

Towards Precision Therapy: A Systematic Review and Meta-Analysis of Targeted Therapy Effectiveness and Safety in Philadelphia Chromosome–Negative Acute Lymphoblastic Leukemia

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HIGHLIGHTS

- ❖ Targeted therapy significantly improves overall survival and disease-free survival in pediatric non-Ph+ acute lymphoblastic leukemia
- ❖ This systematic review and meta-analysis evaluate the effectiveness and safety of targeted therapy compared with conventional chemotherapy in children
- ❖ Targeted therapy increases minimal residual disease negativity and reduces the incidence of severe adverse events, supporting its role in precision oncology for pediatric ALL

ABSTRACT

Acute lymphoblastic leukemia (ALL) non-Philadelphia chromosome–positive (non-Ph+) is a major subtype of leukemia with high relapse rates and significant toxicity from conventional chemotherapy. This study evaluated the efficacy and safety of targeted therapy versus chemotherapy in non-Ph+ ALL. This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. Five databases were searched for randomized controlled trials (RCTs) comparing both interventions, with outcomes including overall survival (OS), event-free survival (EFS), disease-free survival (DFS), minimal residual disease (MRD), and grade ≥ 3 adverse events (AEs). Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool, and pooled estimates were calculated using hazard ratios (HRs) and risk ratios (RRs). Six RCTs from 7,154 records were included. Targeted therapy significantly improved OS (HR 0.59; 95% CI 0.42–0.84) and DFS (HR 0.73; 95% CI 0.55–0.96), with a non-significant trend in EFS (RR 0.69; 95% CI 0.48–1.01). MRD negativity increased after sensitivity analysis (RR 1.85; 95% CI 1.44–2.37), while severe adverse events were reduced (RR 0.88; 95% CI 0.80–0.97). Overall, targeted therapy is associated with improved survival with an acceptable safety profile in non-Ph+ ALL.



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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common hematologic malignancy in children, accounting for approximately 29% of all pediatric cancers worldwide (American Cancer Society, 2018). According to the Global Burden of Disease 2021 study, global childhood ALL incidence was approximately 2.3 per 100,000 children in 2021, with the highest burden in early childhood (Hu et al., 2024). In Indonesia, the annual incidence of pediatric ALL was estimated at approximately 4.3 per 100,000 children in 2022, highlighting a substantial national disease burden (Garniasih et al., 2022). Although ALL occurs most frequently in children, it also affects adolescents and young adults, representing a clinically important population that requires age-specific treatment considerations (Ribera et al., 2014).

In high-income countries such as the United States and Western Europe, five-year survival rates for pediatric ALL have exceeded 80%. This reflects the successful use of risk-adapted treatment protocols, advances in supportive care, and the routine monitoring of minimal residual disease (MRD) (Ramadhan et al., 2024). In contrast, survival outcomes in developing countries, including Indonesia, remain lower. Structural challenges such as delayed diagnosis, limited access to advanced diagnostics, treatment interruptions, and reliance on conventional chemotherapy contribute to these outcomes. Data from referral hospitals in Indonesia indicate that most ALL patients receive standard chemotherapy, and survival rates remain below international benchmarks (Ramadhan et al., 2024). Together, these challenges contribute to inferior survival outcomes in developing countries.

Conventional chemotherapy has been the cornerstone of ALL treatment. However, it has many limitations. High treatment-related toxicities are frequently reported, including secondary malignant neoplasms (SMNs), cardiotoxicity, neurotoxicity, skeletal disorders, hepatic dysfunction, and long-term neurocognitive impairment. These effects are seen especially among younger pediatric patients (Al-Mahayri et al., 2021). Additionally, relapse and drug resistance remain major challenges. They contribute to treatment failure and reduced quality of life during and after therapy (Jędraszek et al., 2022). These limitations underscore the urgent need for more selective and biologically targeted therapies.

Recent advances in targeted therapy have introduced several agents with distinct mechanisms of action, including the bispecific monoclonal antibody blinatumomab, the purine nucleoside analog nelarabine, and the proteasome inhibitor bortezomib. Clinical trials have demonstrated that these agents can improve hematologic response rates and prolong event-free survival (EFS), particularly in patients with relapsed or refractory ALL, while exhibiting toxicity profiles distinct from conventional chemotherapy (Chen et al., 2023; Locatelli et al., 2021). Nevertheless, the current body of evidence remains limited, especially for patients with Philadelphia chromosome-negative (non-Ph+) ALL.

Most existing studies combine data from adult and pediatric populations or fail to clearly differentiate between Philadelphia chromosome-positive (Ph+) and non-Ph+ ALL, potentially introducing bias due to differences in disease biology, pharmacokinetics, immune competence, and adverse event profiles (Chen et al., 2023; Clements et al., 2020). Patients with Ph+ ALL, for example, have distinct molecular characteristics and are typically treated with tyrosine kinase inhibitor-based regimens rather than monoclonal antibodies (Chen et al., 2021; Ravandi, 2017). Consequently, evidence regarding the comparative efficacy and safety of non-TKI targeted therapies in non-Ph+ ALL remains fragmented. To our knowledge, no previous systematic review and meta-analysis has comprehensively synthesized randomized controlled trial evidence evaluating multiple targeted therapies, including blinatumomab, nelarabine, and bortezomib in children, adolescents, and young adults with non-Ph+ ALL. Therefore, this systematic review and meta-analysis aimed to evaluate the efficacy and safety of these targeted therapies compared with

conventional chemotherapy to support their integration into contemporary treatment strategies for non-Ph+ ALL.

MATERIALS AND METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, completeness, and quality in reporting and to enhance the validity and transparency of the research process.

Search strategy

The search strategy employed Boolean operators tailored to each database. In accordance with PRISMA guidelines, a comprehensive literature search was conducted across PubMed, ScienceDirect, the Cochrane Library, Sage, and Taylor & Francis. Article searches in each database were performed between 1 and 10 July 2025 using a general Boolean search strategy combining the terms (“Acute Lymphoblastic Leukemia” OR “ALL”) AND (“Targeted Therapy” OR “Molecular Therapy” OR “Precision Medicine” OR “Targeted Treatment”). In addition, filters were applied to enhance the relevance of the results, including the “Randomized Controlled Trial (RCT)” filter in PubMed and the “Research Article” filter in Sage and Taylor & Francis.

Eligibility criteria

Eligibility criteria were established to ensure the inclusion of studies relevant to the research objectives. These criteria were applied consistently during the screening and selection process to maintain methodological rigor. The eligibility criteria for included studies are presented in **Table 1**.

Table 1. Inclusion and exclusion criteria

	Inclusion criteria*	Exclusion criteria*
Population	Patients with non-Ph+ acute lymphoblastic leukemia (ALL), including B-cell and T-cell subtypes, treated during childhood, adolescence, or young adulthood.	Studies involving patients with Philadelphia chromosome-positive (Ph+) ALL, mixed leukemia populations without separately reported non-Ph+ ALL data, or other hematologic malignancies.
Intervention	Studies using targeted therapy as the intervention	Other targeted therapies, including tyrosine kinase inhibitors (TKIs), CAR T-cell therapy, or other modalities
Control (Comparison)	A comparator group receiving standard conventional chemotherapy	—
Outcome	At least one primary outcome, including: • event-free survival (EFS) • disease-free survival (DFS) • overall survival (OS) • minimal residual disease (MRD) • adverse events (AEs) of grade ≥ 3	—
Publication	• Randomized Controlled Trial (RCT) publications	• Non-interventional studies, including observational studies, case reports,

Inclusion criteria*	Exclusion criteria*
● Published in English or Indonesian ● Available in full-text format	● review articles, or similar publications ● Duplicate data or represented duplicate publications ● Minimal residual low methodological quality based on risk-of-bias assessment.

*Inclusion and exclusion criteria were defined according to the Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework.

Screening and data selection

Search results from all databases were compiled into Rayyan AI (<https://www.rayyan.ai>), a validated platform for study screening and selection. Duplicate records were identified automatically and further checked manually; studies with $\geq 90\%$ similarity were removed. Prior to screening, the “blind-on” mode was activated to minimize subjective bias in study selection. Studies with titles and abstracts that did not meet the eligibility criteria were excluded. The PRISMA flow diagram presents the reasons for exclusion and the number of studies included at each stage of the selection process.

Data extraction

Qualitative and quantitative data from the included studies were extracted and organized into structured tables using Microsoft Excel 2021 (Microsoft Corporation, USA) and Rayyan.ai, and subsequently reviewed by all contributing authors. Qualitative data extraction included key study characteristics, such as author name, year of publication, country of origin, study design, study population characteristics, and control group characteristics. Quantitative data, specifically the number of cases and controls in each study, were also extracted. The results of the data extraction are presented in **Table 2**.

Quality assessment and publication bias

The risk of bias of the included studies was assessed using the Cochrane Risk of Bias tool version 2.0 (RoB 2.0). This tool evaluates five bias domains: arising from the randomization process (D1), due to deviations from the intended interventions (D2), due to missing outcome data (D3), in the measurement of outcomes (D4), and the selection of the reported results (D5). Two reviewers independently conducted the risk-of-bias assessment and resolved discrepancies through discussion or consultation with the first reviewer. Detailed assessments and justifications for each domain are provided in **Figures 2 & 3**.

Statistical analysis

Statistical analyses were performed using Review Manager (RevMan) version 5.4.1. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were used for time-to-event outcomes, whereas risk ratios (RRs) with 95% CIs were used for dichotomous outcomes. Time-to-event outcomes were pooled using the inverse-variance method, and dichotomous outcomes were analyzed using the Mantel–Haenszel method. Heterogeneity was assessed using the Chi-square test and the I^2 statistic in accordance with Higgins' guidelines. A fixed-effect model was applied when heterogeneity was low ($I^2 \leq 50\%$), whereas a random-effects model was used when substantial heterogeneity was present ($I^2 > 50\%$). P-value < 0.05 was considered statistically significant. Meta-analysis results were presented as forest plots, with sensitivity analyses conducted when substantial heterogeneity was detected to explore its sources.

RESULTS

Study selection process

The systematic literature search identified 7,154 records from electronic databases, including 64 from PubMed, 510 from SAGE, 1,890 from Taylor & Francis, 220 from the Cochrane Library, and 4,470 from ScienceDirect. Before screening, 4,043 records were removed as duplicates. This left 3,104 records, which were screened by title and abstract. Of these, 2,996 records were excluded because they did not meet the predefined inclusion criteria for study design, population, intervention, or outcomes of interest.

Subsequently, 108 reports were sought for full-text retrieval. However, 21 reports could not be retrieved, leaving 87 full-text articles to assess for eligibility. During the eligibility assessment, 81 articles were excluded, including 43 studies that investigated different outcomes and 38 review papers or study protocols that did not meet the inclusion criteria for randomized controlled trials. Ultimately, six randomized controlled trials (RCTs) fulfilled all eligibility criteria and were included in the qualitative synthesis. All included studies had sufficient methodological quality and relevant outcome data to incorporate into the final analysis. **Figure 1** presents the detailed process of study identification, screening, eligibility assessment, and inclusion.

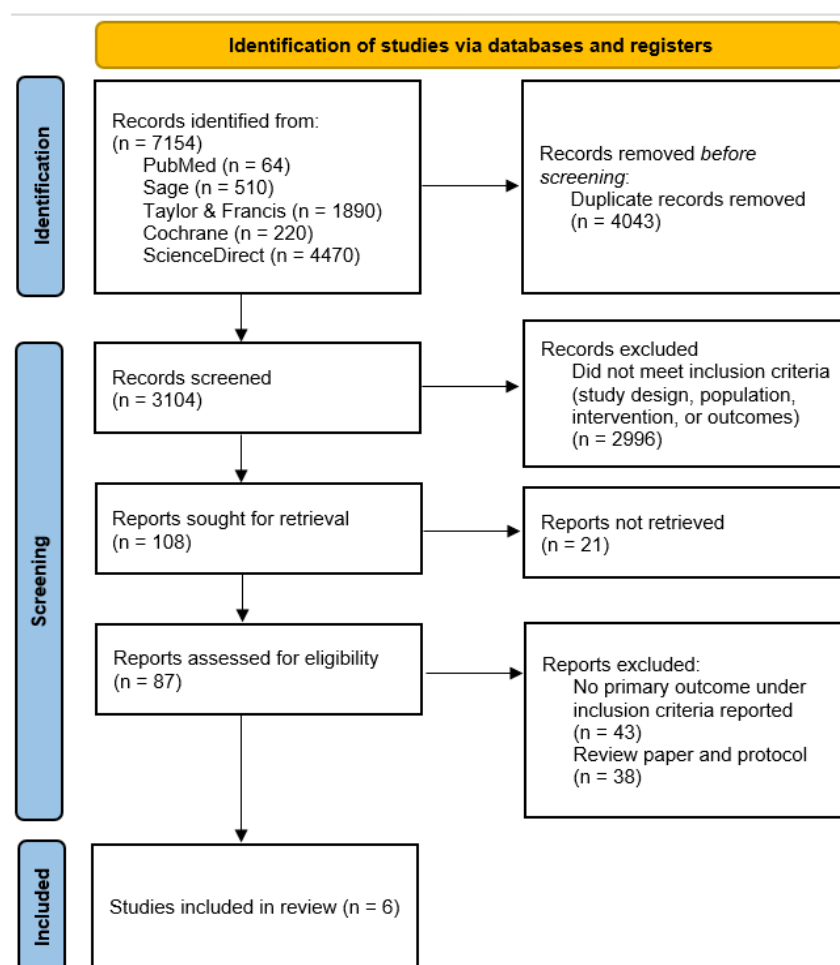


Figure 1. Flow diagram of the literature search strategy for this meta-analysis. This figure summarizes the systematic process of literature identification, screening, eligibility assessment, and final study inclusion for this meta-analysis in accordance with PRISMA guidelines. Records were identified from multiple electronic databases, followed by duplicate removal, title and abstract screening, full-text eligibility assessment, and final inclusion of randomized controlled trials that met all predefined inclusion criteria.

Study characteristics and findings

This review included six randomized controlled trials (RCTs). The main characteristics of the included studies are summarized in **Table 2**. All studies enrolled children, adolescents, and young adults diagnosed with non-Ph+ ALL. The trials were conducted in various clinical settings and represented different geographic regions, reflecting a heterogeneous but clinically relevant study population. Across the included trials, different classes of targeted therapies were evaluated, including immunotherapy with blinatumomab, a bispecific T-cell engager targeting CD19-expressing B cells, as well as non-antibody agents such as nelarabine and bortezomib with distinct cytotoxic mechanisms. Control groups received conventional chemotherapy or standard-of-care regimens as defined in each study protocol.

The included studies varied in treatment phase (e.g., relapsed or refractory disease, consolidation, or post-induction therapy), treatment duration, and follow-up periods. Sample sizes also differed across trials, reflecting differences in study design and recruitment capacity. Despite these variations, all included studies employed randomized allocation and reported adequate methodological details, consistent with their overall low risk of bias. Regarding outcome reporting, all studies provided data on at least one of the predefined outcomes of interest, including event-free survival (EFS), overall survival (OS), disease-free survival (DFS), or minimal residual disease (MRD) status. Several trials additionally reported safety outcomes, including the incidence of grade ≥ 3 adverse events, allowing for comparative assessment of treatment tolerability. Consistent core outcome reporting across studies enabled meaningful qualitative synthesis and supported further quantitative analysis.

Table 2. Characteristics of included studies

Author, Year	Study Location	Sex (n)		Sample Size		Age Median (IQR) years	Drug and Dose	EFS (%)	DFS (%)	OS (%)	MRD Negativity (%)	AEs ≥ Grade 3 (%)
		TT	ST	TT	ST							
Dunsmore et al. (2020)	United States	Male (238) Female (85)	Male (255) Female (81)	323	336	N/A	Nelarabine (650 mg/m ²)	83.7	TT (88.2) ST (82.1)	TT (90.3) ST (87.9)	N/A	TT (41.2) ST (46.1)
Locatelli et al. (2021)	United States	Male (30) Female (24)	Male (22) Female (32)	54	54	5.0 (4.0–10.5)	Blinatumomab (15 µg/m ²)	TT (69) ST (43)	N/A	N/A	TT (90) ST (54)	TT (57.4) ST (82.4)
Brown et al. (2021)	United States	Male (57) Female (48)	Male (54) Female (49)	105	103	TT 9 (6–16) ST 9 (5–16)	Blinatumomab (15 µg/m ²)	N/A	TT (54.4) ST (39.0)	TT 75 (71.3) ST (58.4)	TT (66) ST (32)	TT (81.4) ST (92.8)
Teachey et al. (2022)	United States	Male (295) Female (113)	Male (326) Female (90)	408	416	N/A	Bortezomib (1.3 mg/m ²)	TT (83.8) ST (80.1)	N/A	TT (88.3) ST (85.7)	TT (65.1) ST (61.1)	TT (80.0) ST (76.5)

Author, Year	Study Location	Sex (n)		Sample Size		Age Median (IQR) years	Drug and Dose	EFS (%)	DFS (%)	OS (%)	MRD Negativity (%)	AEs ≥ Grade 3 (%)
		TT	ST	TT	ST							
Hogan et al. (2023)	United States	Male (76) Female (51)	Male (76) Female (52)	127	128	TT 11 (7–15) ST 10 (7–15)	Blinatumomab (15 µg/m²)	N/A	TT 63 (61.2±5.0%) ST (49.5±5.2%)	TT (90.4±3.0%) ST (79.6±4.3%)	N/A	TT (66) ST (87)
Gupta et al. (2025)	United States, Canada, Australia, New Zealand	Male (368) Female (350)	Male (390) Female (332)	718	722	4.3 (2.8–6.4)	Blinatumomab (15 µg/m²)	N/A	TT (96.0±1.2%) ST (87.9±2.1%)	TT (98.4±0.9%) ST (97.1±1.1)	N/A	N/A

*TT (targeted therapy); ST (standard therapy); EFS (event-free survival); DFS (disease-free survival); OS (overall survival); MRD (minimal residual disease); AEs (adverse events); N/A (not available).

Quality assessment and publication bias

The methodological quality of the included randomized controlled trials (RCTs) was evaluated using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool. The traffic light plot in **Figure 2** shows the risk-of-bias judgments for each study across the five assessed domains. All included trials demonstrated a low risk of bias in all domains, as indicated by the predominance of green symbols. Specifically, low risk of bias was observed for the randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), measurement of outcomes (D4), and selection of the reported results (D5).

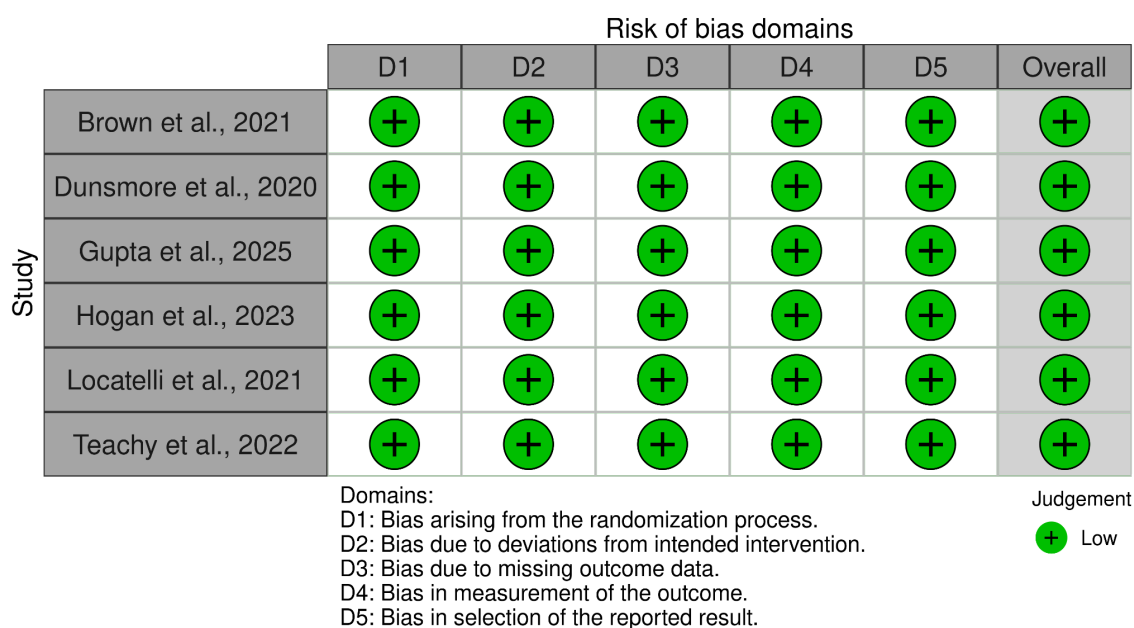


Figure 2. Risk of bias traffic light plot of included studies

Consistent with these findings, the summary plot in **Figure 3** shows the overall distribution of risk-of-bias judgments across all included studies. The plot shows that 100% of the studies were classified as having a low risk of bias in every assessed domain, with no studies rated as having “some concerns” or “high risk” of bias. This uniform distribution of low-risk assessments indicates that the included RCTs were of good methodological quality, thereby supporting a high level of confidence in the qualitative synthesis and subsequent data interpretation.

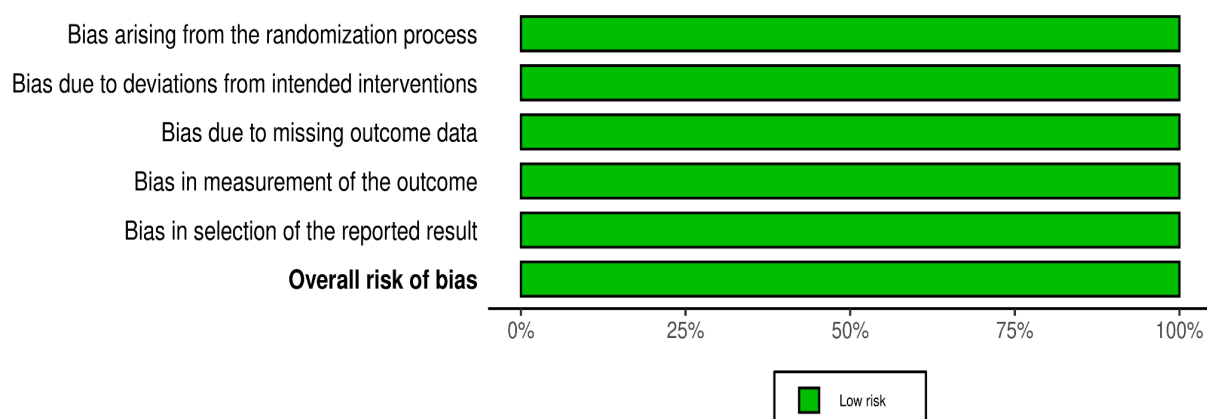


Figure 3. Risk of bias summary plot of included studies

Primary outcome

Targeted therapy significantly improved overall survival (OS) in pediatric patients with non-Ph+ ALL. The pooled analysis demonstrated a hazard ratio (HR) of 0.59 (95% CI: 0.42–0.84; $p = 0.003$), indicating a 41% reduction in the hazard of death compared with standard therapy as shown in **Figure 4**. In contrast, event-free survival (EFS) showed no statistically significant improvement. The pooled analysis shown in **Figure 5** yielded a relative risk (RR) of 0.69 (95% CI: 0.48–1.01; $p = 0.06$), suggesting a trend toward a lower risk of clinical events in the targeted therapy group.

Targeted therapy also demonstrated a significant benefit for disease-free survival (DFS). The pooled HR was 0.73 (95% CI: 0.55–0.96; $p = 0.03$), corresponding to a 27% reduction in the hazard of relapse or death compared with standard therapy shown in **Figure 6**.

For minimal residual disease (MRD) negativity, the initial pooled analysis showed no statistically significant difference between treatment groups (RR = 1.52, 95% CI: 0.98–2.37; $p = 0.06$). However, sensitivity analysis excluding Teachey et al. (2022) shown in **Figure 7** resulted in a significant improvement in MRD negativity with targeted therapy (RR = 1.85, 95% CI: 1.44–2.37; $p < 0.00001$), indicating an 85% greater likelihood of achieving MRD negativity compared with standard therapy.

Similarly, the initial pooled analysis of severe adverse events (AEs) showed no statistically significant difference between treatment groups (RR = 0.86, 95% CI: 0.75–1.00; $p = 0.05$). After sensitivity analysis excluding Hogan et al. (2023), Locatelli et al. (2021), and Teachey et al. (2022), targeted therapy was associated with a significant reduction in severe AEs (RR = 0.88, 95% CI: 0.80–0.97; $p = 0.007$) shown in **Figure 8**, representing a 12% lower risk of severe adverse events than standard therapy.

Quantitative assessment of heterogeneity

Heterogeneity was low ($I^2 = 0\%$) for OS, suggesting highly consistent results across the included studies. For EFS, moderate heterogeneity was observed ($I^2 = 51\%$). DFS also demonstrated low heterogeneity ($I^2 = 0\%$), indicating consistent treatment effects across studies. For MRD, heterogeneity was initially considerable ($I^2 = 91\%$) but decreased to low levels after sensitivity analysis ($I^2 = 28\%$). Similarly, heterogeneity for severe AEs was initially high ($I^2 = 83\%$) but was eliminated after sensitivity analysis ($I^2 = 0\%$). These findings suggest that, although the initial analyses showed substantial between-study variability for MRD negativity and severe adverse events, sensitivity analyses reduced heterogeneity and supported the robustness of the pooled estimates.

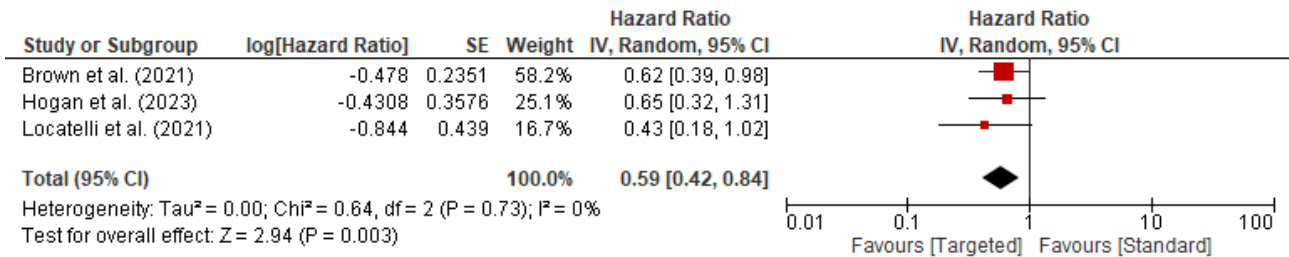


Figure 4. Forest plot used to determine the effect of targeted therapy on overall survival (OS) in non-Ph+ ALL. The vertical line represents the null effect (HR = 1). The HR column presents hazard ratios with 95% confidence intervals (CI), and study weights indicate each study's contribution to the pooled estimate. The diamond represents the pooled effect (HR = 0.59; 95% CI: 0.42–0.84). As the overall effect was statistically significant ($p = 0.003$), targeted therapy significantly improved overall survival compared with standard therapy. No significant heterogeneity was observed ($I^2 = 0\%$), supporting the use of the inverse-variance random-effects model.

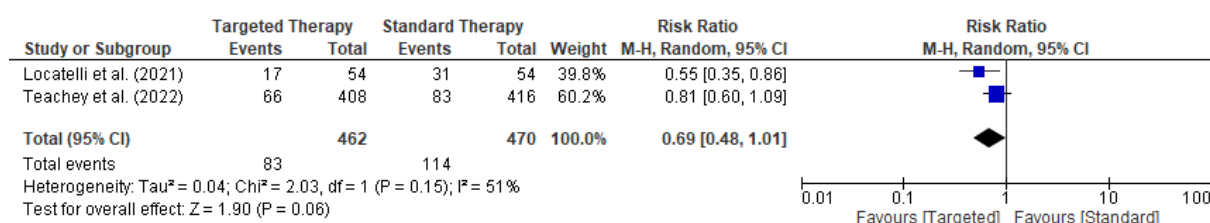


Figure 5. Forest plot used to assess the effect of targeted therapy on event-free survival (EFS) in non-Ph+ ALL. The vertical line represents the null effect ($RR = 1$). The RR column shows relative risks with 95% confidence intervals (CI), and study weights indicate each study's contribution to the pooled estimate. The diamond represents the pooled effect ($RR = 0.69$; 95% CI: 0.48–1.01). As the overall effect was not statistically significant ($p = 0.06$), the null hypothesis of no treatment effect could not be rejected. Moderate heterogeneity was observed ($I^2 = 51\%$), and a Mantel–Haenszel random-effects model was used.

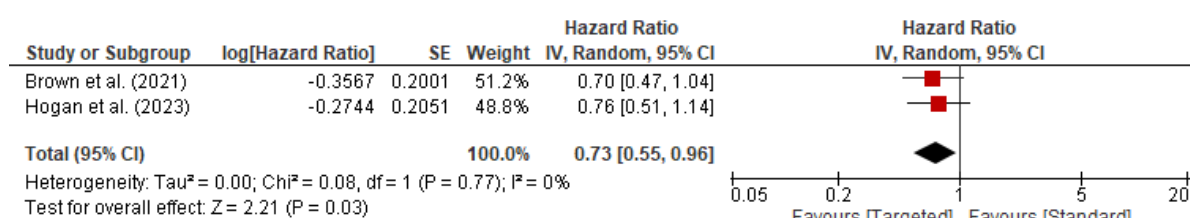
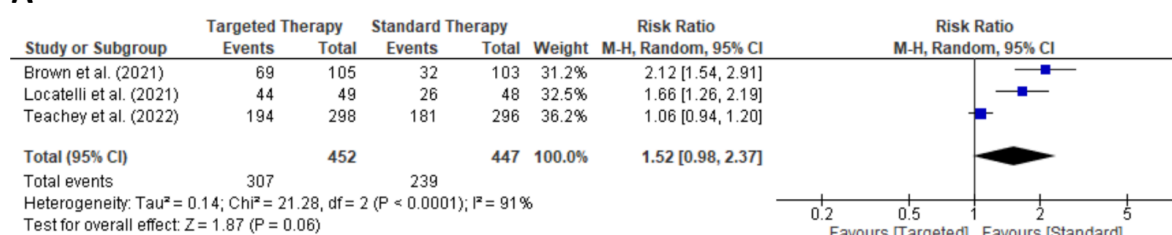


Figure 6. Forest plot of HR for DFS used to determine the effect of targeted therapy on relapse or death in non-Ph+ ALL. The vertical line represents the null effect ($HR = 1$). The HR column shows hazard ratios with 95% confidence intervals (CI), and study weights indicate each study's contribution to the pooled estimate. The diamond represents the pooled effect ($HR = 0.73$; 95% CI: 0.55–0.96). As the overall effect was statistically significant ($p = 0.03$), targeted therapy significantly reduced the hazard of relapse or death compared with standard therapy. No significant heterogeneity was observed ($I^2 = 0\%$), and the inverse-variance random-effects model was used.

A



B

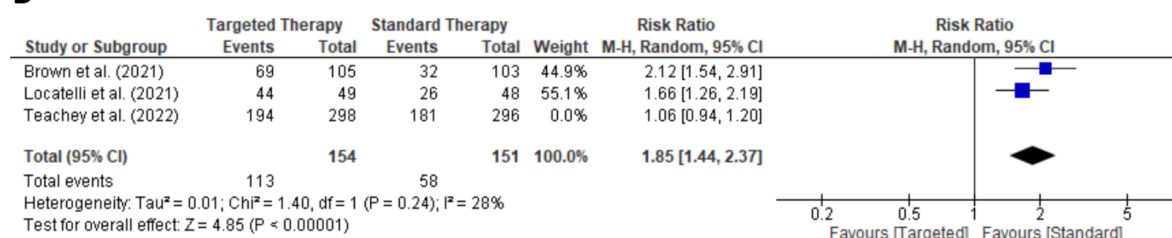
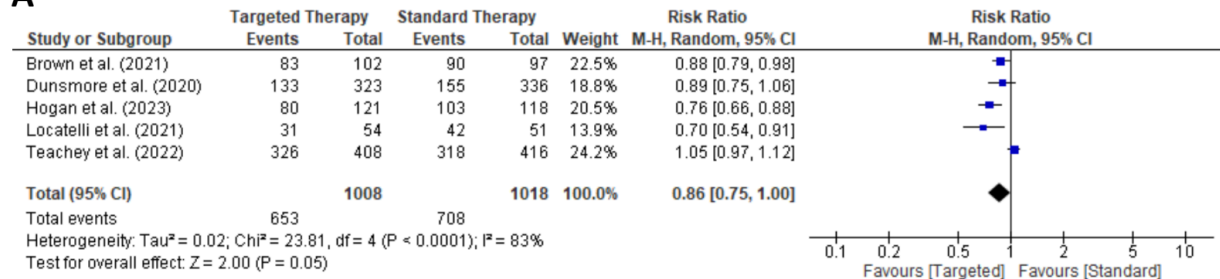


Figure 7. Forest plot of RR for MRD negativity used to assess the effect of targeted therapy on achieving MRD negativity in non-Ph+ ALL. The vertical line represents the null effect ($RR = 1$). The RR column shows relative risks with 95% CI; weight indicates study contribution, I^2 shows heterogeneity, and τ^2 represents variance in true effect sizes. **(A)** Pooled analysis of three studies showed no significant difference in MRD negativity ($RR = 1.52$; 95% CI: 0.98–2.37; $p = 0.06$; $I^2 = 91\%$). **(B)** Sensitivity analysis excluding Teachey et al. (2022) showed a significant increase in MRD negativity with targeted therapy ($RR = 1.85$; 95% CI: 1.44–2.37; $p < 0.00001$; $I^2 = 28\%$). As $p < 0.01$ in the sensitivity analysis, the null hypothesis of no treatment effect is rejected, and the random-effects model was considered in this forest plot.

A



B

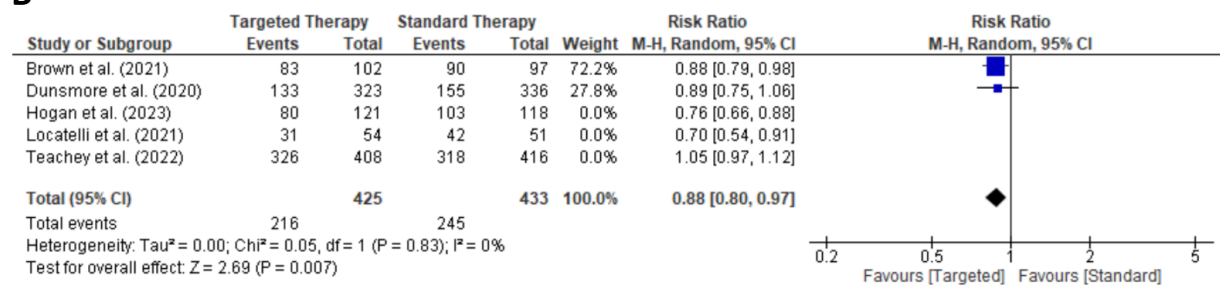


Figure 8. Forest plot of RR for AEs used to assess the effect of targeted therapy on the incidence of severe adverse events in non-Ph+ ALL. The vertical line represents the null effect (RR = 1). The RR column shows relative risks with 95% CI; weight indicates study contribution, I^2 shows heterogeneity, and τ^2 represents variance in true effect sizes. **(A)** Pooled analysis of five studies showed no significant difference in severe AEs (RR = 0.86; 95% CI: 0.75 -- 1.00; $p = 0.05$; $I^2 = 83\%$). **(B)** Sensitivity analysis excluding Hogan et al. (2023), Locatelli et al. (2021), and Teachey et al. (2022) showed a significant reduction in severe AEs with targeted therapy (RR = 0.88; 95% CI: 0.80–0.97; $p = 0.007$; $I^2 = 0\%$). As $p < 0.05$ in the sensitivity analysis, the null hypothesis of no treatment effect is rejected, and the random-effects model was used in this forest plot.

DISCUSSION

Mechanisms of action of targeted therapy

Targeted agents, such as blinatumomab, are bispecific monoclonal antibodies (bispecific T-cell engagers, or BiTEs) that link CD3+ T cells to CD19-expressing B-cell leukemia cells, triggering T-cell activation and cytotoxic tumor lysis. CD19 was selected because it is almost universally expressed in B cells across all maturation stages and is essential for their survival. Blinatumomab has demonstrated lytic potential 100–10,000 times greater than previous constructs (Burt et al., 2019). Nelarabine, a purine nucleoside analog, is selectively taken up by T-cell leukemia cells and metabolized to ara-GTP, which interferes with DNA synthesis, inhibits proliferation, and induces apoptosis (Dunsmore et al., 2020). Bortezomib, a reversible proteasome inhibitor, prevents intracellular protein degradation by binding to the 26S proteasome active site, leading to protein accumulation, endoplasmic reticulum stress, and apoptosis in leukemia cells (Teachey et al., 2022).

Efficacy of targeted therapy

Overall, this meta-analysis suggests that targeted therapies provide clinically meaningful benefits in pediatric, adolescent, and young adult patients with non-Ph+ ALL, particularly for long-term survival. Across the included randomized clinical trials, targeted therapy consistently demonstrated favorable efficacy compared with standard chemotherapy. Studies evaluating nelarabine, blinatumomab, and bortezomib generally reported favorable overall survival outcomes compared with standard therapy (Brown et al., 2021; Dunsmore et al., 2020; Gupta et al., 2025; Hogan et al., 2023; Teachey et al., 2022). Disease-free survival

was consistently higher in trials investigating blinatumomab (Brown *et al.*, 2021; Gupta *et al.*, 2025; Hogan *et al.*, 2023), while higher event-free survival was reported in studies of nelarabine, blinatumomab, and bortezomib (Dunsmore *et al.*, 2020; Locatelli *et al.*, 2021; Teachey *et al.*, 2022). Blinatumomab also achieved higher MRD negativity rates, indicating deeper molecular remission (Brown *et al.*, 2021; Locatelli *et al.*, 2021).

These observations are consistent with the pooled estimates of this meta-analysis. Targeted therapy significantly reduced the hazard of death by 41% (OS, HR = 0.59) and the hazard of relapse or death by 27% (DFS, HR = 0.73), indicating superior long-term disease control compared with standard chemotherapy. In contrast, EFS showed a favorable but non-significant trend with moderate heterogeneity. This variability was likely attributable to differences in patient populations and treatment strategies across studies, particularly between the relapsed population treated with blinatumomab in Locatelli *et al.* (2021) and the newly diagnosed population receiving bortezomib in Teachey *et al.* (2022).

MRD outcomes showed substantial heterogeneity in the primary analysis and were not statistically significant ($I^2 = 91\%$). This inconsistency likely reflects differences in MRD assessment methods, timing, and reporting across studies. Teachey *et al.* (2022) contributed to this heterogeneity due to incomplete and non-uniform MRD reporting, with data available only in a subset of patients and variable MRD thresholds, introducing potential selection bias. After exclusion of this study in sensitivity analysis, MRD negativity became statistically significant with reduced heterogeneity, suggesting a more consistent treatment effect across methodologically comparable trials.

These findings are broadly consistent with previous systematic reviews and meta-analyses evaluating blinatumomab in pediatric ALL, which similarly reported improvements in survival outcomes and MRD response (Chen *et al.*, 2023). However, unlike previous reviews focused on a single targeted agent, this study synthesized evidence on blinatumomab, nelarabine, and bortezomib, providing a more comprehensive evaluation of targeted therapy in pediatric, adolescent, and young adult patients with non-Ph+ ALL.

Safety of targeted therapy

The safety profiles of the three targeted agents differed considerably, which likely contributed to the heterogeneity observed in the pooled analysis. Nelarabine was associated with grade ≥ 3 adverse events in 41.2% of patients compared with 46.1% in the standard chemotherapy group, with neurotoxicity being a particular concern (Dunsmore *et al.*, 2020). Bortezomib showed similarly high rates of severe adverse events in both treatment arms (80.0% vs. 76.5%) (Teachey *et al.*, 2022). In contrast, blinatumomab generally demonstrated lower or comparable rates of grade ≥ 3 adverse events than chemotherapy across the included trials (Brown *et al.*, 2021; Gupta *et al.*, 2025; Hogan *et al.*, 2023; Locatelli *et al.*, 2021). These differences in toxicity profiles, together with variations in chemotherapy backbones and adverse event reporting, likely explain why the initial pooled analysis showed substantial heterogeneity. After sensitivity analysis, targeted therapy was associated with a 12% lower risk of severe adverse events than conventional chemotherapy (RR = 0.88, 95% CI: 0.80–0.97; $p = 0.007$; $I^2 = 0\%$), indicating a more favorable safety profile under more homogeneous study conditions.

Clinical implications

These findings support the incorporation of targeted therapy into current treatment protocols for pediatric, adolescent, and young adult patients with non-Ph+ ALL. Targeted therapy improved overall survival and disease-free survival while increasing the likelihood of achieving MRD negativity, with no

evidence of increased severe toxicity. Although event-free survival was not statistically significant, the overall evidence suggests that targeted therapy provides meaningful clinical benefits and may contribute to more durable disease control than conventional chemotherapy.

Strengths and limitations

This review included only randomized controlled trials (RCTs), representing the highest level of evidence for evaluating therapeutic interventions. To our knowledge, this is the first systematic review and meta-analysis to synthesize evidence on three targeted therapies (blinatumomab, nelarabine, and bortezomib) in children, adolescents, and young adults with non-Ph+ ALL. The significant improvements observed in overall survival, disease-free survival, MRD negativity, and grade ≥ 3 adverse events provide robust evidence supporting the effectiveness of targeted therapy.

Nevertheless, several limitations remain. The number of eligible studies was limited due to the scarcity of RCTs involving children, adolescents, and young adults with non-Ph+ ALL. Most studies were conducted outside Asia, which may limit the generalizability of the findings to Asian populations. In addition, follow-up durations were relatively short in several trials, limiting the assessment of long-term outcomes. Clinical heterogeneity was present because some studies enrolled only patients with relapsed or refractory disease, whereas others included newly diagnosed patients. Furthermore, several trials administered targeted therapies in combination with conventional chemotherapy, making it difficult to isolate the independent effect of the targeted agents. Finally, nelarabine and bortezomib were represented by only one study each, precluding therapy-specific subgroup analyses and limiting the certainty of conclusions for these agents.

CONCLUSION

This systematic review and meta-analysis support consideration of targeted therapy as part of contemporary treatment strategies for pediatric, adolescent, and young adult patients with non-Ph+ ALL, particularly to improve long-term survival while maintaining an acceptable safety profile. Future large-scale randomized controlled trials with longer follow-up, standardized MRD assessment, and direct comparisons among targeted agents are warranted to confirm these findings and define the optimal integration of targeted therapy into frontline treatment.

AUTHOR CONTRIBUTIONS

DNKK: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Writing – Original Draft, Writing – Review & Editing. **FRE:** Data Curation, Investigation, Validation, Writing – Review & Editing. **INDSD:** Investigation, Writing – Review & Editing.

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COMPETING INTERESTS

The authors declare that they have no competing interests related to this study.

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ADDITIONAL INFORMATION

None.

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