MINIMAL RESIDUAL DISEASE–NEGATIVE COMPLETE REMISSION AS A PROGNOSTIC INDICATOR OF LONG-TERM SURVIVAL IN ADULT PATIENTS WITH PHILADELPHIA CHROMOSOME–POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

ALL-438

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Background

- Acute lymphoblastic leukemia (ALL) is a rare malignancy characterized by abnormal proliferation of lymphoid progenitor cells.
- Minimal residual disease (MRD) is an established, prognostic indicator for patients with acute lymphoblastic leukemia (ALL) and Philadelphia-positive (Ph+) ALL.

Aim

- To evaluate the association between MRD-negative complete remission and long-term outcomes (overall survival [OS] and event-free survival [EFS]) in adult patients with Ph+ ALL receiving first-line therapy.

Methods

- The Systematic Literature Review examined indexed and non-indexed citations; eligible studies included interventional and observational studies evaluating survival outcomes by MRD status in adults ≥18 years of age with Ph+ ALL receiving first-line therapy.
- Key outcomes of interest included OS, EFS, and MRD status assessed at the end of induction (EOI) and at the end of consolidation (EOC).
- Both aggregate study–level and individual patient data (IPD) meta-analyses were conducted.
- The IPD approach included a log-level MRD analysis to evaluate the concordance of deepening levels of molecular response with long-term OS or EFS in patients with complete remission (CR)† and an analysis evaluating the utility of MRD-negative CR over CR alone. Where applicable, survival analysis methods were used, such as log-rank tests, Kaplan-Meier analyses, and Cox regression analyses.
- In the aggregate analysis, log-HRs for the comparison between MRD-negative vs MRD-positive patients were pooled using standard meta-analysis model techniques including fixed- and random effects models along with frequentist and Bayesian approaches.
- Complete remission is defined as <5% blasts in the bone marrow, no circulating blasts, ANC >1.0 × 109/L and platelets >100 × 109/L
- EFS is defined as the time from the last date of week 12 for Study AP24534-11-001 or Study INCB84344-201 or the last date of week 4 for Study GRAAPH-2005 until death due to any cause or relapse. OS is defined as the time from treatment initiation until death. MRD negativity is defined as a MR 4-log reduction (BCR-ABL1/ABL1 ≤0.01%).

Results

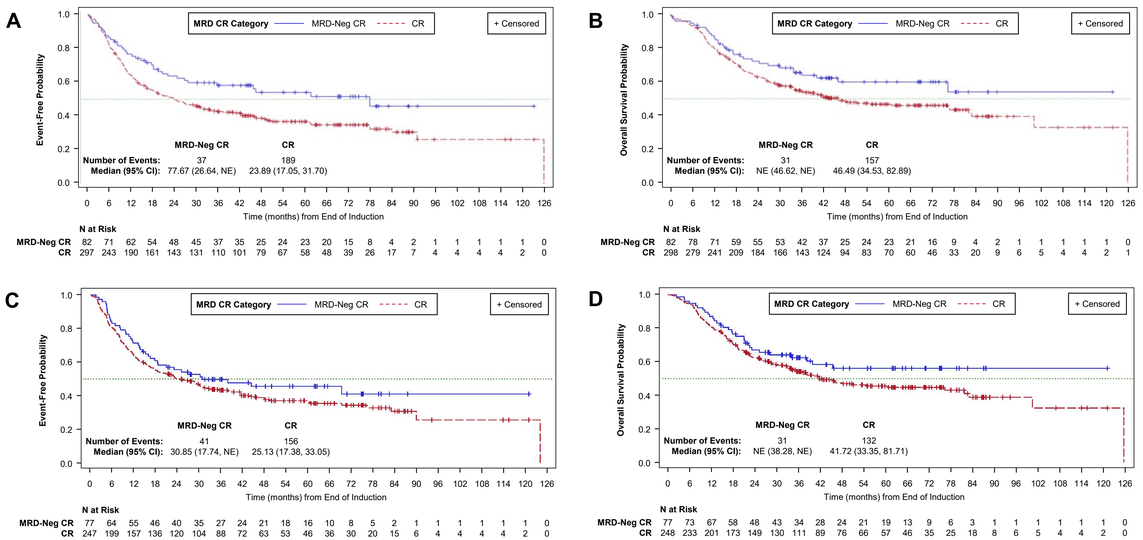
- The SLR identified 19 publications (18 unique studies) related to MRD and OS or EFS. Among these, 9 studies had sufficient MRD and OS/EFS data, and IPD was available from 3 trials.
- The IPD analysis included 3 trials (Jabbour 2015/AP24534-11-001, GIMEMA-INCB 84344-201 and GRAAPH-2005 RCT/Chalandon 2015)
- Analyses with and without adjustment for prognostic factors (age, gender, white blood cell counts and stem cell transplant) showed that MRD-negative CR status (BCR-ABL1/ABL1 ≤0.01%) was predictive of longer EFS or OS both at EOI and EOC (results not shown).
- Median EFS and OS were longer for patients with MRD-negative CR at both timepoints (EOI and EOC) compared to those with CR alone (Figure 1/Table 1).
- The findings from the IPD analysis were consistent with the results from the aggregate study-level meta-analysis (results not shown), which also demonstrated a survival benefit among patients with MRD-negative disease response.

Table 1. EFS and OS for Patients with MRD-Negative CR vs CR* at EOI and EOC

	EOI		EOC	
	MRD-Negative CR	CR*	MRD-Negative CR	CR*
EFS				
Events, n	37	189	41	156
Median (95% CI), months	77.67 (26.64, NE)	23.89 (17.05, 31.70)	30.85 (17.74, NE)	25.13 (17.38, 33.05)
OS				
Events, n	31	157	31	132
Median (95% CI), months	NE (46.62, NE)	46.49 (34.53, 82.89)	NE (38.28, NE)	41.72 (33.35, 81.71)

BCR-ABL1, breakpoint cluster region Abelson1; CI, confidence interval; CR, complete remission; MRD, minimal residual disease; MRD-Neg CR, MRD-negative CR; NE, not evaluable.
**independent of MRD status*

Figure 1. EFS and OS for patients with MRD-negative CR vs. CR* at EOI and EOC



***A:** EFS for Patients with MRD-Negative CR Versus CR* at EOI*
***C:** EFS for Patients with MRD-Negative CR Versus CR* at EOC*
**independent of MRD status*

***B:** OS for Patients with MRD-Negative CR Versus CR* at EOI*
***D:** OS for Patients with MRD-Negative CR versus CR* at EOC*

Conclusions

These analyses

- Demonstrate that deeper responses at the EOI or EOC in patients with Ph+ ALL results in longer OS and EFS
- Suggest that MRD-negative CR has a greater prognostic value than CR and is associated with longer OS and EFS in patients with Ph+ ALL.

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