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Relapse risk and survival benchmarks for non-transplanted acute myeloid leukemia patients in first complete remission

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Short title: Outcomes of AML in First Remission Without Transplant

Authors' Contributions

E.K.: Writing-original draft; formal analysis; data curation; visualization; methodology; investigation. F.R., C.D.D., N.D., M.Y., N.J.S., W.Y.J., J.S., A.M., G.B., G.G.M., H.M.K.: Writing—review and editing. A.B.: Data curation; writing—review and editing. T.M.K.: Conceptualization; methodology; supervision; writing—review and editing.

Data-sharing Statement

The data underlying this article cannot be publicly shared due to patient privacy and institutional restrictions. De-identified data may be made available upon request to the corresponding author, subject to approval by the relevant institutional authorities.

Disclosures

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Abstract

Survival outcomes of patients with acute myeloid leukemia (AML) who achieve complete remission (CR) without allogeneic stem cell transplantation (allo-SCT) remain largely undefined, yet these benchmarks are essential for developing post-remission strategies. We retrospectively analyzed 362 adults with newly diagnosed de novo AML who achieved CR/Incomplete CR (CRi) (between 2016–2023) and did not undergo allo-SCT in first remission. Patients with APL and core-binding factor AML, which are rarely consolidated with allo-SCT, were excluded. The cohort was stratified by low-intensity (LIT, n=257) and intensive therapy (IT, n=105), and survival was evaluated across predefined subgroups. Median relapse-free survival (RFS) and overall survival (OS) were 11 and 19 months, respectively. Venetoclax was associated with significantly lower 24-month relapse rates in both LIT (68% to 45%) and IT (49% to 27%) ($p<0.01$ for both). ELN 2022 classification in IT and ELN 2024 in LIT showed clear prognostic separation across favorable, intermediate, and adverse groups, with median RFS of 58.0, 25.5, and 9.6 months for IT, and 13.7, 10.2, and 5.3 months for LIT, respectively. On multivariable analysis, ELN 2024 and measurable residual disease (MRD) positivity were independently associated with RFS in venetoclax-treated LIT patients, while ELN 2022 risk classification was most strongly associated with survival outcomes in IT. Notably, within the favorable-risk LIT subgroup, *RUNX1* mutations were independently associated with inferior RFS. These findings establish benchmarks for post-remission strategies in non-transplanted AML.

Introduction

Acute myeloid leukemia (AML) affects approximately 20,000 individuals annually in the United States, with a median age at diagnosis of 68 years[1, 2]. Despite therapeutic advances in recent years, disease relapse remains a major cause of treatment failure, and AML continues to be largely incurable. While allogeneic stem cell transplantation (allo-SCT) improves cure rates and extends remission durations, it remains an option for only a subset of patients due to age limitations, comorbidities, or lack of suitable donor availability.

For patients ineligible for allo-SCT, post-remission therapy is essential to extending remission and improving survival [3, 4]. In this setting, lower-intensity regimens incorporating venetoclax or IDH inhibitors are typically continued until relapse or unacceptable toxicity. Patients with intermediate or poor-risk cytogenetics who receive intensive induction chemotherapy but are not candidates for transplant have shown improved survival with oral azacitidine maintenance therapy[5]. Among patients with *FLT3* mutations, emerging data support the use of quizartinib in first remission (CR1), regardless of measurable residual disease (MRD) status, for patients not proceeding to transplant[6, 7].

The role of emerging targeted therapies in the post-remission setting, particularly for high-risk patients who may benefit from maintenance strategies, remains an important area of investigation. To efficiently develop such post-remission therapeutic strategies, a comprehensive understanding of relapse and survival outcomes among different subgroups of patients in CR1 is essential. However, few studies report outcomes exclusively in non-transplanted AML patients maintaining first remission. Robust benchmarks are therefore urgently needed to inform future clinical trials. To establish these essential reference parameters, we retrospectively analyzed outcomes of adult AML patients treated at our institution since 2016 who achieved CR1 but did not undergo allo-SCT. We evaluated relapse free survival (RFS) and overall survival (OS) rates across specific predefined subgroups, aiming to characterize contemporary outcomes and guide future study design for post-remission therapeutic approaches.

Methods

Patients and treatment regimens

This study was conducted in accordance with the Declaration of Helsinki and approved by The University of Texas MD Anderson Cancer Center Institutional Review Board (protocol PA17-0033, IRB00002203). We conducted a retrospective analysis of adult patients (≥18 years) with newly diagnosed de novo AML who received first-line therapy at the University of Texas MD Anderson

Cancer Center between 2016 and 2023. The analysis included patients who achieved complete remission (CR) or CR with incomplete hematologic recovery (CRi) and had not proceeded to allo-SCT. Patients with acute promyelocytic leukemia (APL) and core binding factor (CBF) AML were excluded, as these subtypes are typically not consolidated with allo-SCT in first remission. Intensive chemotherapy (IT) was defined as standard- or high-dose cytarabine–based therapy. Low-intensity therapy (LIT) included hypomethylating agents (azacitidine or decitabine), low-dose cytarabine, nucleoside analog–based regimens (cladribine or clofarabine), and venetoclax. Patients receiving *FLT3* or IDH inhibitors with either IT or LIT, as well as those treated with small-molecule investigational agents in early-phase clinical trials, were included. Of the 362 patients who met eligibility criteria and underwent further analysis, 241 (66.6%) were treated on a clinical trial protocol and 121 (33.4%) received standard-of-care therapy, with a similar distribution across treatment intensity groups (IT: 66.7%, LIT: 66.5%).

Outcomes and procedures

We defined responses according to the recommendations of the International Working Group[8]. Overall survival was measured from the start of treatment until death or last follow-up. Relapse-free survival was calculated from the time of best response to relapse (CR/CRi) or death, with patients censored at last follow-up. MRD-based relapse was not used as a relapse event in RFS calculations. The cumulative incidence of relapse (CIR) was assessed from the date of best response to relapse, with non-relapse mortality considered a competing event. Multiparameter flow cytometry (MFC), cytogenetic analysis, and next-generation sequencing (NGS) using a targeted 81-gene panel, as previously reported[9, 10], were performed for all patients. MRD was assessed locally via MFC with a sensitivity of 10^{-4} at the time of best response (CR/CRi) in all patients. European LeukemiaNet (ELN) risk classification was assigned according to the 2022 ELN criteria for patients treated with IT and the 2024 ELN criteria for those treated with LIT[11-13]. Among IT-treated patients, 27 (21%) transitioned to lower-intensity maintenance therapy following completion of intensive cycles, including HMA+venetoclax (n=18), FLT3 inhibitors (n=4), IDH2 inhibitor (n=3), and other agents (n=2), as clinically indicated.

Statistical analysis

Baseline characteristics were analyzed using descriptive statistics. Continuous variables were compared using the Wilcoxon rank-sum test. Categorical variables were compared using Fisher's exact test. Median follow-up time was calculated using the reverse Kaplan-Meier estimate. OS and RFS distributions were estimated with the Kaplan-Meier method and compared using the log-rank test. Cumulative incidence was calculated using relapse as the primary event and death

without relapse as a competing event, with comparisons performed using Gray's test. Univariate and multivariate analyses were performed using Cox proportional hazards regression, and the proportional hazards assumption was evaluated using Schoenfeld residuals. An exploratory, hypothesis-generating approach using random survival forest (RSF) analysis (randomForestSRC package in R) was applied to the entire venetoclax-treated LIT cohort to identify clinical and molecular variables potentially associated with relapse-free survival. Variable importance was assessed using out-of-bag observations. All statistical analyses were performed using R software version 4.4.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

We evaluated a total of 1,687 patients with newly diagnosed AML who presented for first-line therapy since 2016. Figure 1 presents a flow chart outlining the patient selection process. We excluded patients who are generally not considered candidates for allo-SCT, including those with acute promyelocytic leukemia (APL, n = 97) and core-binding factor AML (CBF, n = 97). Additionally, patients with secondary AML (n = 665) were excluded due to their distinct disease biology and prognosis. For further analysis, we included only those patients who achieved CR or CRi, (n = 612) and did not undergo allo-SCT (n = 362), which comprised the final study cohort.

Patient baseline characteristics are presented in Table 1. A comparison with patients who proceeded to alloSCT is provided in Supplementary Table 1S. Given the heterogeneity of treatment regimens within the cohort (Table 2S), we describe the overall patient population, alongside stratification by LIT and IT. The median age for the entire cohort was 69 years (range, 19–94), with 75% of patients aged ≥60 years; median ages were 74 years (range, 42–94), and 52 years (range, 19–71) in the LIT group and IT group, respectively. Most patients had an ECOG performance status of 0–2 (59%), while 28% had a status of >2. An ECOG performance status of >2 was observed in 32% of patients receiving LIT and 18% of those receiving IT. Among patients treated with IT, 25% were classified as favorable risk, 43% as intermediate, and 32% as adverse according to ELN 2022 criteria. Among patients in the LIT group, ELN 2024 risk stratification classified 48% as favorable risk, 28% as intermediate risk, and 24% as adverse risk. Venetoclax-based therapy was administered in 70% of the cohort overall and was more frequently utilized in the LIT group (77% vs. 54%, $p < 0.001$). The median number of cycles to best response was 1 (range, 1–4) in both treatment groups.

Molecular Characterization

The distribution of baseline molecular and cytogenetic features by treatment intensity is shown in figure1 and table 2. The most frequently detected mutated genes were *NPM1* (29%), *DNMT3A* (23%), *TET2* (20%), *TP53* (19%), and *IDH2* (18%). When stratified by treatment, canonical de novo AML drivers—*NPM1, FLT3-ITD*, and *IDH1*/2—were enriched in the IT group, whereas *TP53* mutations and myelodysplasia-related (MR) gene mutations were more common in the LIT group (45% vs 27%, p = 0.001, figure 1B-C). Cytogenetic analysis similarly demonstrated a higher frequency of adverse-risk features in LIT, including complex karyotype (27% vs 11%, p = 0.002), −5/del(5q) (23% vs 5.7%, p < 0.001), −7/del(7q) (18% vs 5. 7%, p = 0.003), and del(17p) (9.7% vs 1.9%, p = 0.008). In contrast, diploid karyotype was more frequent in IT (54% vs 39%, table 2). These patterns are consistent with current clinical practice, where treatment intensity is guided by underlying disease biology and patient fitness, and support the validity of cohort stratification.

Survival analysis

We next evaluated survival and relapse rates across subgroups—defined by age, treatment intensity, venetoclax use, karyotype, risk group, *TP53* status, MR-gene mutations, and MRD to inform post-remission strategies for patients not undergoing allo-SCT. Overall, without accounting for subgroup classifications, the RFS was 11 months (95% CI, 9-13) and OS was 19 months (95% CI, 15-23, figure 1SA). The following sections present key subgroup-specific survival outcomes, and cumulative incidence of relapse (CIR), with a summary presented in Table 3 and Table 3S.

We first examined survival and relapse outcomes by age group (<60 vs ≥60 years). Overall, median RFS was 18.1 months (95% CI, 10.9–NA) for patients <60 and 9.5 months (95% CI, 7.8–12.4) for those ≥60. Median OS was 26.2 months (95% CI, 16.7–NA) and 16.2 months (95% CI, 14.1–21), respectively (p<0.01, figure 1SB). Among patients treated with IT, age was not significantly associated with outcomes (figure 2A). Median RFS was 23.5 months (95% CI, 11.6–NA) for patients <60 and 20.9 months (95% CI, 9.6–NA) for those ≥60. Median OS was 30.3 months (95% CI, 19–NA) and 27.0 months (95% CI, 18.7–NA), respectively. In addition, NRM in the IT group was similar between age groups (Figure 2A, right panel). As expected, the LIT group was heavily skewed toward older patients, making age-based comparisons within this subgroup uninterpretable.

Next, we evaluated outcomes across treatment intensity groups, comparing regimens with and without venetoclax (figure 2B). In the LIT group, venetoclax exposure was associated with improved RFS, with a median of 10.8 months (95% CI, 8.2–14.2) compared to 6.3 months (95%

CI, 4.9–9.7) without venetoclax ($p < 0.01$). Venetoclax was also associated with a significantly lower 24-month relapse rate in this group, from 68% to 45% ($p < 0.01$), without affecting NRM. In the IT group, venetoclax similarly reduced the 24-month relapse rate from 49% to 27% ($p < 0.01$), with a numerically higher 12-month NRM observed in venetoclax-treated patients (19% vs. 6%), which did not reach statistical significance ($p = 0.1$, figure 2B, right panel). Venetoclax was associated with higher MRD negativity rates in the LIT group: 55.6% (110/198) with venetoclax versus 30.5% (18/59) without ($P = 0.0012$). The association between venetoclax and MRD negativity was less pronounced in the IT group (71.9% vs 64.6%, $P = 0.5$).

When evaluating outcomes by karyotype status (diploid, non-diploid ["other"], and complex), median RFS was 23.3, 8.9, and 5.3 months, and median OS was 31.3, 17.1, and 11.2 months, respectively ($p<0.01$ for both comparisons, figure S1C). In the LIT group, patients with complex karyotype had poor outcomes, with median RFS and OS of 5.3 and 11.2 months, respectively (figure 2C). Complex karyotype was strongly associated with *TP53* mutations, present in 84.1% of *TP53*-mutated cases compared to 8.2% of *TP53*-wildtype cases ($p<0.01$). NRM did not differ significantly across karyotype groups within the LIT cohort (figure 2C, right panel). Notably, although the 36-month cumulative incidence of relapse was similar between patients with diploid and "other" karyotypes, the relapse kinetics differed. In the diploid group, relapse accumulated more gradually over 36 months, while in the "other" group, relapse occurred more rapidly within the first 12 to 24 months (figure 2C, right panel). As expected, only 12 patients with complex karyotype in this cohort received IT, and due to the small sample size and limited use of intensive therapy in this group, outcomes were not analyzed separately.

Survival outcomes by ELN2022 and ELN 2024 risk classifications were evaluated in the IT and LIT cohort, respectively (Figure 3). In the IT group, median RFS was 58.0, 25.5, and 9.6 months, and median OS was not reached (NR), 36.2 months, and 19.0 months for the favorable, intermediate and adverse-risk groups, respectively ($p=0.01$ and $P=0.04$, respectively, figure 3A). The most pronounced survival differences were observed between the favorable and adverse risk groups. The intermediate-risk group did not show a statistically significant difference in survival compared with either the favorable or adverse risk groups. In contrast, the cumulative relapse rate in the intermediate-risk group more closely resembled that of the favorable-risk group and was significantly lower than in the adverse-risk group (26% vs. 65% at 24 months, $p<0.01$). NRM rates were similar across all risk groups (figure 3A, right panel).

In the LIT cohort, median RFS was 13.7, 10.2, and 5.3 months, and median OS was 25.1, 17.5, and 10.6 months for the favorable, intermediate and adverse-risk groups, respectively. In pairwise

comparisons, differences in RFS and OS between the favorable and intermediate-risk groups were not statistically significant (p=0.2 and p=0.054, respectively). As in the IT cohort, the cumulative incidence of relapse was similar between the favorable and intermediate-risk groups, and both were significantly lower than in the adverse risk group (41% vs. 78% at 12 months, p<0.01, figure 3B). NRM rates were comparable across all risk groups (figure 3B, right panel).

Outcomes for patients with *TP53* mutations were poor, with a median RFS of 5.3 months (95% CI, 3.5–7.4) and a median OS of 10.6 months (95% CI, 9.3–12.5) in the LIT cohort (figure 4A). Only six patients with *TP53* mutations received IT. NRM rates did not differ significantly by *TP53* status.

MRD results were assessed by flow cytometry, as NGS-based data were not available for all patients. Notably, the prognostic impact of MRD was more pronounced in the LIT group compared to the IT group. In the IT cohort, MRD-negative patients had a median RFS of 25.5 months (95% CI, 17.0–NA) compared to 9.6 months (95% CI, 8.9–NA) in MRD-positive patients (p=0.2, figure 4B). Median OS was 36.2 months (95% CI, 21.4–NA) and 18.7 months (95% CI, 12.5–NA), respectively (p=0.3). In the LIT cohort, MRD-negative patients had a median RFS of 12.2 months (95% CI, 9.4–23.7) versus 5.9 months (95% CI, 5.0–8.9) for MRD-positive patients (p<0.01, figure 4C). Median OS was 18.8 months (95% CI, 14.4–31.3) and 13.5 months (95% CI, 11.5–17.5), respectively (p=0.01). NRM did not differ significantly between MRD groups (figure 4B-C, right panel). Survival outcomes by MRD status for the overall cohort are provided in figure S1D. MRD outcomes were additionally analyzed by ELN risk group (Figure S1E-F). In the LIT cohort, flow cytometry-based MRD retained significant prognostic discrimination within the ELN Adverse group (RFS 9.4 vs. 5.3 months, p=0.002; OS 15.9 vs. 12.4 months, p=0.036), but showed limited discriminatory value in the Favorable and Intermediate risk groups or in any IT risk subgroup.

According to the ELN 2022 risk classification, MR-genes are considered adverse risk factors unless they co-occur with favorable-risk AML subtypes[11]. To evaluate outcomes in this subgroup, we excluded patients with *NPM1* or *TP53* mutations, as these define distinct risk categories independent of MR-gene status. Whether patients were stratified by the presence or absence of MR-genes, or by the number of MR-genes, no significant impact on outcomes was observed in either the LIT or IT cohorts (figure 2SA-D).

We next examined whether MR-gene co-mutations influenced outcomes specifically within ELN 2022 favorable-risk *NPM1*-mutated patients (n=61; NPM1mut alone n=44, NPM1mut+MR genes n=17). No significant differences in RFS or OS were observed in the overall cohort (median RFS

NR vs. 44.2 months, p=0.899; median OS 43.7 vs. 46.3 months, p=0.709) or in the LIT subgroup (median RFS 26.2 vs. 32.7 months, p=0.943; median OS 43.7 vs. 46.3 months, p=0.808; figure S2E). The IT subgroup included only 1 patient with NPM1mut+MR genes and was therefore not analyzed separately.

Multivariable analysis across treatment intensity groups

We conducted multivariable analyses to identify variables independently associated with survival outcomes, analyzing the LIT and IT cohorts separately. In the LIT cohort, we excluded patients who did not receive venetoclax (n=59/257, 22%), as this agent is now standard in LIT regimens outside of clinical trials. In univariable Cox analysis for RFS, *TP53* mutation (HR 3.61; 95% CI 2.40–5.43; p<0.01) and complex karyotype (HR 3.28; 95% CI 2.09–5.17; p<0.01) were the most significant adverse features (Table 4S). The ELN 2024 classification was associated with a stepwise increase in risk (intermediate: HR 1.58, p=0.031; adverse: HR 4.30, p<0.01), and MRD positivity conferred a 1.59-fold higher relapse risk (95% CI 1.13–2.25; p<0.01). In multivariable analysis, *TP53* mutation, ELN 2024 classification, and MRD positivity remained independently associated with RFS, while complex karyotype lost significance—likely due to its correlation with *TP53* mutations, which demonstrated a more robust prognostic impact on RFS (Table 4S). In the multivariable model for OS, *TP53* status and ELN 2024 classification remained significant, although MRD by flow cytometry showed a weaker association with OS than with RFS (Table 5S). In the IT cohort, after adjustment to co-variates, ELN 2022 risk classification was the only variable significantly associated with both RFS and OS (Table 6S and 7S). *TP53* mutation was excluded from the model due to collinearity with complex karyotype and the small number of patients with this feature in the IT cohort (n=6), reflecting current practice in which intensive chemotherapy is increasingly avoided in this population.

Clinical and molecular predictors of RFS in patients receiving venetoclax-based low-intensity therapy

To identify candidate risk factors associated with relapse among patients receiving venetoclax-based LIT in CR1, we performed random survival forest (RSF) analysis as an exploratory approach to model relapse-free survival based on clinical and molecular predictors. The analysis included 198 patients (132 events) and 12 input variables. Variable importance analysis ranked

ELN 2024 classification, *RUNX1* mutation status, karyotype, age, and MRD status as the top contributors to RFS prediction (Figure 5A). Partial dependence plots suggested that ELN 2024 adverse risk, *RUNX1* mutations, and complex karyotype were associated with higher relapse risk (Figure S3A). Notably, *DDX41* mutations exhibited a protective effect, with predicted relapse risk approximately 15% lower than wild type (Figure S3A). Time-dependent variable importance revealed that ELN 2024 classification maintained consistently high predictive value throughout the follow-up period, whereas the prognostic relevance of *RUNX1* mutations and karyotype increased over time—minimal at 6 months but substantial by 18–24 months (Figure S3B). In contrast, flow-based MRD status was most predictive early in follow-up. Splicing factor and epigenetic modifier mutations contributed minimally to survival predictions at all time points (Figure S3B). Model performance, assessed by out-of-bag error, yielded a C-index of 0.63.

To quantify the independent prognostic impact of candidate predictors identified by RSF, we performed multivariable Cox proportional hazards regression incorporating the top-ranked variables (Figure 5B). Using ELN 2024 favorable risk as the reference category, adverse risk (HR 4.44, 95% CI 2.81–7.02) and intermediate risk (HR 1.53, 95% CI 1.01–2.32) were each independently associated with increased relapse risk. *RUNX1* mutations (HR 1.83, 95% CI 1.14–2.94) and MRD positivity (HR 1.45, 95% CI 1.03–2.06) were also independently associated with increased relapse risk in the multivariable model, whereas karyotype did not retain significance after adjustment. *DDX41* mutations were associated with a lower relapse risk, although this did not reach statistical significance (HR 0.26, 95% CI 0.04–1.86).

Notably, the prognostic impact of *RUNX1* mutation status on RFS was evident across all ELN 2024 risk groups but was most pronounced in the favorable risk subgroup, where *RUNX1*-mutated patients had a median RFS of 10.8 months compared to 32.3 months in *RUNX1* wild-type patients ($p = 0.006$, Figure 5C). The difference in overall survival was not statistically significant. Overall, these results suggest that *RUNX1* mutations confer an increased risk of early relapse despite an otherwise favorable molecular profile. These findings provide interpretable effect size estimates for the candidate predictors identified by RSF and may inform clinical risk stratification and decision-making.

Discussion

This comprehensive analysis of non-transplanted AML patients in CR1 provides important benchmarks for survival outcomes across diverse subgroups. Established prognostic features,

including complex karyotype, *TP53* mutation, MRD status, venetoclax incorporation, and risk classifications, retain their predictive value in this specific population.

In addition to quantifying survival rates, we identified significant patterns in survival dynamics across subgroups. When stratified by treatment modality, the survival benefit of venetoclax was more pronounced in patients treated with LIT compared to IT. This differential effect may be explained by venetoclax's greater impact on MRD clearance in the LIT group, where it significantly improved MRD negativity rates from 30.5% to 55.6% (P=0.0012), compared to a more modest effect in the IT group (64.6% to 71.9%, P=0.5). Interestingly, venetoclax reduced relative relapse rates similarly in both treatment intensity groups (23% and 22% reduction at 48 months, respectively). The discrepancy between relapse rates and RFS outcomes appears to be driven by differences in NRM. While venetoclax had no impact on NRM in the LIT group, it was associated with a numerically higher NRM rate in the IT group (6% versus 23% at 24 months), which did not reach statistical significance. Consistently, venetoclax was not independently associated with RFS on multivariable analysis among IT-treated patients (Tables 6S and 7S).

This observation aligns with prior studies evaluating venetoclax in combination with intensive chemotherapy for newly diagnosed and relapsed/refractory AML, which have demonstrated high early response rates but also raised concerns regarding infectious complications and prolonged cytopenias [14-16]. Furthermore, since patients in this select cohort were not consolidated with allogeneic SCT in remission, they were more likely to have received additional cycles of IT + venetoclax consolidation and therefore at greater risk of complications related to myelosuppression. When administered with protocol adaptations—such as shortened venetoclax exposure, fewer cycles of IT + venetoclax, and adjusted antifungal prophylaxis—the toxicity profile appears comparable to historical controls, as recently shown in analyses of phase 2 trials of FLAG-IDA and CLIA with venetoclax for newly diagnosed and R/R AML [17-19].

We also assessed the performance of baseline risk classification systems in the post-remission setting. ELN2022 and ELN2024 showed clear prognostic separation between favorable and adverse risk groups. However, patients classified as intermediate risk had relapse rates more closely resembling those of the favorable risk group, regardless of treatment intensity. This likely reflects our cohort selection of CR1 patients - a subset with more chemo-sensitive disease than the general AML population. As such, the prognostic relevance of risk classifications in this setting may differ in both magnitude and direction, underscoring the need to refine risk assessment for post-remission therapy decisions.

Our multivariable Cox regression and RSF models confirmed that flow cytometry (FCM)–based MRD retained independent prognostic significance. The association was more pronounced in patients receiving LIT compared to IT. These findings align with the 2022 ELN consensus, which supports FCM-MRD monitoring in patients receiving venetoclax-based HMA therapy[20]. Current guidelines recommend using FCM-MRD for risk stratification and clinical trial design in this setting[21-23], but do not support therapy modification based solely on MRD status[20, 24, 25].

The prognostic impact of FCM was less pronounced in the IT group. This observation is consistent with prior studies showing that NGS-MRD outperforms FCM-MRD in intensive therapy settings. Specifically, in intermediate-risk AML treated with IT, NGS-MRD positivity post-induction has been associated with inferior OS (HR 2.1) and RFS (HR 2.4), while FCM-MRD has demonstrated weaker prognostic discrimination[26, 27]. Notably, the utility of NGS-based MRD in LIT-treated patients remains uncertain, possibly due to the high prevalence of clonal hematopoiesis in older individuals, which can confound molecular MRD interpretation[20].

Several efforts have been made to characterize risk stratification in AML patients receiving LIT [12, 28-30]. We applied ELN 2024 classification, originally designed to predict survival in patients treated with HMA plus venetoclax[13, 28]. Because our LIT cohort included additional venetoclax-based combinations such as cladribine plus low-dose cytarabine (LDAC), we aimed to assess prognostic factors beyond those evaluated in the original setting. Among these, *RUNX1* mutation, classified within the MR-gene ontology group according to the international consensus classification (ICC)[31], was significantly associated with inferior RFS, with the strongest effect seen in the ELN 2024 favorable risk group. In contrast, MR-gene mutations as a group did not show a consistent association with survival outcomes.

Historically, *RUNX1*-mutated AML has been associated with poor outcomes under intensive chemotherapy[32], but its role in LIT remains unclear. In a large series of 301 older or unfit AML patients treated with HMA plus venetoclax, patients with *RUNX1* mutations had a significantly lower CR rate of 44%, compared to 64% in *RUNX1* wild-type patients[33]. *RUNX1* mutations were also overrepresented among venetoclax -refractory cases, with one study reporting their presence in 40% of such patients[34, 35].

More recent studies have yielded conflicting results. In one report of newly diagnosed AML patients treated with HMA plus venetoclax, *RUNX1* mutation was associated with a significantly lower CR/CRi rate and was enriched among non-responders, yet it did not show independent prognostic value for survival[30]. In contrast, other investigations observed that patients with

RUNX1 mutations responded similarly to wild-type patients when treated with HMA plus venetoclax[36]. A multicenter analysis of 279 newly diagnosed patients suggested that the adverse prognostic effect of *RUNX1* was evident only when accompanied by signaling mutations[28].

The discrepancy in findings may reflect our cohort's selection for patients who achieved remission, a group with inherently more favorable disease biology, potentially revealing additional effects of mutation patterns or clinical features that influence relapse, rather than treatment resistance. Whether *RUNX1* status should guide risk assessment or post-remission strategies in venetoclax-based therapy remains a question for future research.

Our study has several limitations, including its retrospective design, heterogeneous treatment regimens including investigational agents within both intensive and lower-intensity therapy groups, MRD assessment limited to flow cytometry, and missing data on reasons for omitting allo-SCT consolidation. As a single large tertiary referral center with broad access to clinical trials and novel agents, the established benchmarks may not be directly generalizable to broader practice settings, though reporting outcomes across multiple predefined subgroups aims to partially address this limitation. In addition, patients with antecedent hematologic conditions or therapy-related AML were excluded by design. Despite these limitations, our findings establish RFS benchmarks across clinically relevant subgroups and identify molecular features that may inform relapse risk and guide future post-remission strategies in non-transplanted AML.

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Table 1. Patient Characteristics

Variable	Overall (n=362)[1]	LIT (n=257)[1]	IT (n=105)[1]	P-value[2]
Age				<0.001
Median (Range)	69 (19-94)	74 (42-94)	52 (19-71)	
Age Group				<0.001
Below 60	91 (25%)	13 (5.1%)	78 (74%)	
60 and Above	271 (75%)	244 (95%)	27 (26%)	
Gender				0.015
Male	182 (50%)	140 (54%)	42 (40%)	
Female	180 (50%)	117 (46%)	63 (60%)	
ECOG (PS)				0.012
0-2	213 (59%)	139 (54%)	74 (70%)	
>2	101 (28%)	82 (32%)	19 (18%)	
Unknown	48 (13%)	36 (14%)	12 (11%)	
ELN 2022				<0.001
Favorable	77 (21%)	51 (20%)	26 (25%)	
Intermediate	96 (27%)	51 (20%)	45 (43%)	
Adverse	189 (52%)	155 (60%)	34 (32%)	
ELN 2024				<0.001
Adverse	69 (19%)	63 (25%)	6 (5.7%)	
Intermediate	110 (30%)	71 (28%)	39 (37%)	
Favorable	183 (51%)	123 (48%)	60 (57%)	
Venetoclax Status				<0.001
Ven not added	107 (30%)	59 (23%)	48 (46%)	
Ven added	255 (70%)	198 (77%)	57 (54%)	
Number of Cycles to Best Response				NS
Median (Range)	1 (1-4)	1 (1-4)	1 (1-4)	
Total Number of Cycles				<0.001
Median (Range)	4 (1-33)	5 (1-33)	3 (1-14)	
Best Response				0.004
CR	304 (84%)	207 (81%)	97 (92%)	
CRi	58 (16%)	50 (19%)	8 (7.6%)	

[1] n (%)

[2] Wilcoxon rank sum test; Fisher's exact test

Table 2. Molecular Frequencies in the Entire Cohort and by Treatment Intensity

Variable	Overall (n=362)[1]	LIT (n=257)[1]	IT (n=105)[1]	P-value[2]
MDS Related Genes				0.001
Negative	219 (60%)	142 (55%)	77 (73%)	
Positive	143 (40%)	115 (45%)	28 (27%)	
Karyotype				0.002
Diploid	156 (43%)	99 (39%)	57 (54%)	
CK	81 (22%)	69 (27%)	12 (11%)	
Other	125 (35%)	89 (35%)	36 (34%)	
Chr 5 (-5/del5q)				<0.001
Normal	298 (82%)	199 (77%)	99 (94%)	
Abnormal	64 (18%)	58 (23%)	6 (5.7%)	
Chr 7 (-7/del7q)				0.003
Normal	310 (86%)	211 (82%)	99 (94%)	
Abnormal	52 (14%)	46 (18%)	6 (5.7%)	
Chr 17 (del17/17p)				0.008
Normal	335 (93%)	232 (90%)	103 (98%)	
Abnormal	27 (7.5%)	25 (9.7%)	2 (1.9%)	
KMT2Ar				0.2
Normal	349 (96%)	250 (97%)	99 (94%)	
Abnormal	13 (3.6%)	7 (2.7%)	6 (5.7%)	
MECOMr				0.6
Normal	357 (99%)	254 (99%)	103 (98%)	
Abnormal	5 (1.4%)	3 (1.2%)	2 (1.9%)	

[1] n (%) [2] Fisher's exact test

Table 3. RFS and OS Across AML Subgroups

Variable	Stratification	n	RFS — Median (95% CI), months			OS — Median (95% CI), months		
			All cohort (n=362)	IT (n=105)	LIT (n=257)	All cohort (n=362)	IT (n=105)	LIT (n=257)
Age	Below 60	91	18.1 (10.9–NA)	23.5 (11.6–NA)		26.2 (16.7–NA)	30.3 (19.0–NA)	
—	60 and above	271	9.5 (7.8–12.4)	20.9 (9.6–NA)		16.2 (14.1–21.0)	27.0 (18.7–NA)	
Tx intensity	IT + Ven	57	—	23.5 (12.5–NA)	—	—	30.3 (19.0–NA)	—
—	IT	48	—	20.9 (9.5–NA)	—	—	27.0 (18.7–NA)	—
—	LIT + Ven	198	—	—	10.8 (8.2–14.2)	—	—	16.6 (13.9–23.0)
—	LIT	59	—	—	6.3 (4.9–9.7)	—	—	12.5 (10.8–19.4)
Karyotype	Diploid	156	23.3 (14.3–44.2)	NR	19.2 (13.0–34.3)	31.3 (22.9–43.7)	39.4 (26.2–NA)	24.6 (18.8–40.3)
—	Other	125	8.9 (7.5–13.0)	18.1 (9.6–NA)	7.7 (5.3–9.7)	17.1 (13.0–24.6)	36.2 (16.3–NA)	13.9 (10.7–23.9)
—	CK	81	5.3 (3.8–7.4)	1.6 (1.5–NA)	5.3 (4.6–8.2)	11.2 (9.6–14.4)	8.0 (6.0–NA)	11.2 (10.1–14.0)
ELN 2022	Favorable	77	—	58.0 (18.1–NA)	—	—	NR	—
—	Intermediate	96	—	25.5 (9.5–NA)	—	—	23.2 (16.7–NA)	—
—	Adverse	189	—	9.6 (8.1–NA)	—	—	19.0 (13.0–NA)	—
ELN 2024	Favorable	183	—	—	13.7 (9.7–23.7)	—	—	25.0 (18.8–43.7)
—	Intermediate	110	—	—	10.2 (7.5–14.9)	—	—	17.5 (13.0–23.3)
—	Adverse	69	—	—	5.3 (3.5–7.4)	—	—	10.6 (9.3–12.5)
TP53 status	WT	293	12.0 (9.0–16.0)	—	—	21.0 (16.2–25.4)	—	—
—	Mutant	69	5.3 (3.5–7.4)	—	—	10.6 (9.3–12.5)	—	—
FLT3-ITD	Mutant	58	14.4 (8.7–NA)	21.5 (6.7–NA)	11.4 (5.2–NA)	23.3 (14.1–59.4)	39.4 (16.7–NA)	21.0 (12.9–59.4)
MRD status	Negative	200	15.6 (12.0–25.4)	25.5 (17.0–NA)	12.2 (9.4–23.7)	24.6 (17.3–35.6)	36.2 (21.4–NA)	18.8 (14.4–31.3)
—	Positive	162	7.5 (5.3–9.6)	9.6 (8.9–NA)	5.9 (5.0–8.9)	14.1 (12.4–18.7)	18.7 (12.5–NA)	13.5 (11.5–18.5)
MR-gene status	No	219	11.5 (7.7–NA)	—	—	20.2 (11.5–41.9)	—	—
—	Yes	143	11.9 (8.1–15.3)	—	—	21.0 (14.3–25.4)	—	—

NR = Not Reached; — = not applicable for subgroup. ELN 2022 applied to IT cohort; ELN 2024 applied to LIT cohort. MR-gene status excludes TP53- and NPM1-mutated patients. CK = complex karyotype; WT = wild-type.

Main Figure Legends

Figure 1. Study cohort and baseline mutational profile. (A) Flow chart of patient selection criteria and cohort derivation. (B) Frequency of recurrent gene mutations stratified by treatment intensity. Asterisks denote statistically significant differences between groups (Fisher's exact test). (C) Oncoprint displaying the mutational landscape of the entire cohort, with overall mutation frequencies shown on the right and individual mutations color-coded by treatment type.

Abbreviations: IT, intensive therapy; LIT, lower-intensity therapy; APL, acute promyelocytic leukemia; CBF, core-binding factor; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; allo-SCT, allogeneic stem cell transplantation.

Figure 2. Survival outcomes stratified by age, treatment intensity, and karyotype. (A) Kaplan-Meier estimates of RFS (left) and OS (center), and CIR (right) among patients treated with IT, stratified by age group (<60 vs ≥60 years). (B) RFS (left), OS (center), and CIR (right) for the entire cohort, stratified by treatment intensity and venetoclax use. (C) RFS (left), OS (center), and CIR (right) among LIT patients, stratified by karyotype (diploid, other, complex karyotype). Median survival times and log-rank p-values are indicated on each panel.

Abbreviations: RFS, relapse-free survival; OS, overall survival; CIR, cumulative incidence of relapse and death in remission; IT, intensive therapy; LIT, lower-intensity therapy; Ven, venetoclax; CK, complex karyotype.

Figure 3. Survival outcomes stratified by ELN risk classification. (A) Kaplan-Meier estimates of RFS (left) and OS (center), and CIR (right) among patients treated with IT, stratified by ELN 2022 risk groups. (B) RFS (left), OS (center), and CIR (right) among patients treated with LIT, stratified by ELN 2024 risk groups. Median survival times and log-rank p-values are indicated on each panel.

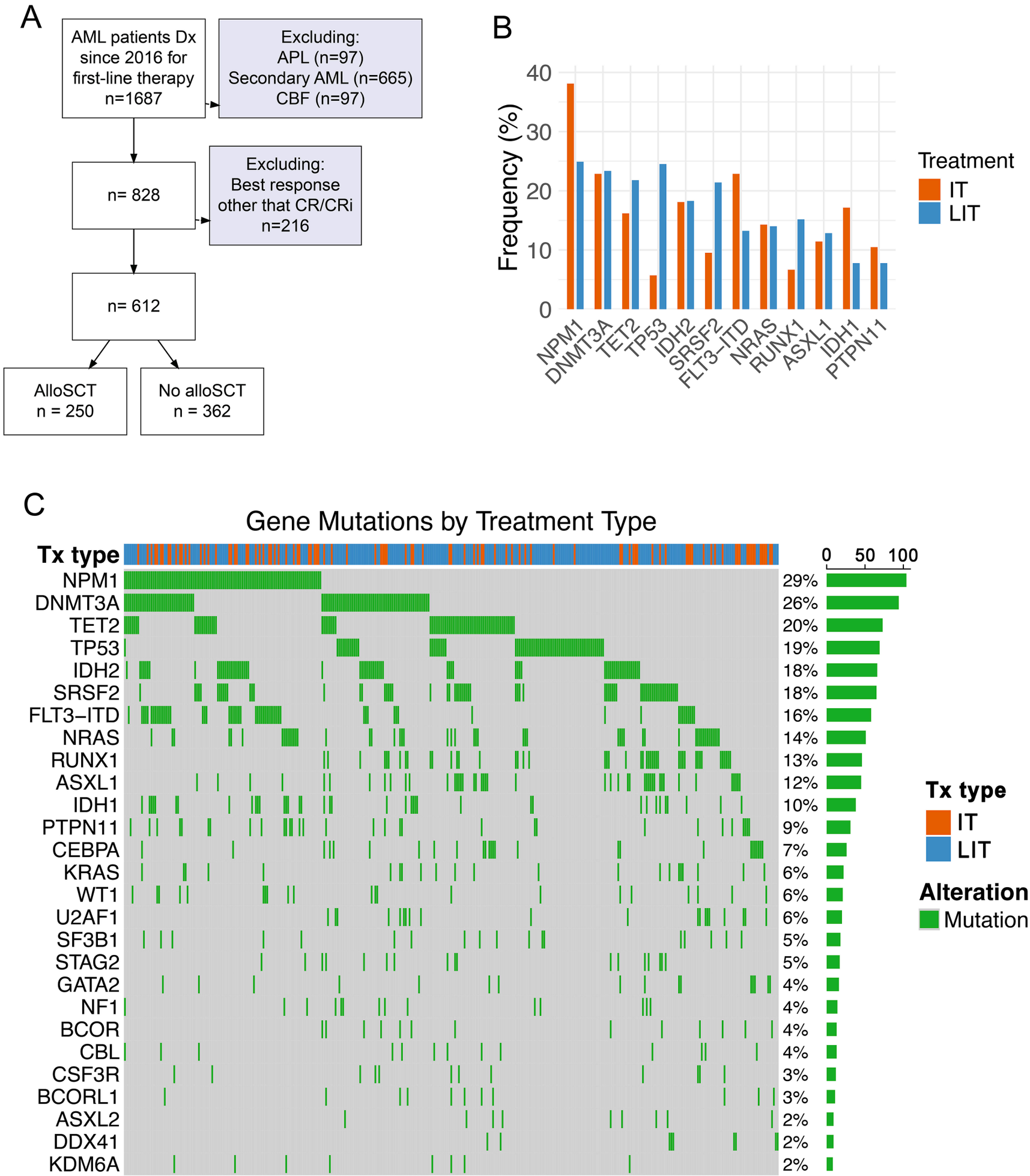
Abbreviations: RFS, relapse-free survival; OS, overall survival; CIR, cumulative incidence of relapse and death in remission; ELN, European LeukemiaNet; IT, intensive therapy; LIT, lower-intensity therapy.

Figure 4. Survival outcomes stratified by TP53 mutation status and measurable residual disease. (A) Kaplan-Meier estimates of RFS (left) and OS (center), and CIR (right) among LIT patients, stratified by TP53 mutation status. (B) RFS (left), OS (center), and CIR (right) among IT patients, stratified by MRD status assessed by multiparameter flow cytometry. (C) RFS (left), OS (center), and CIR (right) among LIT patients, stratified by MRD status. Median survival times and log-rank p-values are indicated on each panel.

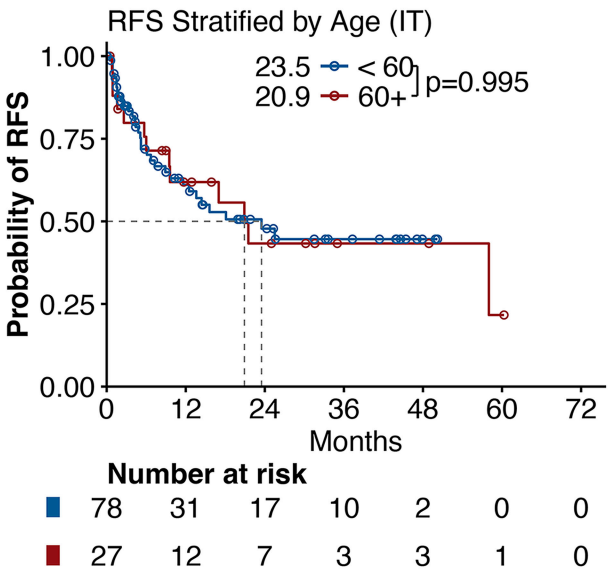
Abbreviations: RFS, relapse-free survival; OS, overall survival; CIR, cumulative incidence of relapse and death in remission; MRD, measurable residual disease; IT, intensive therapy; LIT, lower-intensity therapy; WT, wild-type.

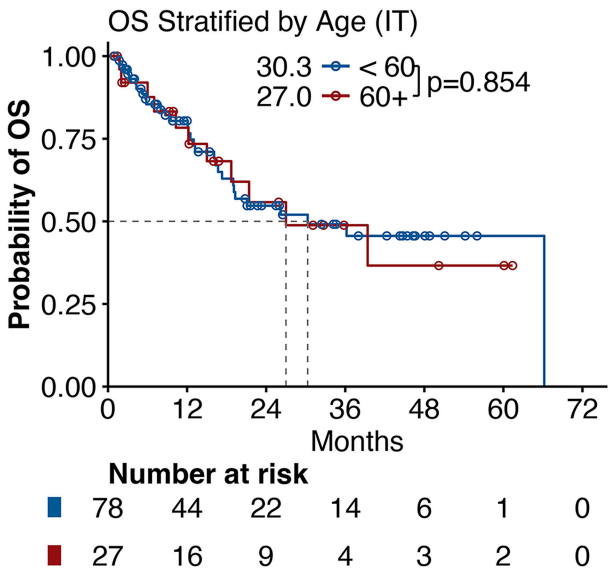
Figure 5. Random survival forest analysis and multivariable modeling of relapse-free survival predictors in venetoclax-based LIT. (A) Variable importance rankings from random survival forest analysis. (B) Partial dependence plots showing the relationship between individual predictors and predicted mortality. (C) Time-dependent variable importance heatmap displaying the predictive contribution of each variable at 6, 12, 18, and 24 months. (D) Forest plot of hazard ratios from stepwise-selected multivariable Cox proportional hazards regression. Red points indicate statistically significant variables ($p<0.05$). (E) Kaplan-Meier estimates of RFS stratified by ELN 2024 risk group and RUNX1 mutation status.

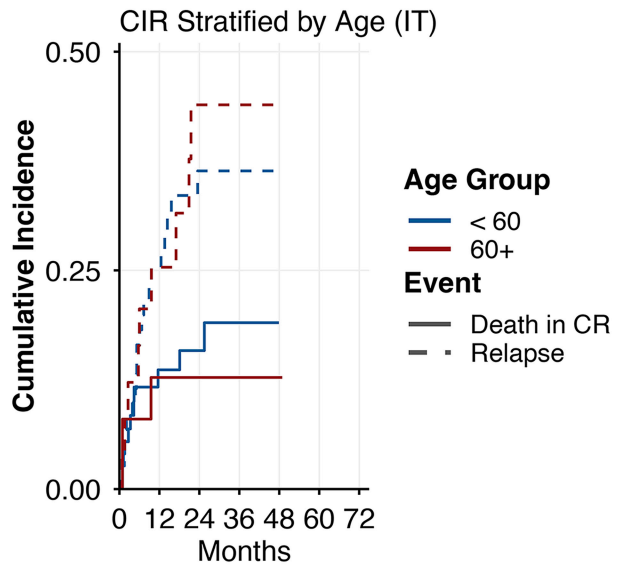
Abbreviations: RSF, random survival forest; RFS, relapse-free survival; LIT, lower-intensity therapy; ELN, European LeukemiaNet; HR, hazard ratio; CI, confidence interval; WT, wild-type; Mut, mutant.


A
AML patients Dx since 2016 for first-line therapy n=1687
Excluding: APL (n=97) Secondary AML (n=665) CBF (n=97)
n= 828
Excluding: Best response other that CR/CRi n=216
n= 612
AlloSCT n = 250
No alloSCT n = 362
B
Frequency (%)
40
30
20
10
0
NPM1
DNMT3A
TET2
TP53
IDH2
SRSF2
FLT3−ITD
NRAS
RUNX1
ASXL1
IDH1
PTPN11
Treatment
IT
LIT
C
Gene Mutations by Treatment Type
Tx type
0 50 100
NPM1 29%
DNMT3A 26%
TET2 20%
TP53 19%
IDH2 18%
SRSF2 18%
FLT3−ITD 16%
NRAS 14%
RUNX1 13%
ASXL1 12%
IDH1 10%
PTPN11 9%
CEBPA 7%
KRAS 6%
WT1 6%
U2AF1 6%
SF3B1 5%
STAG2 5%
GATA2 4%
NF1 4%
BCOR 4%
CBL 4%
CSF3R 3%
BCORL1 3%
ASXL2 2%
DDX41 2%
KDM6A 2%
Tx type
IT
LIT
Alteration
Mutation

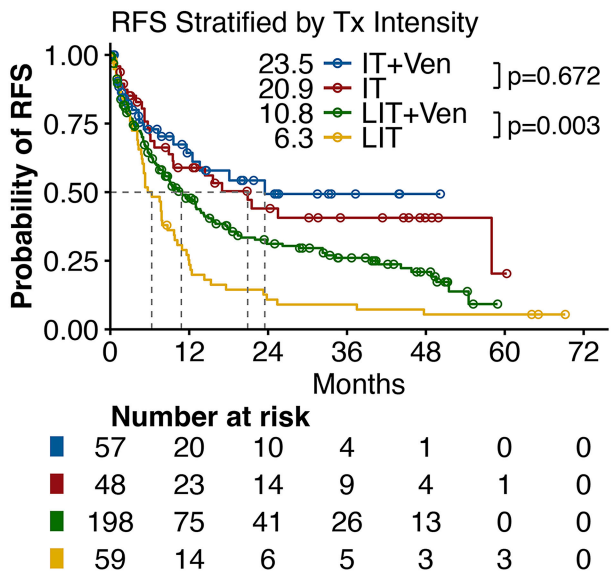
A

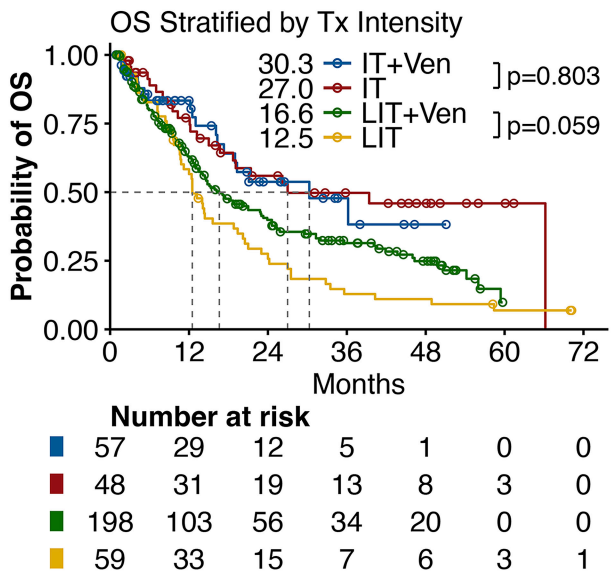

RFS Stratified by Age (IT)
23.5 < 60
20.9 60+
p=0.995
Probability of RFS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
78 31 17 10 2 0 0
27 12 7 3 3 1 0

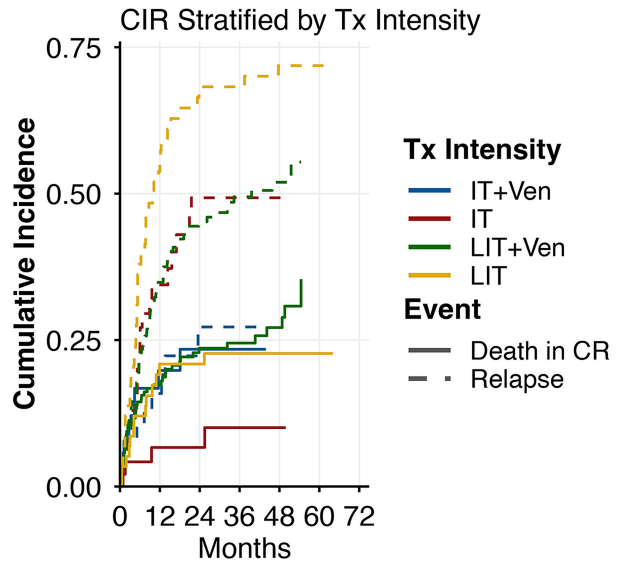

OS Stratified by Age (IT)
30.3 < 60
27.0 60+
p=0.854
Probability of OS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
78 44 22 14 6 1 0
27 16 9 4 3 2 0


CIR Stratified by Age (IT)
Cumulative Incidence
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Age Group
< 60
60+
Event
Death in CR
Relapse

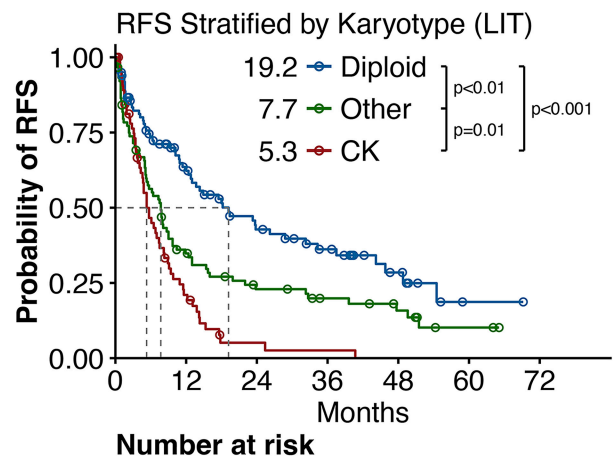
B

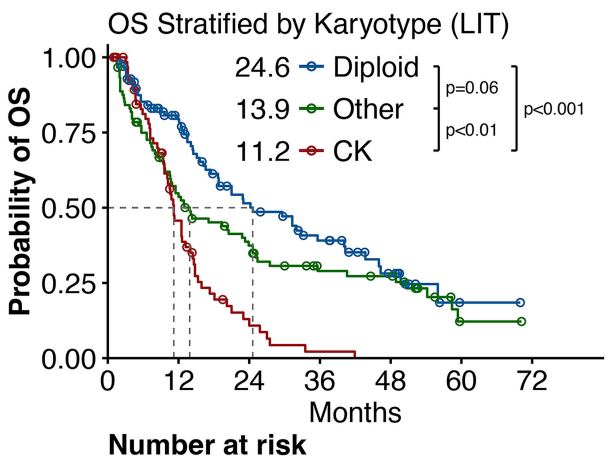

RFS Stratified by Tx Intensity
23.5 IT+Ven
20.9 IT
10.8 LIT+Ven
6.3 LIT
p=0.672
p=0.003
Probability of RFS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
57 20 10 4 1 0 0
48 23 14 9 4 1 0
198 75 41 26 13 0 0
59 14 6 5 3 3 0

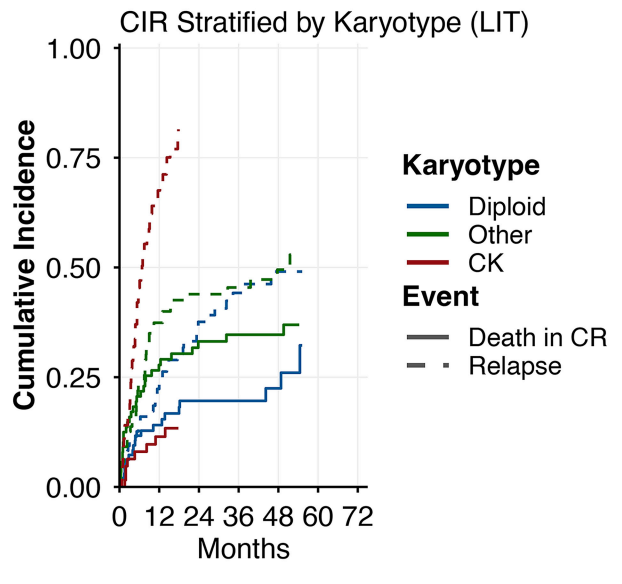

OS Stratified by Tx Intensity
30.3 IT+Ven
27.0 IT
16.6 LIT+Ven
12.5 LIT
p=0.803
p=0.059
Probability of OS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
57 29 12 5 1 0 0
48 31 19 13 8 3 0
198 103 56 34 20 0 0
59 33 15 7 6 3 1


CIR Stratified by Tx Intensity
Cumulative Incidence
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Tx Intensity
IT+Ven
IT
LIT+Ven
LIT
Event
Death in CR
Relapse

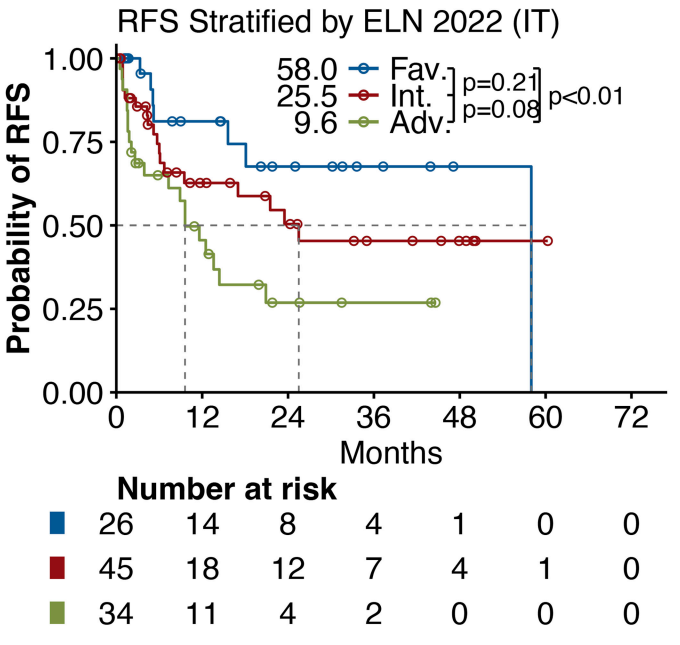
C

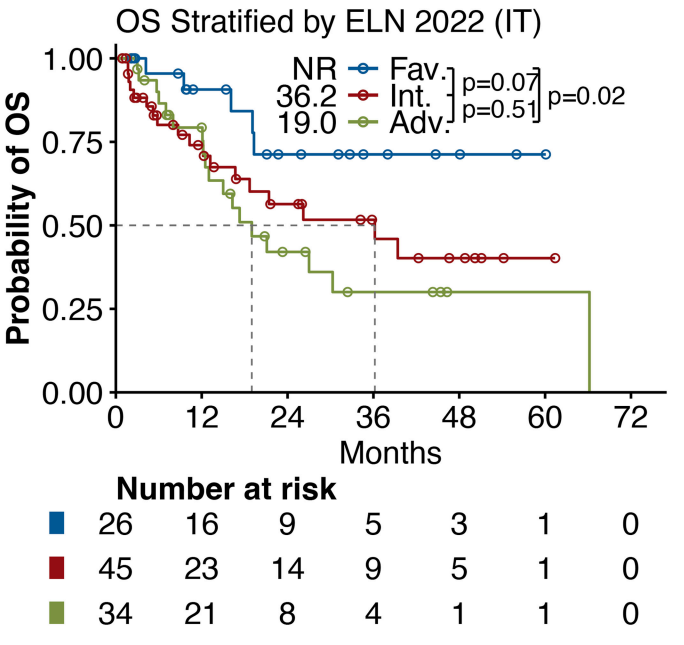

RFS Stratified by Karyotype (LIT)
19.2 Diploid
7.7 Other
5.3 CK
p<0.01
p=0.01
p<0.001
Probability of RFS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
99 49 29 19 9 1 0
89 28 16 11 7 2 0
69 12 2 1 0 0 0

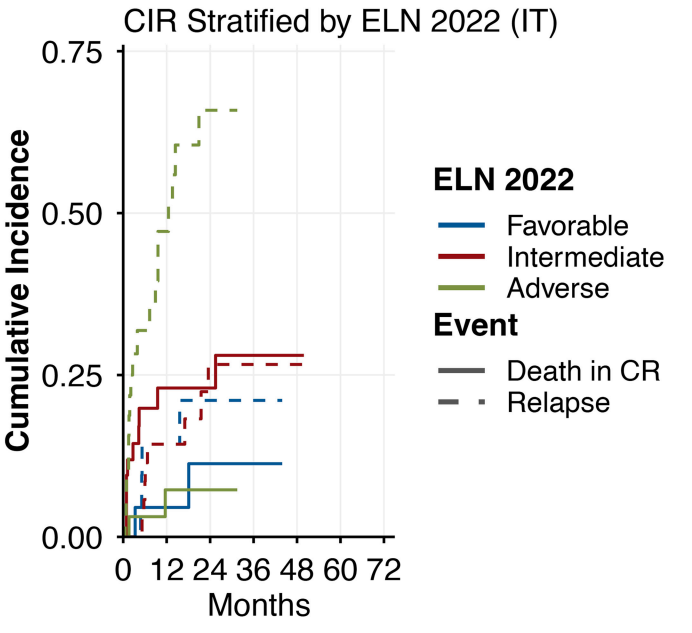

OS Stratified by Karyotype (LIT)
24.6 Diploid
13.9 Other
11.2 CK
p=0.06
p<0.01
p<0.001
Probability of OS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
99 64 36 23 11 1 0
89 46 29 17 15 2 1
69 26 6 1 0 0 0


CIR Stratified by Karyotype (LIT)
Cumulative Incidence
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Karyotype
Diploid
Other
CK
Event
Death in CR
Relapse

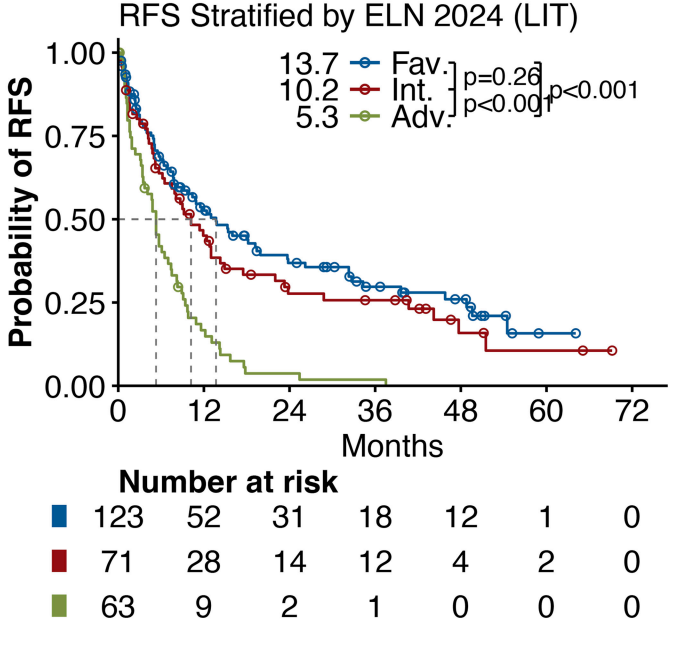
A

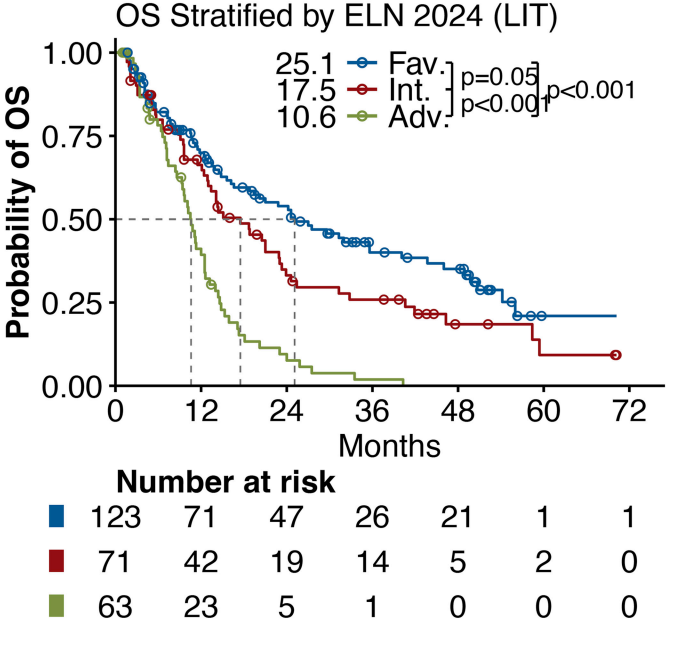

RFS Stratified by ELN 2022 (IT)
Probability of RFS
1.00
0.75
0.50
0.25
0.00
58.0 Fav.
25.5 Int.
9.6 Adv.
p=0.21
p=0.08
p<0.01
0 12 24 36 48 60 72
Months
Number at risk
26 14 8 4 1 0 0
45 18 12 7 4 1 0
34 11 4 2 0 0 0

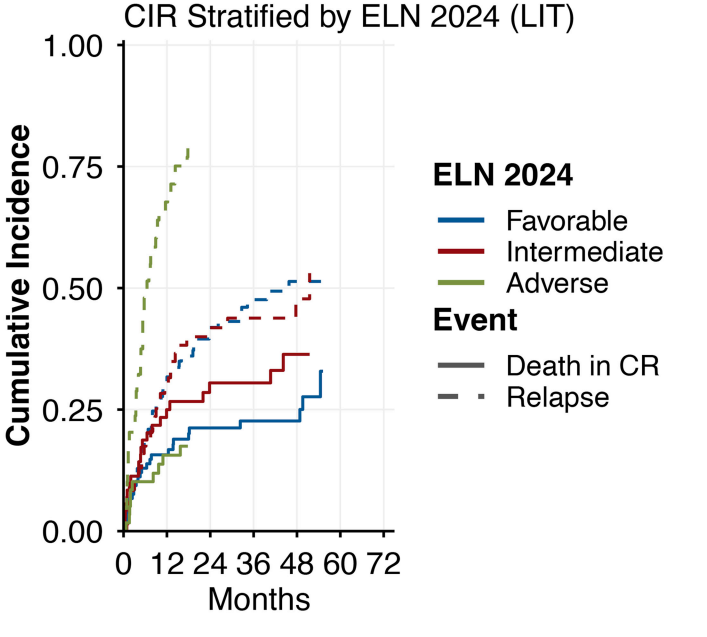

OS Stratified by ELN 2022 (IT)
Probability of OS
1.00
0.75
0.50
0.25
0.00
NR Fav.
36.2 Int.
19.0 Adv.
p=0.07
p=0.51
p=0.02
0 12 24 36 48 60 72
Months
Number at risk
26 16 9 5 3 1 0
45 23 14 9 5 1 0
34 21 8 4 1 1 0


CIR Stratified by ELN 2022 (IT)
Cumulative Incidence
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
ELN 2022
Favorable
Intermediate
Adverse
Event
Death in CR
Relapse

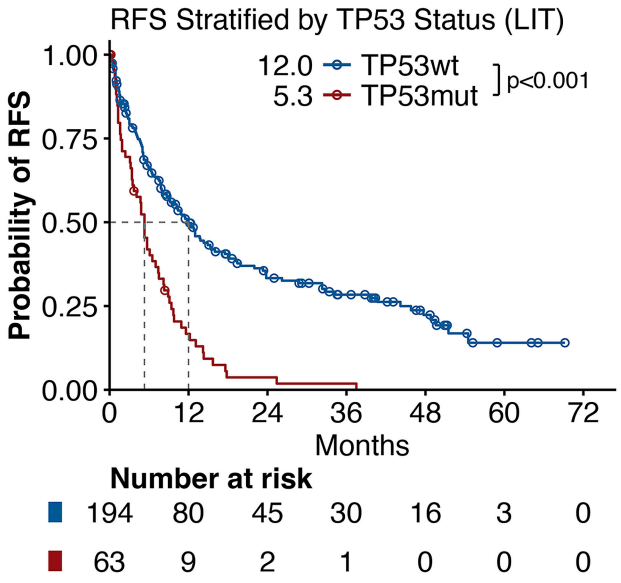
B

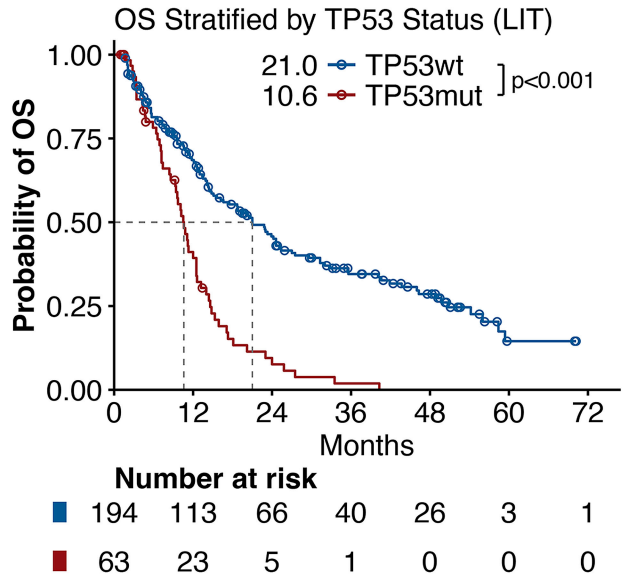

RFS Stratified by ELN 2024 (LIT)
Probability of RFS
1.00
0.75
0.50
0.25
0.00
13.7 Fav.
10.2 Int.
5.3 Adv.
p=0.26
p<0.001
p<0.001
0 12 24 36 48 60 72
Months
Number at risk
123 52 31 18 12 1 0
71 28 14 12 4 2 0
63 9 2 1 0 0 0

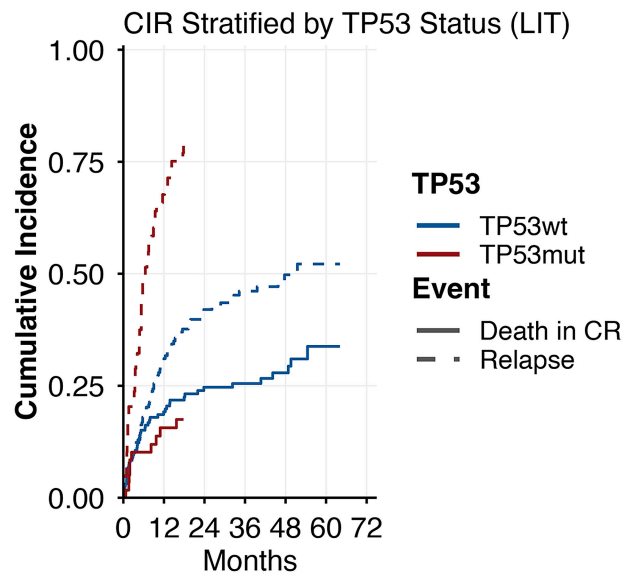

OS Stratified by ELN 2024 (LIT)
Probability of OS
1.00
0.75
0.50
0.25
0.00
25.1 Fav.
17.5 Int.
10.6 Adv.
p=0.05
p<0.001
p<0.001
0 12 24 36 48 60 72
Months
Number at risk
123 71 47 26 21 1 1
71 42 19 14 5 2 0
63 23 5 1 0 0 0


CIR Stratified by ELN 2024 (LIT)
Cumulative Incidence
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
ELN 2024
Favorable
Intermediate
Adverse
Event
Death in CR
Relapse

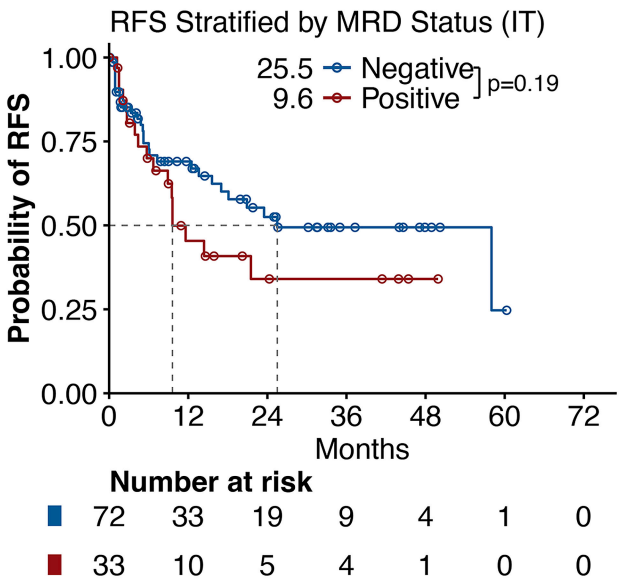
A

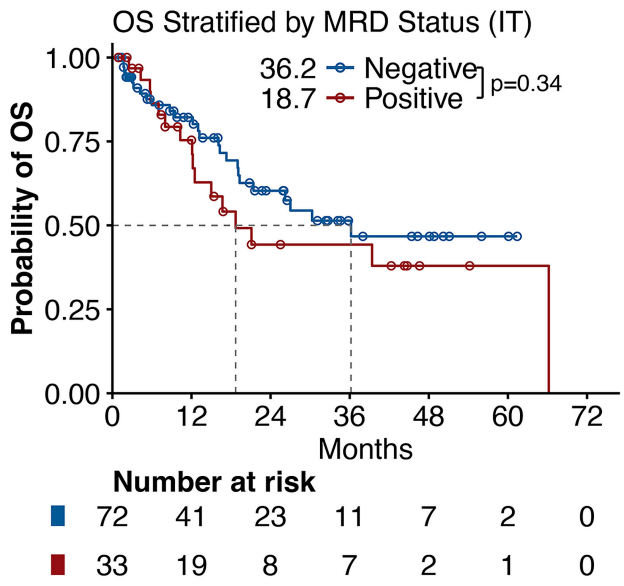

RFS Stratified by TP53 Status (LIT)
12.0 TP53wt
5.3 TP53mut
p<0.001
Probability of RFS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
194 80 45 30 16 3 0
63 9 2 1 0 0 0

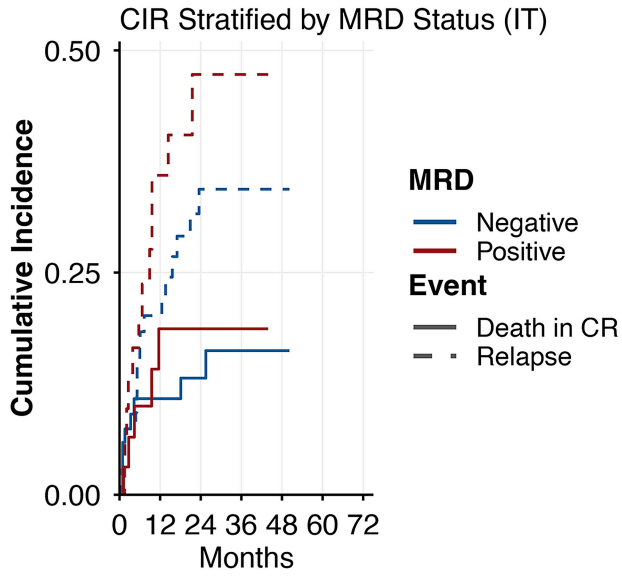

OS Stratified by TP53 Status (LIT)
21.0 TP53wt
10.6 TP53mut
p<0.001
Probability of OS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
194 113 66 40 26 3 1
63 23 5 1 0 0 0


CIR Stratified by TP53 Status (LIT)
Cumulative Incidence
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
TP53
TP53wt
TP53mut
Event
Death in CR
Relapse

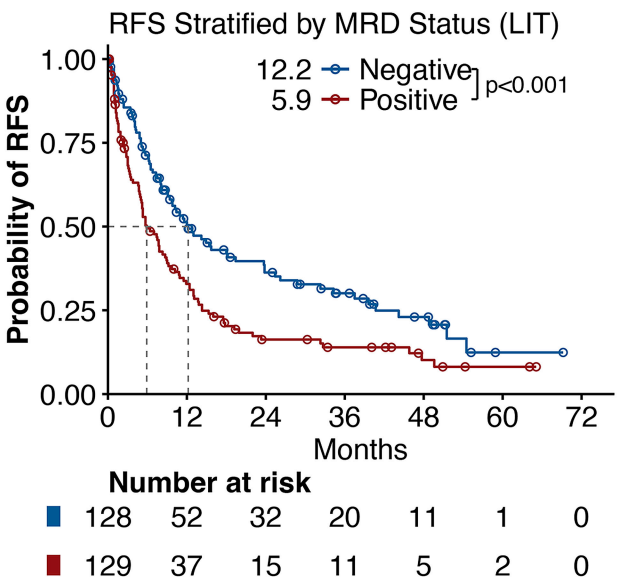
B

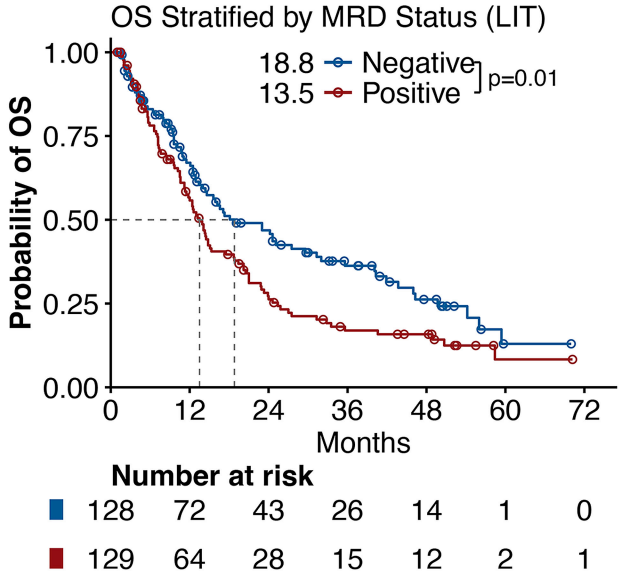

RFS Stratified by MRD Status (IT)
25.5 Negative
9.6 Positive
p=0.19
Probability of RFS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
72 33 19 9 4 1 0
33 10 5 4 1 0 0

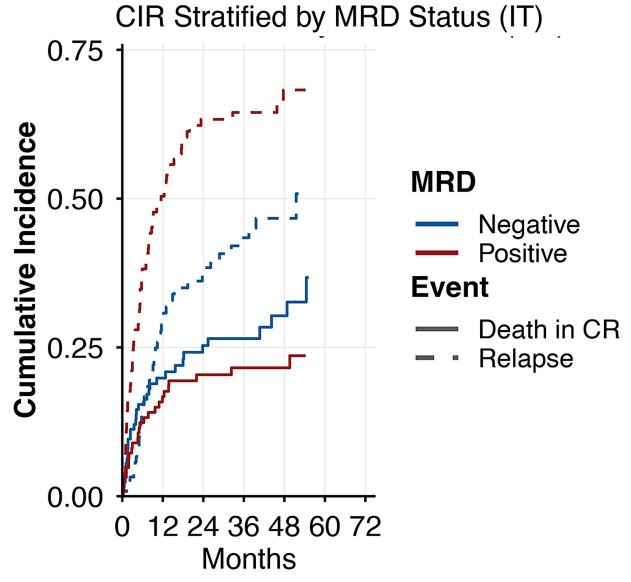

OS Stratified by MRD Status (IT)
36.2 Negative
18.7 Positive
p=0.34
Probability of OS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
72 41 23 11 7 2 0
33 19 8 7 2 1 0


CIR Stratified by MRD Status (IT)
Cumulative Incidence
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
MRD
Negative
Positive
Event
Death in CR
Relapse

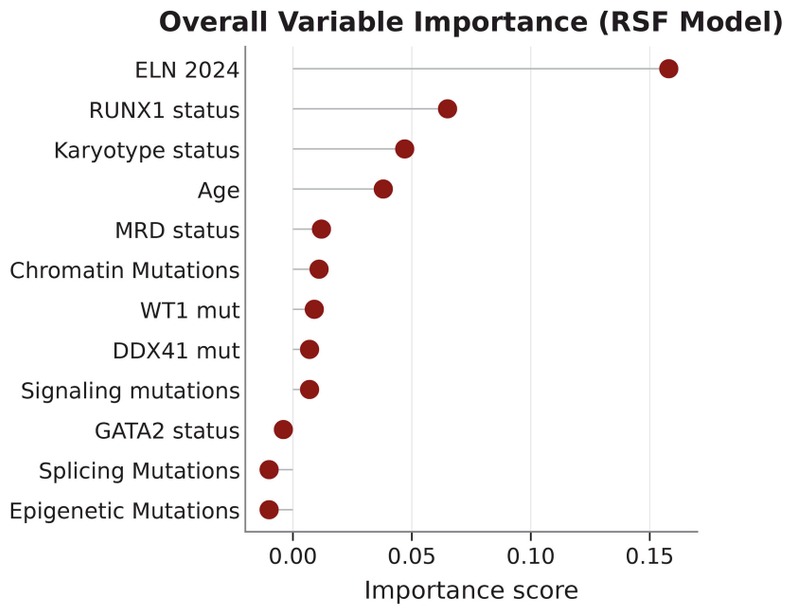
C


RFS Stratified by MRD Status (LIT)
12.2 Negative
5.9 Positive
p<0.001
Probability of RFS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
128 52 32 20 11 1 0
129 37 15 11 5 2 0

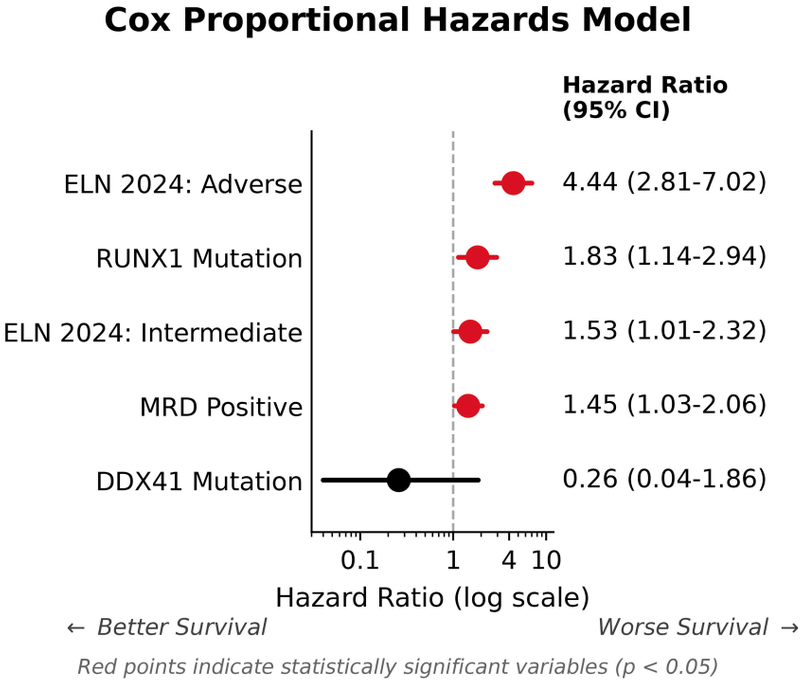

OS Stratified by MRD Status (LIT)
18.8 Negative
13.5 Positive
p=0.01
Probability of OS
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
Number at risk
128 72 43 26 14 1 0
129 64 28 15 12 2 1


CIR Stratified by MRD Status (IT)
Cumulative Incidence
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months
MRD
Negative
Positive
Event
Death in CR
Relapse

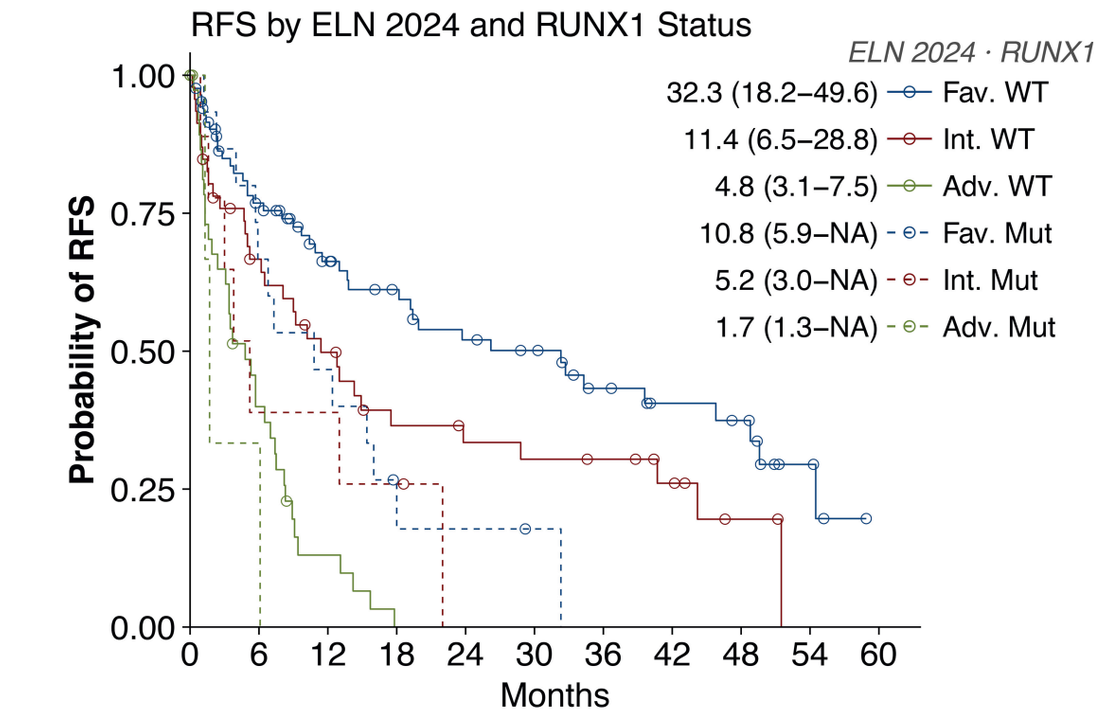
A



B



C



Number at risk

RUNX1 WT	84	56	41	34	28	24	17	13	11	4	0
	46	28	20	13	11	10	9	6	2	0	0
	39	14	4	0	0	0	0	0	0	0	0
RUNX1 Mut	15	10	7	3	2	1	0	0	0	0	0
	9	3	3	2	0	0	0	0	0	0	0
	5	1	0	0	0	0	0	0	0	0	0

Table 1S. Baseline Patient Characteristics

Variable	Study cohort (no alloSCT) N = 362[1]	alloSCT group N = 238[1]	p-value[2]
Age, years	69.3 (59.3, 76.7)	59.0 (44.7, 66.0)	<0.001
Sex			0.739
Female	180 (49.7%)	115 (48.3%)	
Male	182 (50.3%)	123 (51.7%)	
ECOG performance status			<0.001
0–1	213 (58.8%)	179 (75.2%)	
≥2	101 (27.9%)	38 (16.0%)	
Unknown	48 (13.3%)	21 (8.8%)	
Treatment intensity			<0.001
IT	102 (28.2%)	136 (57.1%)	
LIT	260 (71.8%)	102 (42.9%)	
Venetoclax			0.191
Not added	107 (29.6%)	58 (24.4%)	
Added	255 (70.4%)	180 (75.6%)	
BM blasts, %	50.0 (28.0, 71.0)	52.0 (28.0, 71.0)	0.611
Complex karyotype	83 (22.9%)	38 (16.0%)	0.0382
ELN 2022 risk (IT patients)			0.251
Favorable	22 (21.6%)	20 (14.7%)	
Intermediate	46 (45.1%)	58 (42.6%)	
Adverse	34 (33.3%)	58 (42.6%)	
ELN 2024 risk (LIT patients)			0.844
Favorable	141 (54.2%)	59 (57.8%)	
Intermediate	65 (25.0%)	24 (23.5%)	
Adverse	54 (20.8%)	19 (18.6%)	
Somatic mutations			
NPM1	102 (28.2%)	61 (25.6%)	0.513
FLT3-ITD	54 (14.9%)	48 (20.2%)	0.097
TP53	61 (16.9%)	26 (10.9%)	0.0447
ASXL1	31 (8.6%)	20 (8.4%)	0.99
SRSF2	57 (15.7%)	21 (8.8%)	0.0133
RUNX1	33 (9.1%)	21 (8.8%)	0.99
IDH1	30 (8.3%)	22 (9.2%)	0.767
IDH2	52 (14.4%)	35 (14.7%)	0.906
DNMT3A	80 (22.1%)	63 (26.5%)	0.24
TET2	56 (15.5%)	25 (10.5%)	0.0881

[1] Median (Q1, Q3); n (%)

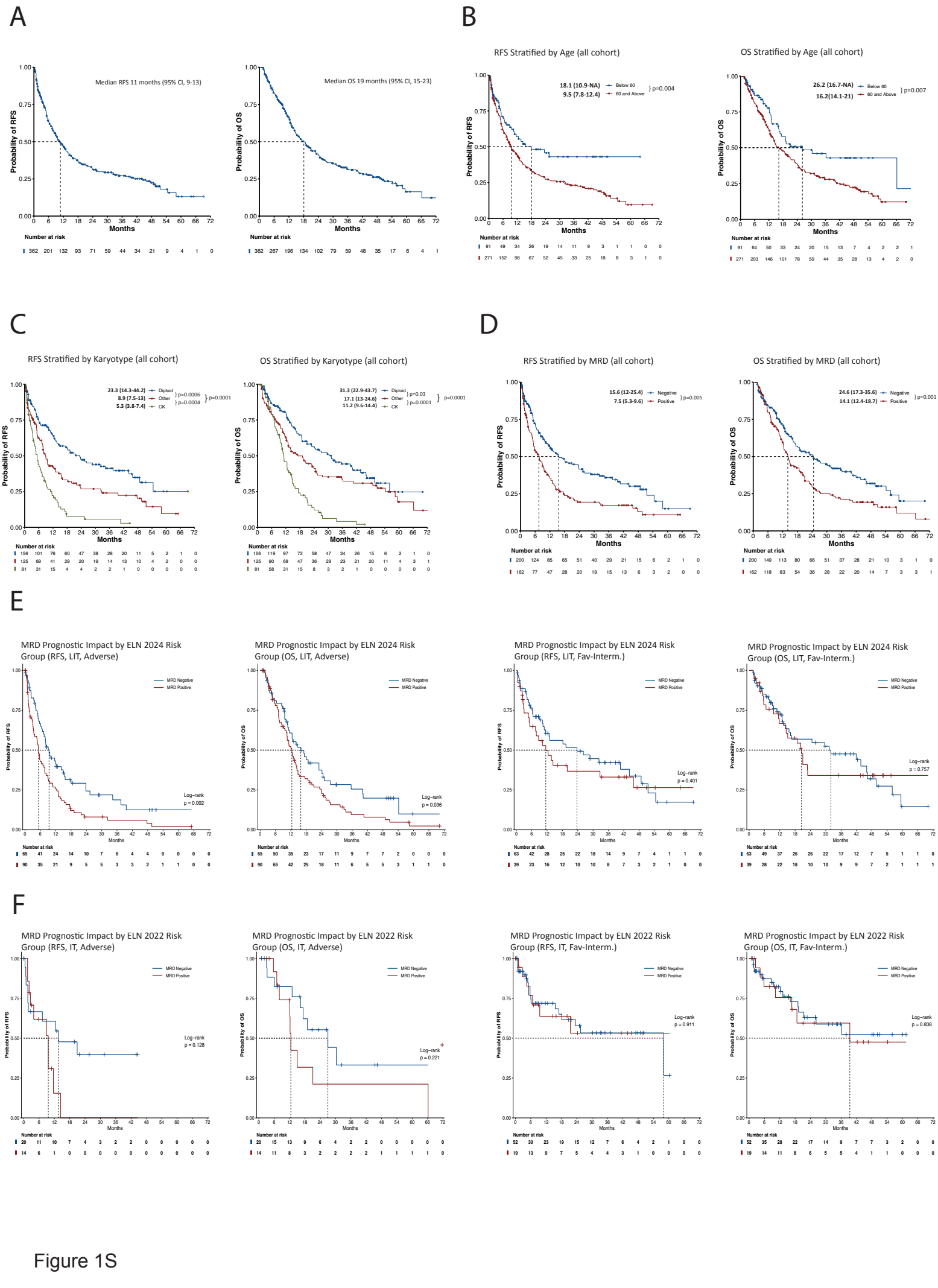

A
Median RFS 11 months (95% CI, 9-13)
Probability of RFS
Months
Number at risk
362 201 132 93 71 59 44 34 21 9 4 1 0
Median OS 19 months (95% CI, 15-23)
Probability of OS
Months
Number at risk
362 267 196 134 102 79 59 48 35 17 6 4 1
B
RFS Stratified by Age (all cohort)
18.1 (10.9-NA) Below 60
9.5 (7.8-12.4) 60 and Above
p=0.004
Probability of RFS
Months
Number at risk
91 49 34 26 19 14 11 9 3 1 1 0 0
271 152 98 67 52 45 33 25 18 8 3 1 0
OS Stratified by Age (all cohort)
26.2 (16.7-NA) Below 60
16.2(14.1-21) 60 and Above
p=0.007
Probability of OS
Months
Number at risk
91 64 50 33 24 20 15 13 7 4 2 2 1
271 203 146 101 78 59 44 35 28 13 4 2 0
C
RFS Stratified by Karyotype (all cohort)
23.3 (14.3-44.2) Diploid
8.9 (7.5-13) Other
5.3 (3.8-7.4) CK
p=0.0006
p=0.0004
p=0.0001
Probability of RFS
Months
Number at risk
156 101 76 60 47 38 28 20 11 5 2 1 0
125 69 41 29 20 19 14 13 10 4 2 0 0
81 31 15 4 4 2 2 1 0 0 0 0 0
OS Stratified by Karyotype (all cohort)
31.3 (22.9-43.7) Diploid
17.1 (13-24.6) Other
11.2 (9.6-14.4) CK
p=0.03
p=0.0001
p=0.0001
Probability of OS
Months
Number at risk
156 119 97 72 58 47 34 26 15 6 2 1 0
125 90 68 47 36 29 23 21 20 11 4 3 1
81 58 31 15 8 3 2 1 0 0 0 0 0
D
RFS Stratified by MRD (all cohort)
15.6 (12-25.4) Negative
7.5 (5.3-9.6) Positive
p=0.005
Probability of RFS
Months
Number at risk
200 124 85 65 51 40 29 21 15 6 2 1 0
162 77 47 28 20 19 15 13 6 3 2 0 0
OS Stratified by MRD (all cohort)
24.6 (17.3-35.6) Negative
14.1 (12.4-18.7) Positive
p=0.001
Probability of OS
Months
Number at risk
200 149 113 80 66 51 37 28 21 10 3 1 0
162 118 83 54 36 28 22 20 14 7 3 3 1
E
MRD Prognostic Impact by ELN 2024 Risk Group (RFS, LIT, Adverse)
MRD Negative
MRD Positive
Log-rank p = 0.002
Probability of RFS
Months
Number at risk
65 41 24 14 10 7 6 4 4 0 0 0 0
90 35 21 9 5 5 3 3 2 1 1 0 0
MRD Prognostic Impact by ELN 2024 Risk Group (OS, LIT, Adverse)
MRD Negative
MRD Positive
Log-rank p = 0.036
Probability of OS
Months
Number at risk
65 50 35 23 17 11 9 7 7 2 0 0 0
90 65 42 25 18 11 6 5 5 3 1 1 0
MRD Prognostic Impact by ELN 2024 Risk Group (RFS, LIT, Fav-Interm.)
MRD Negative
MRD Positive
Log-rank p = 0.401
Probability of RFS
Months
Number at risk
63 42 28 25 22 18 14 9 7 4 1 1 0
39 23 16 12 10 10 8 7 3 2 1 0 0
MRD Prognostic Impact by ELN 2024 Risk Group (OS, LIT, Fav-Interm.)
MRD Negative
MRD Positive
Log-rank p = 0.757
Probability of OS
Months
Number at risk
63 49 37 26 26 22 17 12 7 5 1 1 0
39 28 22 18 10 10 9 9 7 2 1 1 1
F
MRD Prognostic Impact by ELN 2022 Risk Group (RFS, IT, Adverse)
MRD Negative
MRD Positive
Log-rank p = 0.128
Probability of RFS
Months
Number at risk
20 11 10 7 4 3 2 2 0 0 0 0 0
14 6 1 0 0 0 0 0 0 0 0 0 0
MRD Prognostic Impact by ELN 2022 Risk Group (OS, IT, Adverse)
MRD Negative
MRD Positive
Log-rank p = 0.221
Probability of OS
Months
Number at risk
20 15 13 9 6 4 2 2 0 0 0 0 0
14 11 8 3 2 2 2 2 1 1 1 1 0
MRD Prognostic Impact by ELN 2022 Risk Group (RFS, IT, Fav-Interm.)
MRD Negative
MRD Positive
Log-rank p = 0.911
Probability of RFS
Months
Number at risk
52 30 23 19 15 12 7 6 4 2 1 0 0
19 13 9 7 5 4 4 3 1 0 0 0 0
MRD Prognostic Impact by ELN 2022 Risk Group (OS, IT, Fav-Interm.)
MRD Negative
MRD Positive
Log-rank p = 0.838
Probability of OS
Months
Number at risk
52 35 28 22 17 14 9 7 7 3 2 0 0
19 14 11 8 6 5 5 4 1 1 0 0 0

Figure 1S

Table 2S. Treatment Regimens by Intensity

Regimen	n	%
Intensive therapy (IT), n = 105		
Cladribine-based (CLIA)		
CLIA + venetoclax	30	28.6
CLIA (no venetoclax)	23	21.9
CLIA + FLT3 inhibitor (no venetoclax)	14	13.3
CLIA + Mylotarg (gemtuzumab ozogamicin) ± venetoclax	2	1.9
FLAG-Ida-based		
FLAG-Ida + venetoclax	23	21.9
Anthracycline + cytarabine (3+7 / IA)-based		
3+7 + targeted agent (IDH or FLT3 inhibitor)	6	5.7
Idarubicin + cytarabine + nivolumab	2	1.9
Liposomal anthracycline (CPX-351)-based		
CPX-351 + venetoclax	2	1.9
CPX-351 + IDH inhibitor	1	1.0
Other	2	1.9
Lower-intensity therapy (LIT), n = 257		
HMA + venetoclax (standard)		
HMA (azacitidine or decitabine/oral decitabine) + venetoclax	78	30.4
Cladribine + LDAC + venetoclax	60	23.3
HMA + venetoclax + novel/targeted agent		
HMA + venetoclax + FLT3 inhibitor	15	5.8
HMA + anti-CD47 antibody (magrolimab or Hu5F9) ± venetoclax	20	7.8
HMA + venetoclax + pevonedistat	5	1.9
HMA + venetoclax + IDH inhibitor	4	1.6
HMA + nivolumab ± venetoclax	2	0.8
HMA + other investigational agent	7	2.7
HMA or cladribine-based (no venetoclax)		
Cladribine + LDAC	23	8.9
HMA (azacitidine or decitabine) alone	10	3.9
Guadecitabine (SGI-110) ± idarubicin	5	1.9
HMA + IDH inhibitor	13	5.1
HMA + FLT3 inhibitor	4	1.6
Other	11	4.3

Abbreviations: IT – intensive therapy; LIT – lower-intensity therapy; HMA – hypomethylating agent; LDAC – low-dose cytarabine; CLIA – cladribine + idarubicin + cytarabine; FLAG-Ida – fludarabine + cytarabine + G-CSF + idarubicin; CPX-351 – liposomal daunorubicin/cytarabine

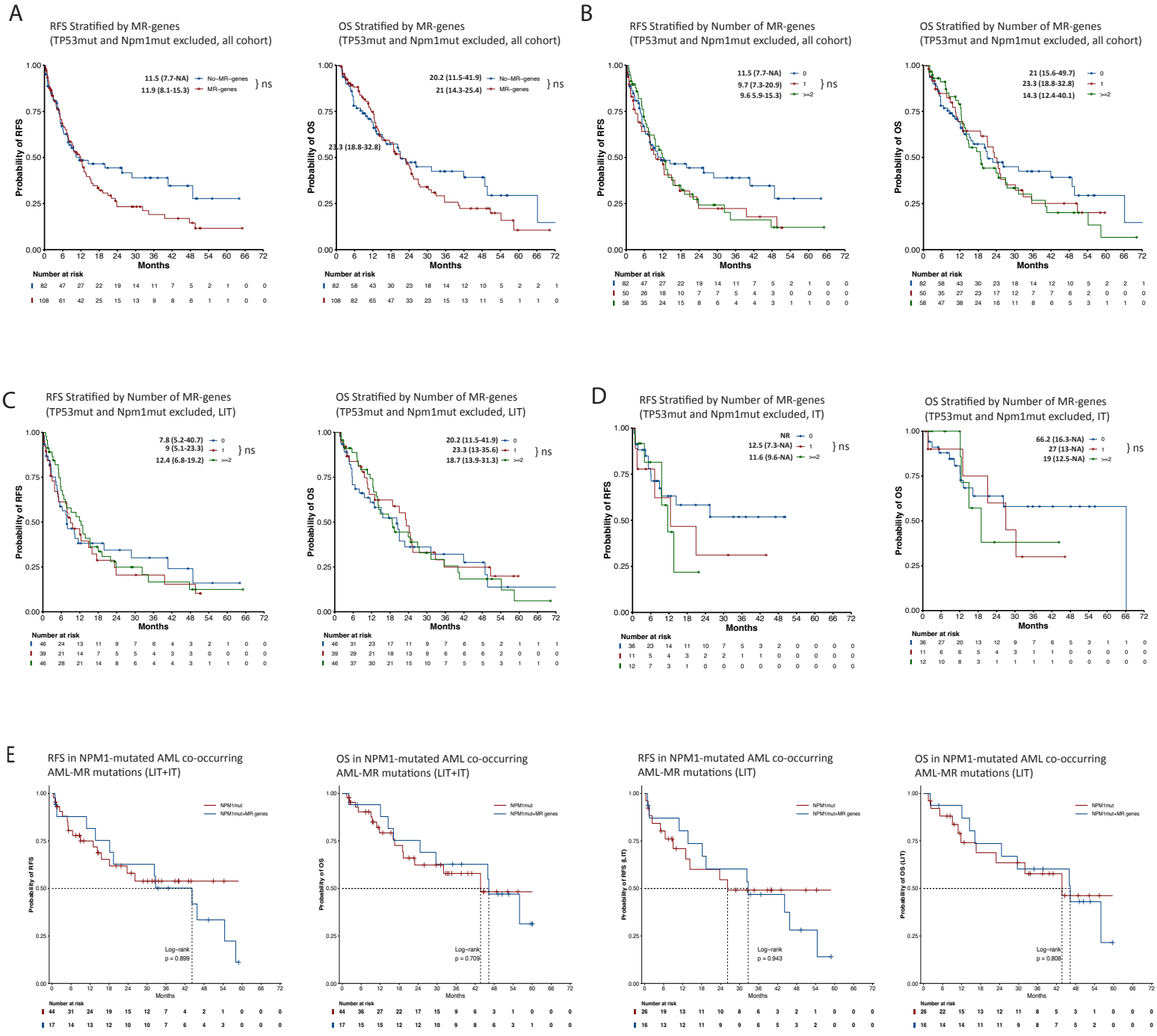

A
RFS Stratified by MR-genes
(TP53mut and Npm1mut excluded, all cohort)
11.5 (7.7-NA)
11.9 (8.1-15.3)
No−MR−genes
MR−genes
} ns
Probability of RFS
Months
Number at risk
OS Stratified by MR-genes
(TP53mut and Npm1mut excluded, all cohort)
20.2 (11.5-41.9)
21 (14.3-25.4)
23.3 (18.8-32.8)
Probability of OS
B
RFS Stratified by Number of MR-genes
(TP53mut and Npm1mut excluded, all cohort)
11.5 (7.7-NA)
9.7 (7.3-20.9)
9.6 5.9-15.3)
OS Stratified by Number of MR-genes
(TP53mut and Npm1mut excluded, all cohort)
21 (15.6-49.7)
23.3 (18.8-32.8)
14.3 (12.4-40.1)
C
RFS Stratified by Number of MR-genes
(TP53mut and Npm1mut excluded, LIT)
7.8 (5.2-40.7)
9 (5.1-23.3)
12.4 (6.8-19.2)
OS Stratified by Number of MR-genes
(TP53mut and Npm1mut excluded, LIT)
20.2 (11.5-41.9)
23.3 (13-35.6)
18.7 (13.9-31.3)
D
RFS Stratified by Number of MR-genes
(TP53mut and Npm1mut excluded, IT)
NR
12.5 (7.3-NA)
11.6 (9.6-NA)
OS Stratified by Number of MR-genes
(TP53mut and Npm1mut excluded, IT)
66.2 (16.3-NA)
27 (13-NA)
19 (12.5-NA)
E
RFS in NPM1-mutated AML co-occurring
AML-MR mutations (LIT+IT)
NPM1mut
NPM1mut+MR genes
Log−rank
p = 0.899
OS in NPM1-mutated AML co-occurring
AML-MR mutations (LIT+IT)
Log−rank
p = 0.709
RFS in NPM1-mutated AML co-occurring
AML-MR mutations (LIT)
Probability of RFS (LIT)
Log−rank
p = 0.943
OS in NPM1-mutated AML co-occurring
AML-MR mutations (LIT)
Probability of OS (LIT)
Log−rank
p = 0.808

Figure 2S

Table 3S. Cumulative Incidence of Relapse and Death, by Group

Cohort[1]	Stratifier	Group	Relapse (%)[2]				Death (%)[2]				p-value (Relapse)	Sig.[3]	p-value (Death)	Sig.[3]
			12m	24m	36m	48m	12m	24m	36m	48m				
All	Tx Intensity	IT	34.4	49.3	49.3	49.3	6.7	6.7	10.1	10.1	6e-04	***	0.1059	ns
All	Tx Intensity	IT+Ven	15.9	27.2	27.2	27.2	19.8	23.4	23.4	23.4	6e-04	***	0.1059	ns
All	Tx Intensity	LIT	55.6	68.2	68.2	71.9	20.9	20.9	22.7	22.7	6e-04	***	0.1059	ns
All	Tx Intensity	LIT+Ven	34.9	45.2	49.5	51.9	17.4	23.6	24.5	27.1	6e-04	***	0.1059	ns
IT	Age Group	60 and Above	25.4	43.9	43.9	43.9	12.8	12.8	12.8	12.8	0.7545	ns	0.6571	ns
IT	Age Group	Below 60	25.3	36.4	36.4	36.4	13.6	15.8	19.0	19.0	0.7545	ns	0.6571	ns
IT	Karyotype	CK	63.6	72.7	72.7	NA	9.1	9.1	9.1	NA	2e-04	***	0.7281	ns
IT	Karyotype	Diploid	16.9	27.8	27.8	27.8	16.6	16.6	20.3	20.3	2e-04	***	0.7281	ns
IT	Karyotype	Other	27.1	47.3	47.3	47.3	9.6	16.1	16.1	16.1	2e-04	***	0.7281	ns
IT	ELN 2022	Adverse	47.2	65.9	65.9	NA	7.3	7.3	7.3	NA	2e-04	***	0.0562	ns
IT	ELN 2022	Favorable	14.3	21.1	21.1	21.1	4.5	11.3	11.3	11.3	2e-04	***	0.0562	ns
IT	ELN 2022	Intermediate	14.3	26.6	26.6	26.6	23.0	23.0	28.0	28.0	2e-04	***	0.0562	ns
IT	MRD Status	Negative	20.2	34.4	34.4	34.4	10.8	13.1	16.2	16.2	0.2551	ns	0.7433	ns
IT	MRD Status	Positive	35.9	47.3	47.3	47.3	18.7	18.7	18.7	18.7	0.2551	ns	0.7433	ns
LIT	Karyotype	CK	67.5	81.5	81.5	NA	11.5	13.4	15.9	NA	5.77e-08	***	0.0518	ns
LIT	Karyotype	Diploid	23.6	37.6	44.2	49.1	14.1	19.6	19.6	22.5	5.77e-08	***	0.0518	ns
LIT	Karyotype	Other	37.4	43.9	45.4	49.5	27.8	33.2	34.7	34.7	5.77e-08	***	0.0518	ns
LIT	ELN 2024	Favorable	31.7	41.9	47.6	51.4	15.7	21.2	22.7	22.7	2.09e-07	***	0.3111	ns
LIT	ELN 2024	Intermediate	29.9	41.8	43.8	47.8	25.0	30.5	30.5	36.4	2.09e-07	***	0.3111	ns
LIT	ELN 2024	Adverse	67.7	78.8	78.8	NA	15.6	17.5	19.3	NA	2.09e-07	***	0.3111	ns
LIT	MRD Status	Negative	29.8	38.4	43.4	46.7	19.8	25.3	26.5	30.3	7.95e-05	***	0.1831	ns
LIT	MRD Status	Positive	50.4	63.3	64.5	68.3	16.7	20.4	21.6	21.6	7.95e-05	***	0.1831	ns
LIT	TP53 status	TP53mut	67.7	78.8	78.8	NA	15.6	17.5	19.3	NA	3.06e-08	***	0.3505	ns
LIT	TP53 status	TP53wt	31.1	42.0	46.1	49.8	19.2	24.7	25.5	27.9	3.06e-08	***	0.3505	ns

[1] IT: Intensive Therapy; LIT: Low Intensity Therapy. [2] Values represent cumulative incidence percentages at each time point. [3] Significance codes: *** p<0.001, ** p<0.01, * p<0.05, ns: not significant.

Table 4S. Cox Proportional Hazards Regression Analysis (RFS, LIT)

	Univariate			Multivariate	
Parameter	**HR**	**95% CI**	**p-value**	**HR**	**p-value**
TP53 mut vs WT	**3.61**	**2.40–5.43**	**<0.001**	**2.52**	**0.009**
CK vs diploid	**3.28**	**2.09–5.17**	**<0.001**	—	—
Other karyo vs diploid	**1.82**	**1.21–2.73**	**0.0041**	—	—
Age <60 vs above 60	1.14	0.47–2.80	0.771	—	—
ELN 2024 – Intermediate vs Favorable	**1.58**	**1.04–2.38**	**0.0309**	—	—
ELN 2024 – Adverse vs Favorable	**4.30**	**2.75–6.72**	**<0.001**	**1.57**	**0.032**
MRD pos vs neg	**1.59**	**1.13–2.25**	**0.0078**	**1.42**	**0.05**

Bold values indicate p ≤ 0.05

Abbreviations: CK – complex karyotype; Other – non-CK and not diploid; LIT – lower intensity therapy; RFS – relapse-free survival

Table 5S. Cox Proportional Hazards Regression Analysis (OS, LIT)

	Univariate			Multivariate	
Parameter	**HR**	**95% CI**	**p-value**	**HR**	**p-value**
TP53 mut vs WT	**3.82**	**2.52–5.79**	**<0.001**	**2.72**	**0.0091**
CK vs diploid	**3.13**	**1.98–4.95**	**<0.001**	—	—
Other karyo vs diploid	1.47	0.96–2.24	0.0729	—	—
Age <60 vs above 60	1.14	0.46–2.79	0.781	—	—
ELN 2024 – Intermediate vs Favorable	**1.83**	**1.20–2.81**	**0.0055**	—	—
ELN 2024 – Adverse vs Favorable	**4.90**	**3.08–7.80**	**<0.001**	**1.80**	**0.0074**
MRD pos vs neg	**1.52**	**1.06–2.17**	**0.0222**	—	—

Bold values indicate p ≤ 0.05

Abbreviations: CK – complex karyotype; Other – non-CK and not diploid; LIT – lower intensity therapy; OS – overall survival

Table 6S. Cox Proportional Hazards Regression Analysis (RFS, IT)

	Univariate			Multivariate		
Parameter	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age (per year)	1.01	0.99–1.03	0.453	—	—	—
ELN 2022 – Intermediate vs Favorable	1.75	0.73–4.20	0.207	1.70	0.70–4.08	0.239
ELN 2022 – Adverse vs Favorable	**3.26**	**1.37–7.78**	**0.008**	**2.93**	**1.20–7.13**	**0.018**
MRD pos vs neg	1.50	0.81–2.75	0.196	—	—	—
Ven vs standard	0.88	0.49–1.60	0.677	—	—	—
Other karyo vs diploid	**1.75**	**0.97–3.14**	**0.064**	1.46	0.80–2.67	0.222

Bold values indicate p ≤ 0.1 (univariate) and p ≤ 0.05 (multivariate). — = not included in multivariable model.

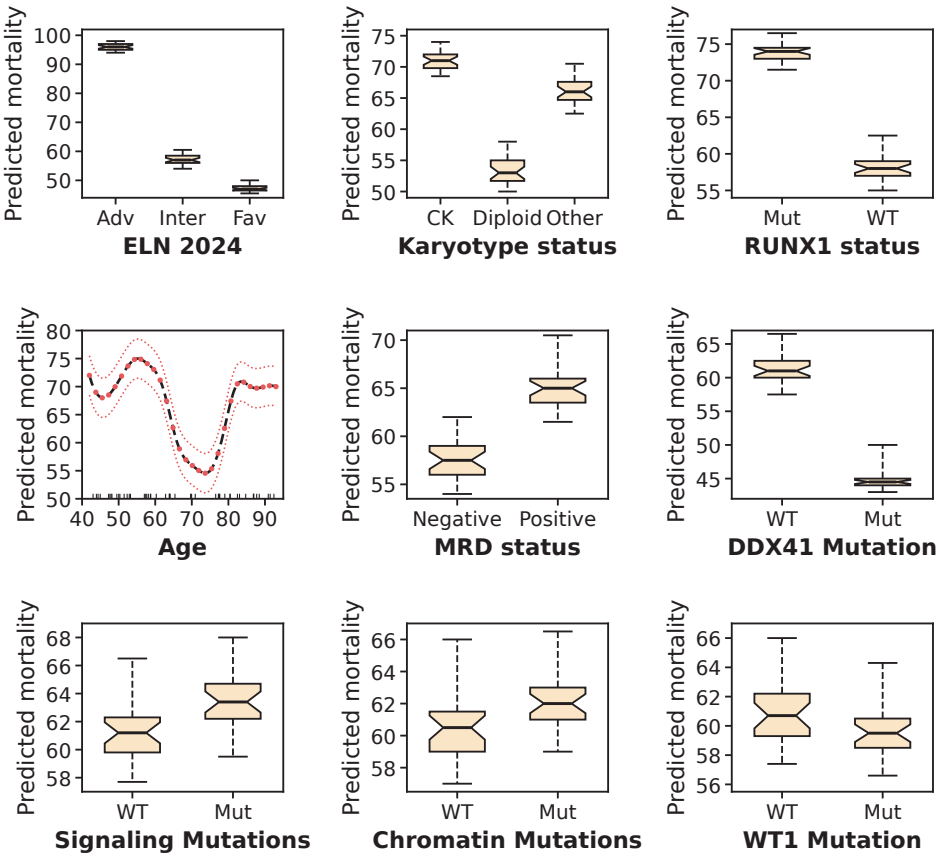
Abbreviations: CI – Confidence Interval; HR – Hazard Ratio; IT – intensive therapy; RFS – relapse-free survival; Other – non-CK and not diploid

Table 7S. Cox Proportional Hazards Regression (OS, IT)

	Univariate			Multivariate		
Parameter	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age (per year)	1.01	0.99–1.03	0.355	1.01	0.99–1.04	0.320
ELN 2022 – Intermediate vs Favorable	**2.51**	**0.93–6.77**	**0.069**	2.44	0.90–6.65	0.081
ELN 2022 – Adverse vs Favorable	**3.15**	**1.16–8.54**	**0.024**	**3.09**	**1.13–8.48**	**0.028**
MRD positive vs negative	1.37	0.72–2.60	0.340	1.19	0.62–2.28	0.605
Venetoclax vs standard	1.08	0.58–2.03	0.802	—	—	—
Other karyotype vs diploid	1.60	0.86–2.99	0.137	—	—	—

Bold values indicate p ≤ 0.1 (univariate) and p ≤ 0.05 (multivariate). — = not included in multivariable model. Multivariable model included Age, ELN 2022, and MRD status based on clinical relevance.

A


Predicted mortality
Adv
Inter
Fav
ELN 2024
CK
Diploid
Other
Karyotype status
Mut
WT
RUNX1 status
Age
Negative
Positive
MRD status
DDX41 Mutation
Signaling Mutations
Chromatin Mutations
WT1 Mutation

B

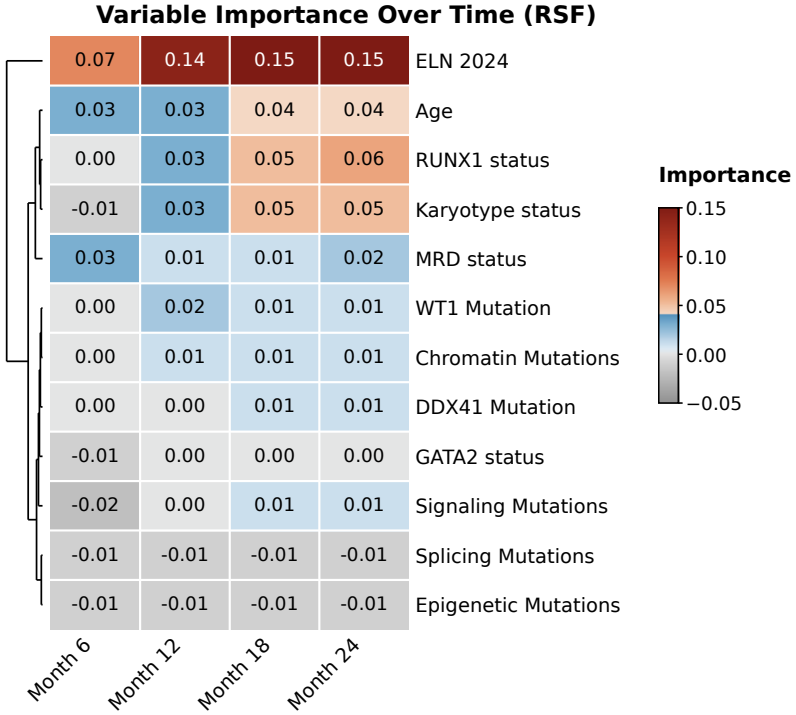

Variable Importance Over Time (RSF)
0.07 0.14 0.15 0.15 ELN 2024
0.03 0.03 0.04 0.04 Age
0.00 0.03 0.05 0.06 RUNX1 status
-0.01 0.03 0.05 0.05 Karyotype status
0.03 0.01 0.01 0.02 MRD status
0.00 0.02 0.01 0.01 WT1 Mutation
0.00 0.01 0.01 0.01 Chromatin Mutations
0.00 0.00 0.01 0.01 DDX41 Mutation
-0.01 0.00 0.00 0.00 GATA2 status
-0.02 0.00 0.01 0.01 Signaling Mutations
-0.01 -0.01 -0.01 -0.01 Splicing Mutations
-0.01 -0.01 -0.01 -0.01 Epigenetic Mutations
Month 6
Month 12
Month 18
Month 24
Importance
0.15
0.10
0.05
0.00
−0.05

Figure 3S

Supplementary Figure 1. Survival outcomes for the entire cohort stratified by age, karyotype, and MRD status. (A) Kaplan-Meier estimates of RFS (left) and OS (right) for the entire study cohort. (B) RFS (left) and OS (right) for the entire cohort, stratified by age group (<60 vs ≥60 years). (C) RFS (left) and OS (right) for the entire cohort, stratified by karyotype (diploid, other, complex karyotype). (D) RFS (left) and OS (right) for the entire cohort, stratified by MRD status. Median survival times and log-rank p-values are indicated on each panel. (E) Survival estimates of RFS and OS stratified by MRD status among LIT patients with ELN 2024 Adverse risk and Favorable/Intermediate risk. (F) Survival estimates of RFS and OS stratified by MRD status among IT patients with ELN 2022 Adverse risk and Favorable/Intermediate risk.

Abbreviations: RFS, relapse-free survival; OS, overall survival; MRD, measurable residual disease; CK, complex karyotype.

Supplementary Figure 2. Survival outcomes stratified by myelodysplasia-related gene mutations. (A) RFS (left) and OS (right) for the entire cohort, stratified by the presence or absence of MR-gene mutations (TP53-mutant and NPM1-mutant patients excluded). (B) RFS (left) and OS (right) for the entire cohort, stratified by the number of MR-gene mutations (0, 1, ≥2; TP53-mutant and NPM1-mutant patients excluded). (C) RFS (left) and OS (right) among LIT patients, stratified by the number of MR-gene mutations. (D) RFS (left) and OS (right) among IT patients, stratified by the number of MR-gene mutations. Median survival times are indicated on each panel.

Abbreviations: RFS, relapse-free survival; OS, overall survival; MR, myelodysplasia-related; IT, intensive therapy; LIT, lower-intensity therapy.

Supplementary Figure 3. Random survival forest analysis and multivariable modeling of relapse-free survival predictors in venetoclax-based LIT. (A) Partial dependence plots showing the relationship between individual predictors and predicted mortality. (B) Time-dependent variable importance heatmap displaying the predictive contribution of each variable at 6, 12, 18, and 24 months.