Research letter

Oncology

Frontline inotuzumab ozogamicin in older adults with Philadelphia chromosome-negative B-ALL: an exploratory pooled analysis of efficacy and safety

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Older adults (aged ≥ 55 years) with Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia (B-ALL) frequently present with adverse cytogenetic features, poor treatment tolerance, and inferior long-term outcomes [1, 2]. While intensive chemotherapy remains the standard first-line approach, its clinical efficacy in this cohort is limited. This poor prognosis is further compounded by a higher incidence of adverse genetic abnormalities, such as TP53 mutations, which confer resistance to conventional chemotherapy [3, 4]. In addition to genetic factors, immune dysregulation and inflammatory signatures are critical drivers of chemotherapy resistance in older adults. For instance, overexpression of the inflammatory biomarker TREM1 has been shown to promote an immunosuppressive microenvironment and predict intrinsic chemotherapy resistance and poor survival in acute myeloid leukemia [5]. Furthermore, exploring novel molecular pathways like ferroptosis and profiling specific circulatory growth factors have emerged as critical strategies for predicting chemotherapy responsiveness and improving clinical outcomes in acute leukemias [6, 7]. This suggests that inflammatory pathway activation may serve as a shared mechanism of treatment failure across acute leukemias, further justifying the need for novel targeted therapies like inotuzumab ozogamicin (InO) in this population.

InO is a CD22-directed antibody–drug conjugate carrying the cytotoxic agent calicheamicin to selectively eliminate leukemic cells [8]. In the relapsed/refractory (R/R) B-ALL setting, the INO-VATE trial demonstrated an overall response rate (ORR) of 70% and a median overall survival (OS) of 5.6 months in patients aged ≥ 55 years [9]. Among older responders, the minimal residual disease (MRD) negativity rate reached 78.6%, comparable to the 75.6% observed in younger cohorts [9]. These efficacy data have prompted the investigation of InO-based regimens as frontline therapy for older adults. However, the optimal InO dosing schedule and the appropriate intensity of concurrent chemoimmunotherapy remain to be established.

To evaluate the efficacy and safety of frontline InO in older adults with B-ALL, we performed a systematic review and exploratory meta-analysis in accordance with the PRISMA 2020 guidelines [10] (PROSPERO: CRD420251168606), focusing on the impact of chemoimmunotherapy intensity and InO dosing schedules. Based on the PICOS framework, prospective studies investigating InO in newly diagnosed B-ALL patients aged ≥ 55 years were included. A systematic search of PubMed,

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Embase, and the Cochrane Library (through July 31, 2026) identified three prospective single-arm clinical trials: INITIAL-1 [11], EWALL-INO [12], and NCT01371630 [13] (Supplementary Table SI, Supplementary Figure S1). Methodological quality was assessed using the MINORS tool, yielding scores of 14–15 out of 16 for all included trials, the detailed item-level scoring across all eight methodological domains is provided in Supplementary Table SV. Given the small number of included studies (k = 3), a common-effect model was deemed appropriate to calculate pooled descriptive estimates for the primary effect measure (pooled proportion) of binary endpoints (ORR, treatment-related mortality [TRM], and veno-occlusive disease [VOD]). To stabilize variances, a Freeman-Tukey double arcsine transformation was applied prior to pooling. Studies were weighted using the inverse variance method, and a standard continuity correction of 0.5 was applied to studies reporting zero events. The 95% confidence intervals (CIs) for individual studies were calculated using the exact binomial (Clopper-Pearson) method. Statistical heterogeneity across studies was assessed using the Cochran's Q test. All meta-analytical statistical procedures were performed using R software (v4.5.0). For time-to-event endpoints, digitized survival-data reconstruction was performed. Kaplan-Meier curves from the original source publications were extracted using digital tracing software. To accurately reconstruct the survival data, we incorporated published numbers at risk (risk tables) and reported total event counts into the Guyot algorithm [14] ensuring event count matching. Assuming independent random loss to follow-up, survival rates were estimated using a Weibull parametric survival model [14]. The Weibull model was selected based on optimal fit indices, including the lowest Akaike Information Criterion (AIC), and visual congruence with the source curves. Sensitivity analyses evaluating alternative parametric distributions (such as log-normal and log-logistic) yielded consistent survival estimates, confirming the robustness of this approach (Supplementary Table SIV). Importantly, this pooled analysis compares cohort-level treatment strategies rather than individual treatment effects, providing hypothesis-generating insights to guide future prospective evaluations.

To ensure cross-trial consistency, clinical endpoints were harmonized as follows: (1) ORR comprised complete remission (CR) and CR with incomplete hematologic recovery (CRi); (2) Survival (OS and EFS) was calculated from treatment initiation or study enrollment; (3) EFS events included primary failure, morphological relapse, or death; (4) Veno-occlusive disease (VOD) incidence encompassed all grades (Grades 1–5) of clinically diagnosed events based on established criteria; and (5) Treatment-related mortality (TRM) encompassed any non-relapse mortality (e.g., early induction deaths or deaths in remission).

A total of 226 newly diagnosed patients aged 55 to 84 years were enrolled across the three studies. Baseline patient characteristics (Supplementary Table SII) and specific trial protocols (Supplementary Table SIII) differed across the included cohorts. Excluding 4 patients in the NCT01371630 cohort who were enrolled in complete remission after exactly one cycle of prior therapy (without prior InO exposure) according to the original trial's frontline inclusion criteria, 222 patients were evaluable for morphological response. Among these patients, the pooled ORR – defined collectively as CR and CRi – was 92% (208/222) (Supplementary Figure S2). Based on the digitized survival-data reconstruction for the entire cohort (n = 226), the pooled 1- and 3-year OS rates were 74.9% (95% CI: 69.5–80.8%) and 52.0% (95% CI: 45.2–59.9%), respectively (Figure 1 A). The corresponding 1- and 3-year event-free survival (EFS) rates were 69.7% (95% CI: 63.9–76.0%) and 40.4% (95% CI: 33.7–48.5%) (Figure 1 B). Sensitivity analyses utilizing a DerSimonian-Laird random-effects method yielded consistent pooled estimates (Supplementary Figure S5).

Hypothesis-generating, exploratory cross-study comparisons stratified by relative treatment intensity revealed variations in safety, though evidence was insufficient to confirm statistical differences in efficacy. Patients receiving a relatively less intensive chemoimmunotherapy backbone (INITIAL-1 and EWALL-INO cohorts; n = 174) exhibited an ORR of 91%, compared to 98% in those receiving a relatively more intensive regimen (NCT01371630 cohort; n = 52) (p = 0.1393) (Supplementary Figure S2). Similarly, digitized survival-data reconstruction did not demonstrate statistically significant differences between the less and more intensive groups in either OS (p = 0.3993; Figure 1 C) or EFS (p = 0.4409; Figure 1 D). However, in these exploratory comparisons, the less intensive approach appeared to be associated with a lower TRM (3/174 [2%] vs. 6/52 [12%], p < 0.01) (Supplementary Figure S3).

The overall pooled incidence of VOD, a severe hepatic complication associated with InO [15], was 4% (Supplementary Figure S2). Notably, an exploratory comparison by InO dosing schedule observed a significantly lower VOD rate in studies utilizing fractionated administration compared to the single-dose regimen (2/174 [1%] vs. 4/52 [8%], p < 0.05) (Supplementary Figure S4). This substantial reduction suggests a potential safety advantage, though it must be interpreted cautiously given the cross-trial nature of the data.

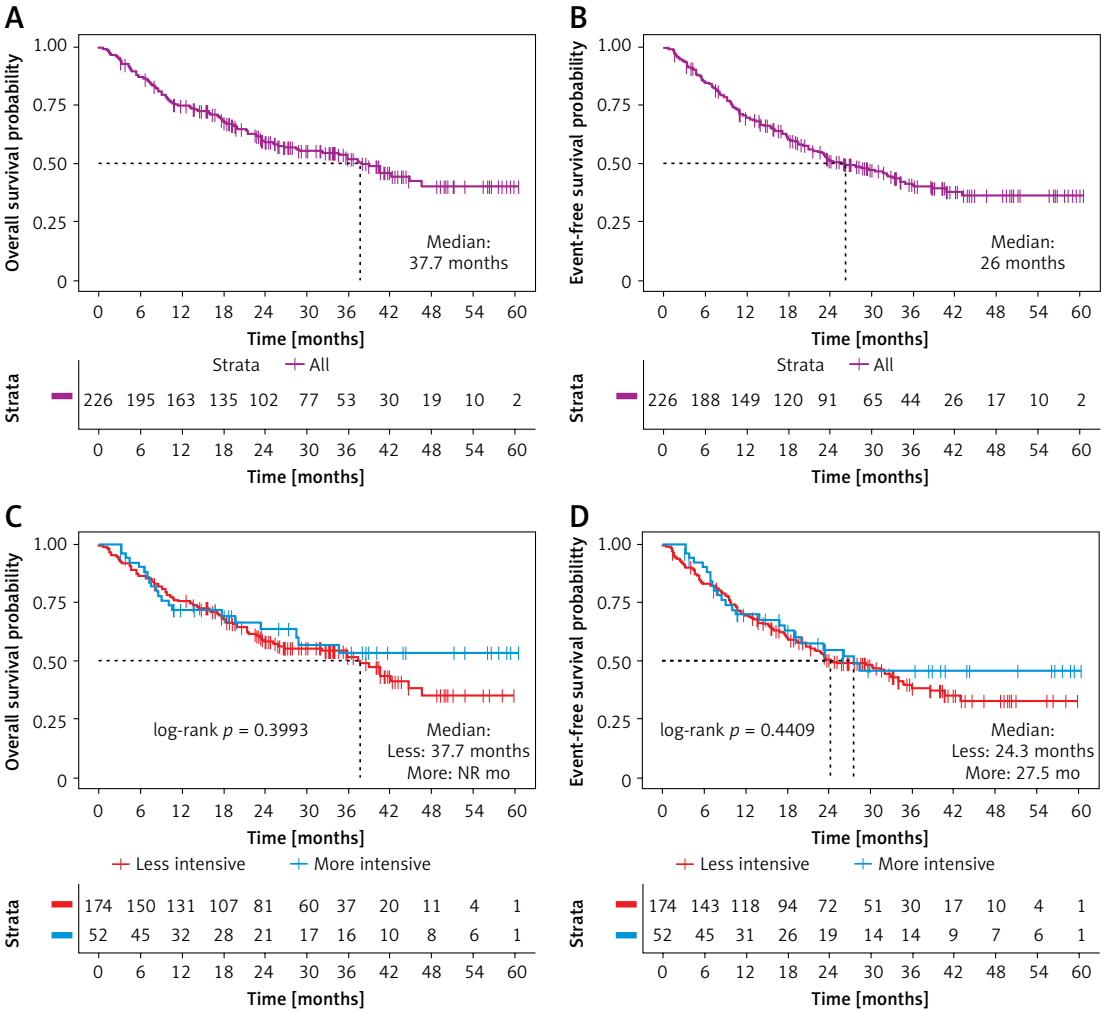

Figure 1. Kaplan-Meier estimates of survival outcomes based on digitized survival-data reconstruction. Overall survival (**A**) and event-free survival (**B**) for the entire pooled cohort (n = 226). Exploratory cross-study comparisons of overall survival (**C**) and event-free survival (**D**) stratified by relative chemoimmunotherapy intensity

Mechanistically, it is hypothesized that fractionated administration may reduce peak calicheamicin plasma exposure. This dosing strategy could potentially limit cumulative toxic effects on hepatic sinusoidal endothelial cells, which might mitigate direct liver injury and the subsequent inflammatory cascade that precipitates VOD [16].

Our pooled analysis supports the optimization of InO dosing and chemoimmunotherapy intensity to improve frontline tolerability in older adults with B-ALL. Although specific immunological biomarkers were not measured in the included trials, exploring these hypothetical inflammatory signatures in future studies could prove critical for contextualizing clinical outcomes and refining patient selection.

The present analysis has several limitations. First, it relies on only three single-arm trials, resulting in a relatively small sample size with sparse events for safety outcomes, alongside potential variations in endpoint definitions across different study protocols. Second, significant study-level confounding exists; crucially, in the cohorts analyzed, relative treatment intensity and InO dosing schedule are collinear. Therefore, their independent effects on clinical outcomes cannot be statistically separated. Finally, while the digitized survival-data reconstruction provides a pooled survival overview, its inherent limitations must be acknowledged. This approach relies on the assumption of independent random loss to follow-up and is subject to potential inaccuracies during the curve digitization process. Additionally, this survival analysis functions primarily as a cross-trial observation because the reconstructed data methodology cannot statistically account for clustering within the source studies or adjust for patient-level baseline risk differences. Furthermore, the lack of centralized biomarker or minimal residual disease (MRD) data across all three trials limits our ability to assess deeper molecular responses.

In conclusion, for older adults with newly diagnosed Philadelphia chromosome-negative B-ALL,

the combination of a relatively less intensive chemoimmunotherapy backbone and fractionated InO dosing may represent a clinically viable frontline option. Future prospective randomized trials should incorporate correlative biomarker analyses to identify which patients are most likely to benefit from InO-based regimens.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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