLL) treatment has shifted from chemoimmunotherapy to targeted agents. Venetoclax and ibrutinib, which act through complementary mechanisms, have shown promise in achieving deep remissions. Their combination may enhance efficacy, but pooled evidence from randomized trials is lacking.

Methods: We systematically searched CENTRAL, MEDLINE, PubMed, Web of Science, and Scopus through April 1, 2025, for phase II/III randomized controlled trials (RCTs) comparing venetoclax-ibrutinib based combinations to standard regimens in treatment-naive CLL. Outcomes included progression-free survival (PFS) at predefined time points, overall survival (OS), undetectable measurable residual disease (uMRD) in blood and bone marrow, and safety. Risk ratios (RRs) were synthesized using inverse-variance weighted random-effects models.

Results: Four RCTs (n=1.343; CAPTIVATE, GLOW, GAIA-CLL13, and FLAIR were eligible. Venetoclax-ibrutinib combinations significantly prolonged PFS at 12 months [RR 1.10; 95% confidence interval (CI) 1.05-1.15], 24 months (RR 1.21; 95% CI 1.15-1.28), 36 months (RR 1.27; 95% CI 1.14-1.42), and 48 months (RR 1.47; 95% CI 1.18-1.84), with attenuation at 60 months (RR 1.74; 95% CI 0.88-3.43), when the effect was no longer statistically significant. Rates of uMRD were higher in peripheral blood (RR 1.55, 95% CI 1.35-1.79) and in bone marrow (RR 2.15, 95% CI 1.37-3.38). OS at 36 months was similar between groups (RR, 1.05; 95% CI, 0.93-1.17). Safety outcomes were broadly comparable, though diarrhea (RR 2.10) and hypertension (RR 2.86) were more frequent with venetoclax-ibrutinib. Subgroup analysis revealed a transient 24-month PFS benefit in patients with unmutated immunoglobulin heavy chain variable.

Conclusion: Venetoclax-ibrutinib combinations significantly improve disease control in first-line CLL, achieving higher uMRD and sustained PFS benefits without compromising safety.

Keywords: Venetoclax, ibrutinib, chronic lymphocytic leukemia, progression-free survival, meta-analysis

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries, characterized by the accumulation of mature clonal B cells in the peripheral blood (PB), bone marrow, and lymphoid tissues. Although the disease course is heterogeneous, many patients eventually require therapy, and historically, chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab or bendamustine-based regimens represented standard first-line approaches.[1]

CLL treatment has shifted from chemoimmunotherapy to targeted agents that disrupt key pathogenic pathways.[2] Among these, the Bruton's tyrosine kinase inhibitor ibrutinib and the B-cell lymphoma-2 (BCL-2) inhibitor venetoclax have each demonstrated durable remissions as monotherapy in CLL. The combination of ibrutinib and venetoclax is supported by a

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strong biological rationale. The lymph node microenvironment provides CLL cells with protective signals from T cells, natural killer cells, macrophages, endothelial cells, and stromal cells, which collectively promote CLL cell survival and suppress immune responses.[3,4] B-cell receptor (BCR) activation and cluster of differentiation 40 (CD40)-CD40 ligand interactions upregulate antiapoptotic proteins such as B-cell lymphoma-extra large (BCL-XL) and myeloid cell leukemia-1 (MCL-1),[5] while Toll-like receptor stimulation and CD40 overexpression reduce sensitivity to venetoclax.[6,7] Furthermore, loss of the tumor-suppressor microRNAs miR-15a/miR-16-1 leads to aberrant upregulation of BCL-2 and impaired apoptosis.[8]

Preclinical studies also reinforce this synergy. *Ex vivo* drug profiling showed that ibrutinib-treated CLL cells became more venetoclax-sensitive through reductions in MCL-1 and BCL-XL.[9,10] BH3 profiling confirmed increased BCL-2 dependence, and *in vivo* models demonstrated cooperative activity with distinct effects on proliferative versus quiescent CLL subpopulations.[11] Together, these findings highlight that combining these agents, as suggested by National Comprehensive Cancer Network guideline v3.2024,[12] exploits complementary mechanisms: ibrutinib inhibits tumor cell proliferation, mobilizes malignant cells from their protective niches in the lymphoid organs into the circulation, and impairs BCR signaling, while venetoclax induces apoptosis by inhibiting BCL-2.[1] This strategy promises minimal residual disease (MRD) negativity and improved progression-free survival (PFS).[12]

We conducted a meta-analysis to evaluate the efficacy, safety, and tolerability of venetoclax-ibrutinib combinations (VIC) in treatment-naive CLL patients.

MATERIAL AND METHODS

This study was a systematic review and meta-analysis of previously published studies and did not involve human participants directly; therefore, ethics committee approval and informed consent were not required.

MAIN POINTS

- Venetoclax-ibrutinib combinations (VIC) significantly improved progression-free survival (PFS) versus standard regimens across multiple time points—12 months [Risk ratio (RR) 1.10; 95% confidence interval (CI) 1.05-1.15], 24 months (RR 1.21; 95% CI 1.15-1.28), 36 months (RR 1.27; 95% CI 1.14-1.42), 48 months (RR 1.47; 95% CI 1.18-1.84)—with attenuation at 60 months (RR 1.74; 95% CI 0.88-3.43).
- Undetectable minimal residual disease was achieved more frequently with VIC, both in peripheral blood (RR 1.55; 95% CI 1.35-1.79) and in bone marrow (RR 2.15; 95% CI 1.37-3.38).
- Safety profiles were comparable, with no significant differences in serious adverse events (RR 1.10; 95% CI 0.74-1.62) or deaths (RR 0.70; 95% CI 0.22-2.29).
- Both the doublet (venetoclax + ibrutinib) and the triplet (venetoclax + ibrutinib + obinutuzumab) regimens yielded comparable efficacy for 36-month PFS [RR 1.28 (1.12-1.46) versus 1.26 (1.05-1.51)].

Eligibility criteria

We included randomized controlled trials (RCTs) (parallel-group, phase II or III) enrolling adults with previously untreated CLL that compared venetoclax-ibrutinib-based combinations against chemoimmunotherapy or other targeted regimens.

Information Sources

We searched Cochrane CENTRAL, Ovid MEDLINE, PubMed, Web of Science, and Scopus from database inception through April 1, 2025. No language restrictions were applied.

Search Strategy

The search combined controlled vocabulary and free-text terms for "venetoclax-," "ibrutinib-," and "CLL-," adapted to each database.

Study Selection

Two reviewers independently screened titles and abstracts, and then the full texts of potentially eligible records, using prespecified criteria. Discrepancies were resolved by consensus. Reasons for exclusion at full-text review were documented and summarized in the PRISMA flow diagram (Figure 1).

Data Collection Process

Two reviewers independently extracted data using a piloted form. Extracted items included trial characteristics (design, phase, setting, sample size), patient features (age, comorbidity status, genomic risk including immunoglobulin heavy chain variable (IGHV), del(17p)/tumor protein 53 (TP53) when

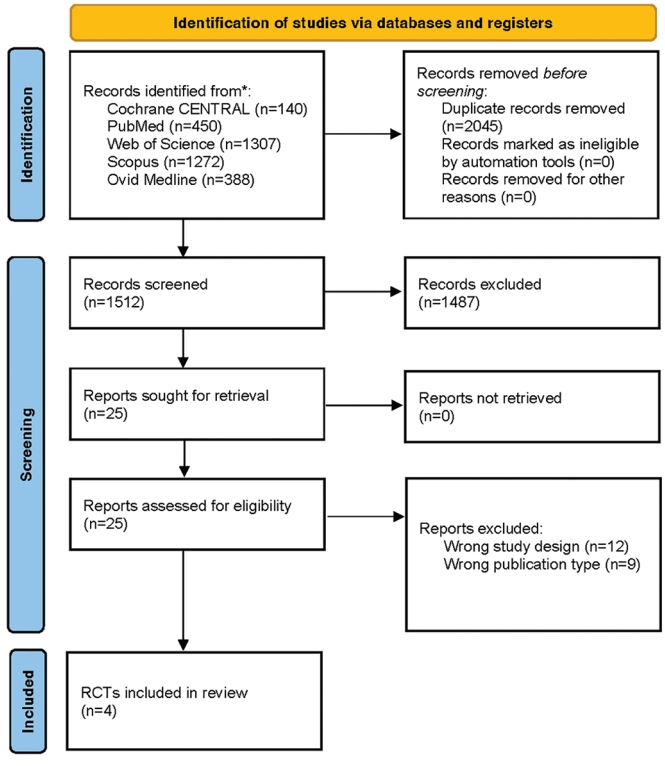

Figure 1. Flow diagram of literature search.

RCT, randomized controlled trial.

reported), intervention details (drug(s), dosing, treatment duration, MRD-guided versus fixed-duration strategy), comparator regimens, outcome definitions and assessment schedules, follow-up duration, and effect estimates for all outcomes. Any disagreements were resolved through discussion.

Study Outcomes

The primary efficacy outcome was PFS at 36 months; secondary outcomes included landmark PFS at additional time points (12, 24, 48, and 60 months, as available), overall survival (OS), undetectable minimal residual disease (uMRD) in PB and/or bone marrow, treatment discontinuation due to adverse events (AEs), serious AEs, infection outcomes, and selected AEs of special interest (e.g., diarrhea, hypertension). Trials of relapsed/refractory disease, non-randomized trials, single-arm trials, and trials in pediatric populations were excluded.

Definitions and Outcome Measures

PFS and OS were used as defined by each trial. When time-to-event hazard ratios (HRs) were unavailable at a given landmark time, we abstracted aggregate data at prespecified time points for binary outcomes and calculated risk ratios (RRs). uMRD was accepted as defined in each trial (typically < 10^{-4} by flow cytometry or next-generation sequencing) and was abstracted separately for PB and bone marrow, when available. Safety outcomes followed trial-reported grading (e.g., Common Terminology criteria for Adverse Events version used in each study).

Statistical Analysis

For dichotomous outcomes (e.g., landmark PFS, uMRD, AEs), we calculated RRs with 95% confidence intervals (CIs). For rare events, the Mantel-Haenszel method, with a continuity correction when required.[13] For time-to-event outcomes with available HRs, we planned to synthesize log HRs and their standard errors. Primary analyses used inverse-variance-weighted random-effects models. Between-study variance (τ^2) was estimated with the Paule-Mandel method[14], and statistical heterogeneity was quantified using I^2. Planned sensitivity analyses included fixed-effect models; exclusion of studies at high risk of bias (RoB); and leave-one-out analyses. When ≥ 10 studies were available for an outcome, we planned to explore small-study effects via funnel plots and Egger's test; with fewer studies, we did not formally assess publication bias and instead interpreted pooled results with caution. All analyses were conducted in R (version 4.5.1; www.r-project.org; R Foundation for Statistical Computing, Vienna, Austria), using the validated meta and metafor packages.http://www.r-project.org/

RoB Assessment

The RoB for each included randomized controlled trial was independently assessed by two reviewers using the Cochrane RoB 2 tool[15], evaluating five domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. Any disagreements were resolved through discussion. The overall RoB judgment for each trial was determined in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, version 6.5.

Assessing of Certainty of Evidence

The certainty of the evidence for the primary outcome (PFS at 36 months) was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation approach, considering RoB, inconsistency, indirectness, imprecision, and publication bias as described in our prior study.[16] Evidence was rated as high, moderate, low, or very low.

Subgroup Analysis

A priori subgroups, contingent on data availability, included IGHV mutational status (mutated versus unmutated) and regimen composition (venetoclax + ibrutinib doublet versus venetoclax + ibrutinib + anti-CD20 triplet). Additional exploratory subgroups (age- or comorbidity-defined populations, MRD-guided vs fixed-duration strategies, and comparator category) were also considered.

Assessment of Reporting Bias and Study Registration

Because this was a synthesis of published randomized trials with ≤ 10 studies per outcome, formal statistical tests for small-study effects were generally not applicable.

RESULTS

Four RCTs (n=1343) met eligibility criteria: CAPTIVATE[17], global study of venetoclax and obinutuzumab in previously untreated CLL (GLOW)[18], global assessment of ibrutinib and venetoclax in previously untreated CLL (GAIA-CLL13)[19], and frontline therapy with ibrutinib, venetoclax and rituximab (FLAIR)[20]; three of which explored venetoclax + ibrutinib[17,18,20], while one explored venetoclax + ibrutinib + obinutuzumab (Table 1).[19]

Study Characteristics

CAPTIVATE evaluated fixed-duration venetoclax-ibrutinib in patients age < 70 years (median age 58). After a 3-cycle ibrutinib lead-in followed by 12 cycles of combination therapy, 75% of patients achieved undetectable MRD in PB, and 68% of patients achieved undetectable MRD in bone marrow. One-year disease-free survival in the confirmed uMRD group was 95% with placebo and 100% with ibrutinib; PFS rates were ≥ 95% at approximately 30 months' follow-up compared with placebo.[17]

GLOW compared fixed-duration venetoclax-ibrutinib with chlorambucil–obinutuzumab in older and/or comorbid patients (median age 71 years). At 27.7 months, PFS favored venetoclax-ibrutinib (HR 0.216; 95% CI, 0.13-0.36; $P < 0.001$). The estimated 30-month PFS rates were ~80% with venetoclax-ibrutinib versus ~36% with chlorambucil-obinutuzumab, consistent across subgroups. Sustained uMRD in blood was achieved in 84.5% versus 29.3%.[18]

GAIA-CLL13 enrolled 926 fit patients without TP53 aberrations and randomized them to chemoimmunotherapy, venetoclax–rituximab, venetoclax–obinutuzumab, or venetoclax-obinutuzumab-ibrutinib. At three years, PFS was 90.5% with venetoclax-obinutuzumab-ibrutinib (HR for disease progression

or death, 0.32; 97.5% CI, 0.19-0.54; $P < 0.001$) and 87.7% with venetoclax-obinutuzumab (HR for disease progression or death, 0.42; 97.5% CI, 0.26-0.68; $P < 0.001$), compared with chemoimmunotherapy. The venetoclax-rituximab arm (80.8%) did not significantly outperform chemoimmunotherapy. The triple regimen venetoclax-ibrutinib-obinutuzumab yielded the highest uMRD rate (92.2%).[19]

FLAIR randomized 523 previously untreated patients eligible for fludarabine, cyclophosphamide, rituximab (FCR) to MRD-guided venetoclax-ibrutinib or FCR. At a median follow-up of 43.7 months, venetoclax-ibrutinib strongly reduced the risk of disease progression or death (HR, 0.13; 95% CI, 0.07-0.24; $P < 0.001$). By five years, 65.9% of patients had bone marrow uMRD, and 92.7% had PB uMRD.[20]

RoB

The overall RoB was low for Kater et al.,[18] of some concern for Wierda et al.[17] and Eichhorst et al.,[19], and high for Munir et al.[20] (Figure 2).

Table 1. Study Characteristics of the Included Trials

Study (year)	Trial / registration	Design	Setting	Population	n	Intervention	Comparator	Primary end point(s)
Wierda et al.[17]	CAPTIVATE; NCT02910583	Phase II RCT	46 sites across 6 countries	Age ≥ 18 to < 70 y with previously untreated CLL/SLL	149	Leadin ibrutinib × 3 cycles, then 12 cycles ibrutinib + venetoclax	Placebo or Ibrutinib	1year diseasefree survival in confirmed uMRD population
Kater et al.[18]	GLOW; NCT03462719	Phase 3, open-label RCT	67 sites across 14 countries	Previously untreated CLL, older or 18 to 64 years of age with comorbidities	211	Ibrutinib 420 mg qd ×3 lead-in cycles, then 12 cycles of ibrutinib + venetoclax	Obinutuzumab + chlorambucil	IRC assessed PFS (time from randomization to progression or death from any-cause)
Eichhorst et al.[19]	GAIA-CLL13; NCT02950051; EudraCT 2015-004936-36	Phase 3, open-label RCT	159 sites in 9 European countries and Israel	Previously untreated, fit CLL; ECOG 0-2	460	Venetoclax 400 mg qd for 10 cycles after 5 wk ramp-up; Ibrutinib 420 mg qd starting C1D1; Obinutuzumab per label; 12 cycles total with MRD guided	Chemoimmunotherapy (FCR for ≤ 65 y or bendamustine-rituximab for > 65 y); 6 × 28 day cycles	uMRD in peripheral blood at month 15 and PFS (time from randomization to progression or death)
Munir et al.[20]	FLAIR; ISRCTN01844152; EudraCT 2013-001944-76	Phase 3, open-label RCT	96 sites in United Kingdom	Previously untreated CLL/SLL; considered fit for FCR	523	Ibrutinib 420 mg qd for 8 weeks, then add venetoclax (ramp up to 400 mg qd)	FCR every 28 days × 6 cycles	PFS (time from randomization to progression or all-cause death)

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; uMRD, undetectable minimal residual disease; RCT, randomized controlled trial; FCR, fludarabine-cyclophosphamide-rituximab; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; PFS, progression-free survival; qd, once daily; C1D1, cycle 1 day 1; wk, week; MRD, minimal residual disease; GLOW, global study of venetoclax and obinutuzumab in previously untreated CLL; GAIA-CLL, global assessment of ibrutinib and venetoclax in previously untreated CLL; FLAIR, frontline therapy with ibrutinib, venetoclax and rituximab.

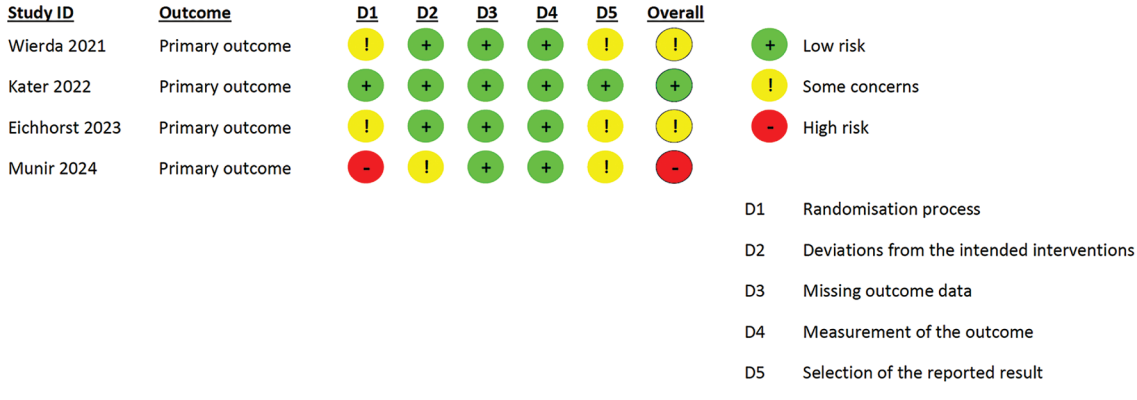

Figure 2. Risk of bias assessment of the included trials per each primary outcome.

Primary and Secondary Efficacy Outcomes

VIC significantly prolonged PFS compared to controls at early timepoints: month 12 (RR 1.10; 95% CI, 1.05-1.15), month 24 (RR 1.21; 95% CI, 1.15-1.28), month 36 (RR 1.27; 95% CI, 1.14-1.42; moderate certainty of evidence), and month 48 (RR 1.47; 95% CI, 1.18-1.84) (Table 2), but not at month 60 (RR 1.74; 95% CI, 0.88-3.43) (Figure 3).

MRD negativity was more frequent with VIC in peripheral blood (RR 1.55; 95% CI, 1.35-1.79) and in bone marrow (RR 2.15; 95% CI, 1.37-3.38) (Figure 4). OS at 36 months was similar between groups (RR 1.05; 95% CI, 0.93-1.17).

Safety and Tolerability Outcomes

Compliance and safety outcomes were generally comparable (Table 3). Rates of withdrawal due to AEs (RR 1.29; 95% CI, 0.43-3.87), of any serious AEs (RR 1.10; 95% CI, 0.74-1.62), of pneumonia (RR 0.86; 95% CI, 0.22-3.30), of upper respiratory tract infection (RR 0.75; 95% CI, 0.24-2.33), and of death (RR 0.70; 95% CI, 0.22-2.29) did not differ significantly. However, VIC was associated with an increased risk of diarrhea (RR 2.10; 95% CI, 1.00-4.40) and hypertension (RR 2.86; 95% CI, 1.26-6.49).

Subgroup Analysis

Subgroup analyses by IGHV mutational status are presented in Supplementary Figures S1-S5. At most time points (12, 36, 48, and 60 months), no statistically significant interaction was detected between IGHV mutational status and the effect of regimens containing venetoclax and ibrutinib on PFS. However, at 24 months, there was evidence of a differential treatment effect, with patients harboring unmutated IGHV deriving a greater relative benefit than those with mutated IGHV (P for interaction < 0.1).

In an additional subgroup analysis stratified by VIC regimen composition, venetoclax plus ibrutinib (RR, 1.28; 95% CI, 1.12-1.46) and venetoclax plus ibrutinib plus obinutuzumab (RR, 1.26; 95% CI, 1.05-1.51) yielded comparable relative benefits for the primary outcome. This indicates that the addition of obinutuzumab to venetoclax-ibrutinib did not substantially alter efficacy in terms of PFS at 36 months, consistent with the absence of significant subgroup interaction.

Furthermore, we performed additional subgroup analyses for the primary outcome of PFS at 36 months by management strategy (specifically, fixed-duration versus MRD-guided venetoclax–ibrutinib regimens; Figure S6) and by overall RoB classification of the included RCTs (Figure S7). The pooled estimates demonstrated similar effect sizes between the two management strategies. The RRs for both analyses were consistent with the main analysis, and the test for subgroup differences yielded P = 0.9074, indicating no statistically significant interaction for management type or RoB classification.

DISCUSSION

No previous meta-analysis had been published on this topic. However, Wen et al.[21] conducted a network meta-analysis (NMA) evaluating first-line treatment strategies for CLL using a frequentist approach and incorporating 30 RCTs (n=12,818) across chemotherapy, chemoimmunotherapy, and targeted regimens. Inclusion criteria encompassed treatment-naive adults with CLL or small lymphocytic lymphoma requiring therapy per the International Workshop on CLL guidelines; eligible trials were phase II/III RCTs reporting PFS, OS, objective response, uMRD, or AEs. The authors conducted comprehensive database searches, applied Cochrane risk-of-bias assessments, and used frequentist NMA with P-scores to rank regimens, complemented by subgroup analyses stratified by age, comorbidities, IGHV status, and cytogenetic features. PFS of acalabrutinib-obinutuzumab in the overall population was found to be statistically superior to that of all chemotherapy-free regimens and chemoimmunotherapies, except for ibrutinib-venetoclax and MRD-guided ibrutinib-venetoclax regimens. Specifically, acalabrutinib-obinutuzumab demonstrated significant benefit compared with ibrutinib (HR = 0.19; 95% CI, 0.12-0.32), zanubrutinib (HR = 0.23; 95% CI, 0.13-0.43), obinutuzumab-venetoclax (HR = 0.34; 95% CI, 0.22-0.53), and ibrutinib-obinutuzumab (HR = 0.56; 95% CI, 0.32-0.98). Both ibrutinib-venetoclax (HR = 0.53; 95% CI, 0.32-0.87) and MRD-guided ibrutinib-venetoclax (HR = 0.43; 95% CI, 0.22-0.85) yielded superior PFS compared with obinutuzumab-venetoclax.[21] Furthermore, they reported that zanubrutinib consistently exhibited the most favorable safety profile, with significantly fewer grade ≥ 3 AEs than were observed with acalabrutinib, acalabrutinib-obinutuzumab, ibrutinib-obinutuzumab, ibrutinib-venetoclax, and obinutuzumab-venetoclax. Acalabrutinib also demonstrated lower rates of severe toxicity compared with ibrutinib-obinutuzumab, ibrutinib-venetoclax, and obinutuzumab-venetoclax. The triplet regimen obinutuzumab-ibrutinib-venetoclax was associated

Table 2. Summary of Findings on Progression-free Survival at 36 Months for VIC Compared to Control Regimens

Outcome no of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Control	VIC	Difference	
Progression-free survival at 36 months assessed with: as defined by each trial follow-up: range 38.8 months to 43.7 months no of participants: 970 (2 RCTs)	RR 1.27 (1.14 to 1.42)	50.7%	64.4% (57.8 to 72)	13.7% more (7,1 more to 21,3 more)	⨁⨁⨁◯ Moderate[a]

[a]Risk of bias: Downgraded one levels as Munir[20] were at high RoB due to randomization process and Eichhorst[19] was at some concerns of RoB in the randomisation process and selection of the reported results.
CI, confidence interval; RR, risk ratio; RoB, risk of bias; RCT, randomized controlled trial; VIC, venetoclax-ibrutinib combinations.

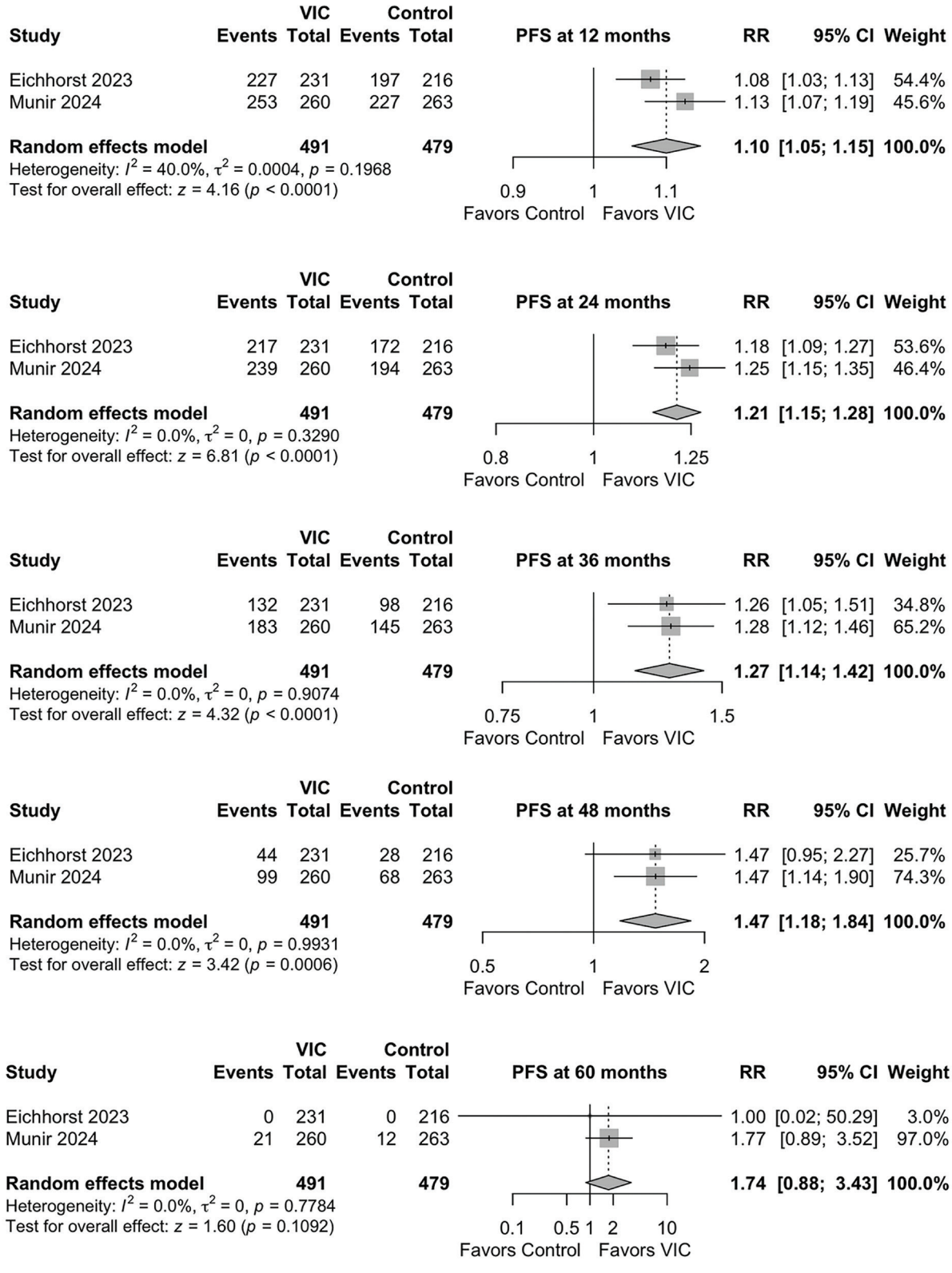

Figure 3. Forest plots of progression-free survival (PFS) during follow-up.

VIC, venetoclax-ibrutinib combinations; RR, risk ratio; CI, confidence interval.

Table 3. Effects of Venetoclax-ibrutinib Combinations on Safety and Tolerability Outcomes

Outcomes	Number of studies	Number of participants	Pooled effect size RR (95% CI)	*P* value	I-square (%)
Overall survival at 36 months	2	970	1.05 (0.93; 1.17)	0.44	71
Death	4	1212	0.70 (0.22; 2.29)	0.56	51
Diarrhea	4	1212	2.10 (1.00; 4.40)	0.49	94
Hypertension	4	1212	2.86 (1.26; 6.49)	0.01	77
Pneumonia	3	1149	0.86 (0.22; 3.30)	0.83	48
Upper respiratory infections	3	1149	0.75 (0.24; 2.33)	0.61	91
Serious or severe AEs	3	1149	1.10 (0.74; 1.62)	0.64	89
Withdrawal due to AEs	3	1162	1.29 (0.43; 3.87)	0.64	67

AEs, adverse events; RR, risk ratio; CI, confidence interval.

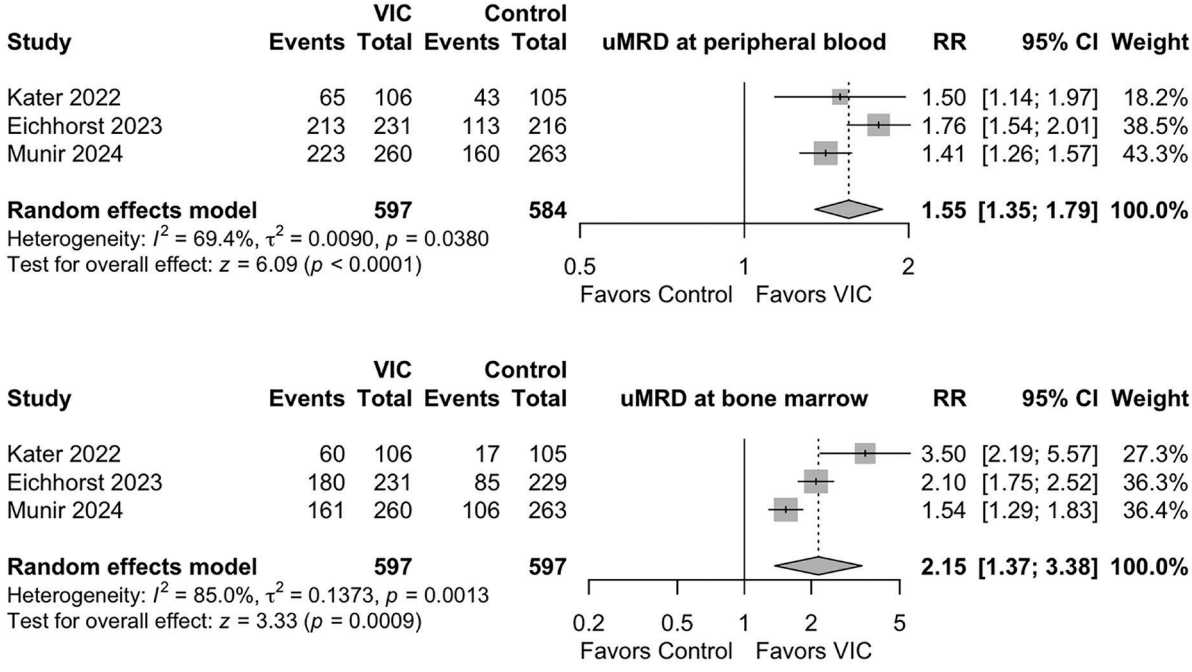

Figure 4. Forest plots of undetected minimal residual disease rates in peripheral blood and bone marrow.

VIC, venetoclax-ibrutinib combinations; uMRD, undetectable minimal residual disease; RR, risk ratio; CI, confidence interval.

with increased dose reductions (> 20%) and treatment discontinuations, whereas ibrutinib-venetoclax carried a higher risk of grade ≥ 3 diarrhea than acalabrutinib, ibrutinib, acalabrutinib-obinutuzumab, and obinutuzumab-venetoclax. Neutropenia rates, both overall and grade ≥ 3, were lowest with zanubrutinib and highest with obinutuzumab-venetoclax. Notably, they found that ibrutinib-venetoclax showed a significantly lower incidence of neutropenia compared with obinutuzumab-venetoclax (any grade: odds ratios (OR) 0.50; 95% CI, 0.26-0.98; grade ≥ 3: OR 0.50; 95% CI, 0.26-0.97).[21]

While the NMA by Wen et al.[21] provides valuable network-level insights by incorporating 30 RCTs and enabling indirect comparisons across diverse regimens, its findings must be interpreted with caution. Notably, the exclusion of the CAPTIVATE trial[17], a pivotal study of venetoclax-ibrutinib with MRD-guided discontinuation, may have introduced bias by underrepresenting key data on time-limited VIC therapy. Moreover, the reliance on indirect comparisons can amplify heterogeneity from varying trial populations and designs. In contrast, our meta-analysis synthesized direct, head-to-head evidence. Additionally, we assessed detailed landmark PFS outcomes at 12, 24, 36, and 48 months that the NMA did not address.

A recently published Bayesian NMA[22] restricted to physically fit, untreated CLL patients synthesized RCTs of first-line targeted regimens (venetoclax, obinutuzumab, ibrutinib, and their combinations) and analyzed PFS and uMRD negativity in PB [MRD(-)PB]. Searches spanned MEDLINE, Embase,

and CENTRAL. The authors found no statistically significant differences between regimens in PFS; however, ibrutinib-rituximab and venetoclax-obinutuzumab-ibrutinib ranked highest according to the surface under the cumulative ranking curves (PFS: 91% and 83% at matched follow-up; 75% and 74% at the longest follow-up). For uMRD in peripheral blood, venetoclax-obinutuzumab-ibrutinib was significantly superior to other targeted options, with large OR; for example, in comparisons with the most similar follow-up: vs. venetoclax-rituximab, OR 10.58 (95% CI 5.46-22.38); vs. venetoclax-obinutuzumab, OR 2.21 (95% CI 1.04-4.94); vs. ibrutinib-rituximab, OR 127.8 (95% CI 59.24-295.77); and vs. ibrutinib-venetoclax, OR 9.43 (95% CI 3.43-27.06).[22]

Our meta-analysis synthesizes direct head-to-head evidence exclusively from RCTs of VIC (with or without obinutuzumab) in untreated patients and quantifies landmark PFS at 12, 24, 36, 48, and 60 months, rather than relying solely on the longest follow-up or on indirect comparisons. We found that VIC significantly prolonged PFS at 12-48 months (RRs 1.10-1.47), with attenuation at 60 months; increased uMRD rates in blood and bone marrow; and revealed no meaningful difference in PFS at 36 months between venetoclax-ibrutinib [RR 1.28 (1.12-1.46)] and venetoclax-obinutuzumab-ibrutinib [RR 1.26 (1.05-1.51)]. In IGHV-defined subgroups, only the 24-month signal favored unmutated IGHV (pinteraction < 0.1). Although all trials applied the standard 10^{-4} threshold, minor methodological differences—such as the use of next-generation sequencing versus flow cytometry, and varying sampling schedules (fixed versus MRD-guided)—may introduce subtle heterogeneity. However, because the sensitivity thresholds were harmonized and concordance between blood and marrow uMRD has been shown to be high, these differences are unlikely to have meaningfully impacted the pooled uMRD estimates in this meta-analysis.

That the study[22] concludes that venetoclax-ibrutinib and venetoclax-obinutuzumab-ibrutinib are among the most effective therapies for prolonging PFS aligns with our observation that triplet therapy is highly efficacious. Importantly, our results extend the literature by demonstrating, with direct evidence, that the doublet (venetoclax-ibrutinib) also achieves robust PFS benefits in untreated CLL, and that adding obinutuzumab did not materially change 36-month PFS in our pooled RCT data. Moreover, to our knowledge, our study is the first meta-analysis built solely on direct randomized evidence on VIC in the frontline setting and the first to provide granular, time-anchored PFS estimates at 12, 24, 36, 48, and 60 months, which can inform shared decision-making regarding time-limited strategies.

Study Limitations

Limitations include heterogeneity in comparator arms (chemoimmunotherapy vs. targeted combinations) and variability in outcomes due to differing definitions and timelines of efficacy endpoints across trials. Nevertheless, the consistent PFS benefit and favorable safety profile support incorporating VIC as a standard frontline option. Although the included RCTs differed in comparator regimens (chemoimmunotherapy vs. targeted agents), subgroup analysis by comparator type could not be performed due to the limited number of studies reporting the primary outcome. This variability should therefore be considered when interpreting the pooled results. Finally, because there is a lack of published systematic reviews and meta-analyses on this subject, we were unable to compare our findings with other studies.

CONCLUSION

Our analysis showed that VIC provides superior disease control compared with established regimens in first-line treatment of CLL, particularly by achieving prolonged PFS and sustained MRD negativity. The inclusion of both fit and older patients across trials strengthens the generalizability of these results.

Ethics

Ethics Committee Approval: This study was a systematic review and meta-analysis of previously published studies and did not involve human participants directly; therefore, ethics committee approval and informed consent were not required.

Acknowledgment

Preliminary results of this study were presented at 11th Society of Hematologic Oncology Türkiye Meeting, April 27-28, 2024, İstanbul and the abstract was published at the Clinical Lymphoma Myeloma and Leukemia.

Footnotes

Author Contributions

Concept Design – L.H.T., A.S.; Data Collection or Processing – L.H.T., A.S.; Analysis or Interpretation – L.H.T., A.S.; Literature Review – L.H.T., A.S.; Writing, Reviewing and Editing – L.H.T., A.S.

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Supplementary Figures

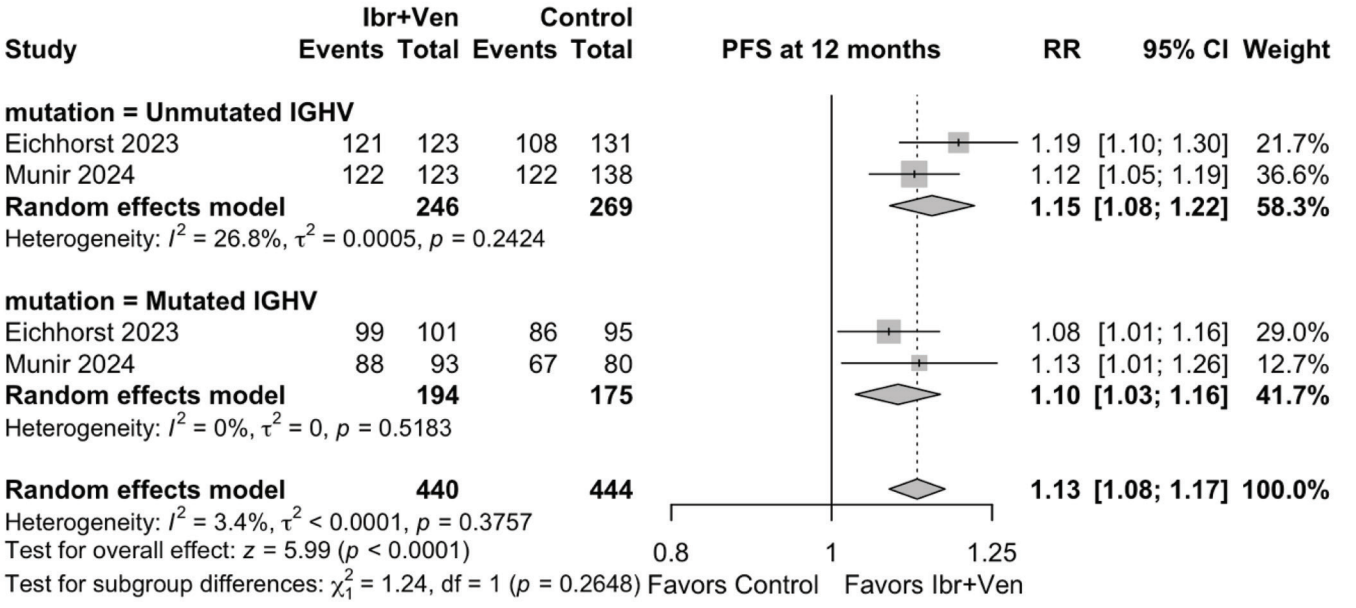

Figure S1. Subgroup analyses of progression-free survival at 12 months by IGHV mutation status.

RR, risk ratio; PFS, progression-free survival; CI, confidence interval; IGHV: immunoglobulin heavy chain variable.

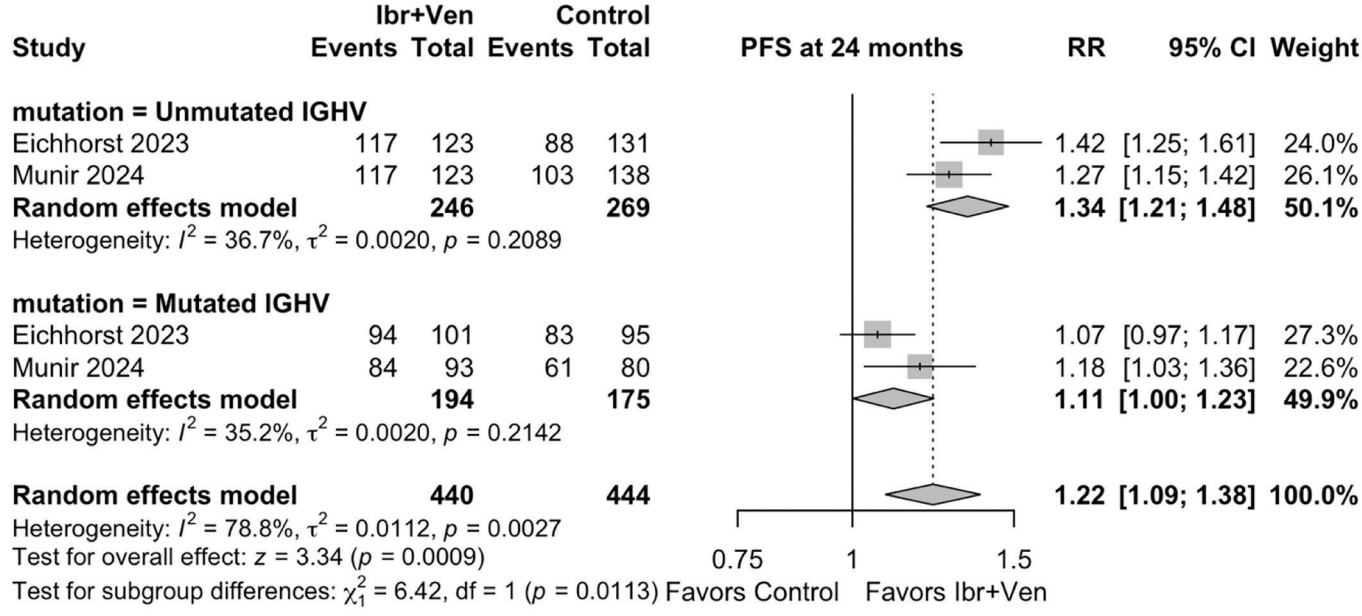

Figure S2. Subgroup analyses of progression-free survival at 24 months by IGHV mutation status.

RR, risk ratio; PFS, progression-free survival; CI, confidence interval; IGHV: immunoglobulin heavy chain variable.

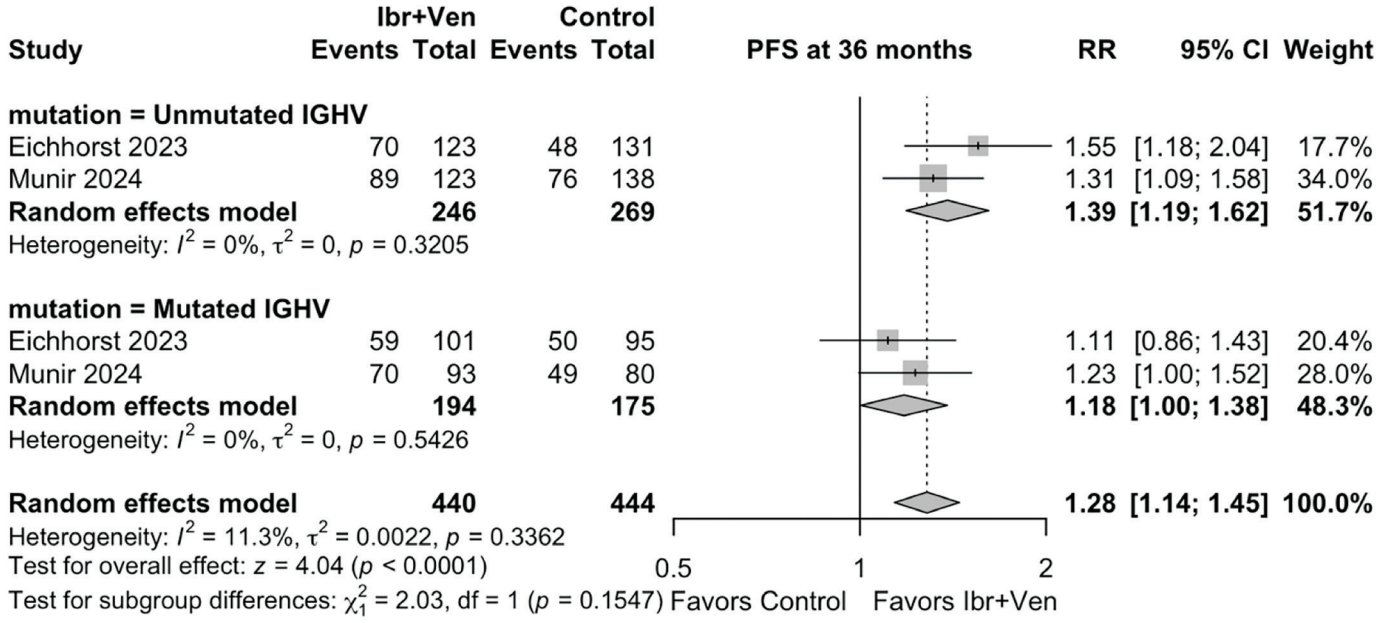

Figure S3. Subgroup analyses of progression-free survival at 36 months by IGHV mutation status.

RR, risk ratio; PFS, progression-free survival; CI, confidence interval; IGHV: immunoglobulin heavy chain variable.

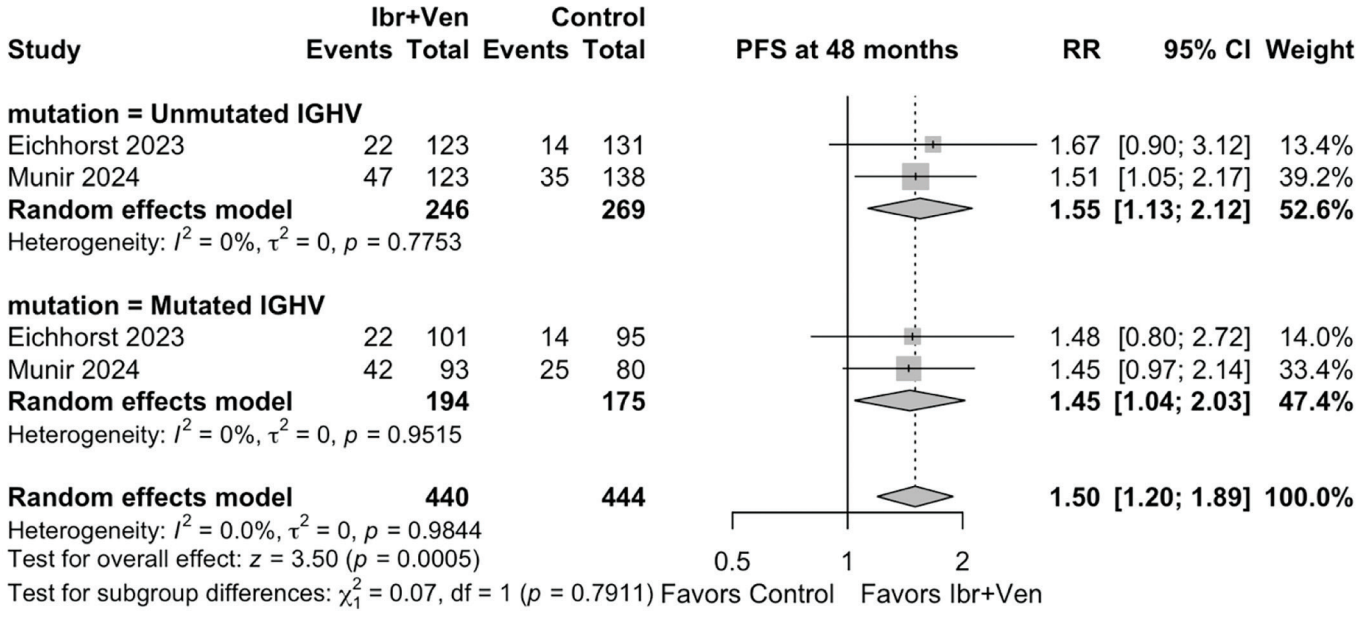

Figure S4. Subgroup analyses of progression-free survival at 48 months by IGHV mutation status.

RR, risk ratio; PFS, progression-free survival; CI, confidence interval; IGHV: immunoglobulin heavy chain variable.

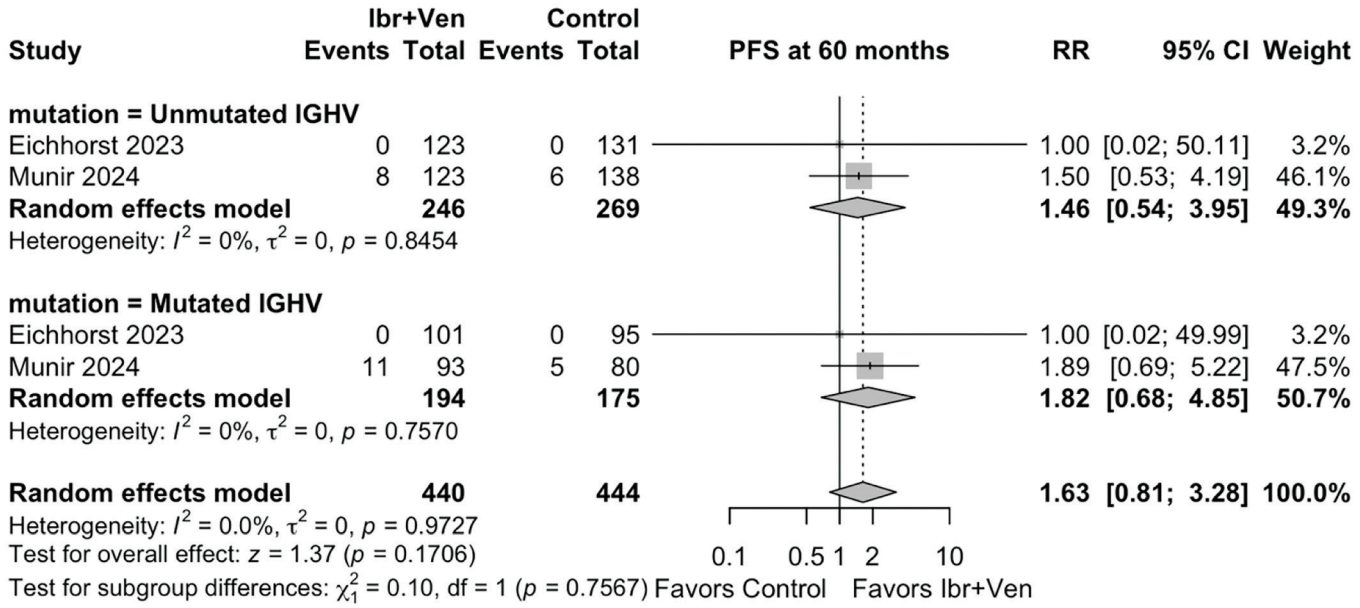

Figure S5. Subgroup analyses of progression-free survival at 60 months by IGHV mutation status.

RR, risk ratio; PFS, progression-free survival; CI, confidence interval.

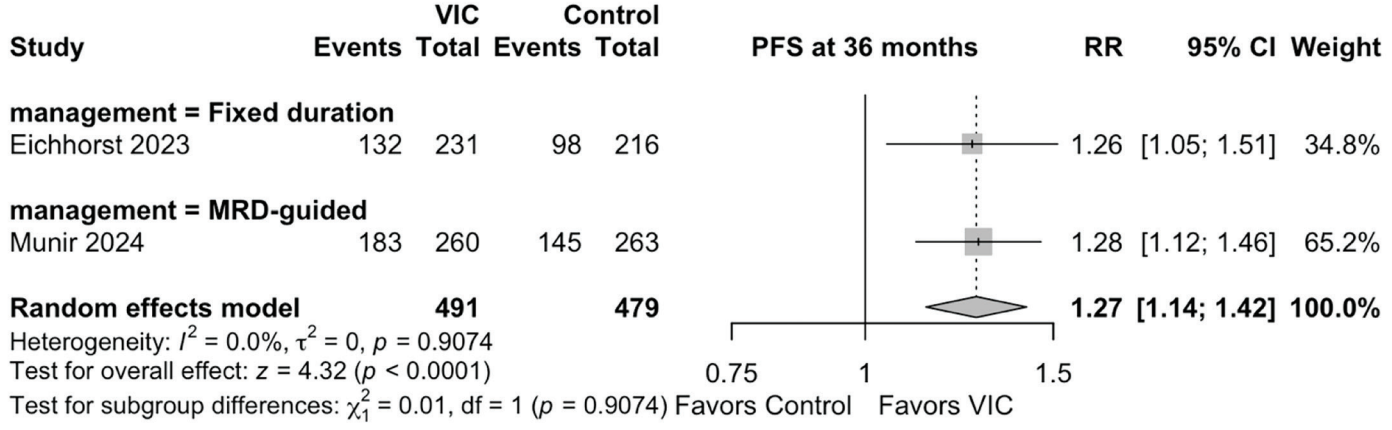

Figure S6. Subgroup analyses of progression-free survival at 36 months by type of management.

RR, risk ratio; PFS, progression-free survival; VIC, venetoclax-ibrutinib combinations.

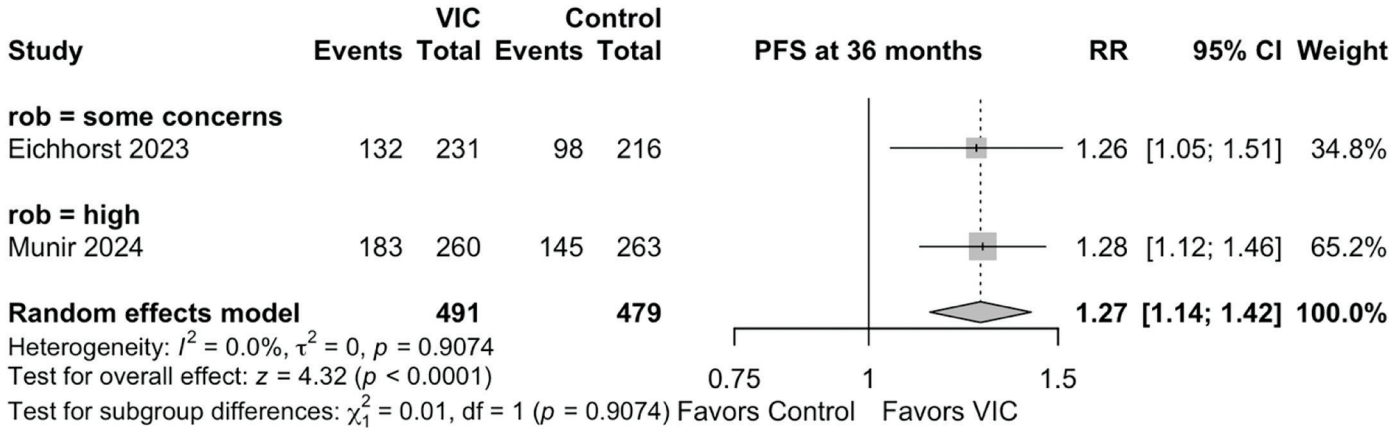

Figure S7. Subgroup analyses of progression-free survival at 36 months by type of risk of bias.

RR, risk ratio; PFS, progression-free survival; VIC, venetoclax-ibrutinib combinations.