Long-term outcomes in *FLT3*-mutated acute myeloid leukemia after frontline hypomethylating agent, venetoclax and a FLT3 inhibitor

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Abstract

Triplet regimens with a hypomethylating agent, venetoclax and a FLT3 inhibitor yield high rates of response in newly diagnosed *FLT3*-mutated acute myeloid leukemia (AML). However, the long-term outcomes and patterns of relapse with these triplet regimens are not well-established. In this retrospective analysis, 73 patients with newly diagnosed *FLT3*-mutated AML received a frontline FLT3 inhibitor-containing triplet regimen. The composite complete remission and complete remission with incomplete hematologic recovery rate was 93%. According to next-generation sequencing (sensitivity: 0.005%), *FLT3*-ITD minimal residual disease negativity was achieved in 60% of patients after cycle 2 and 90% after cycle 4. The estimated 3-year relapse-free survival for *FLT3*-ITD-mutated and *FLT3* TKD-mutated AML was 38% and 76%, respectively, and the 3-year overall survival (OS) was 45% and 76%, respectively. Neither age, *NPM1* co-mutation, European LeukemiaNet 2022 risk category, nor allogeneic stem cell transplantation in first remission significantly impacted OS. Baseline RAS pathway mutations were associated with poor long-term survival (3-year OS 22% *vs*. 63% in those without a RAS pathway mutation). *FLT3* wild-type relapses accounted for 65% of relapses, and new RAS pathway mutations were observed in 24% of relapses. Outcomes were poor after relapse (median OS of 6.1 months), particularly for those with persistently detectable *FLT3* mutations. Triplet combinations of a hypomethylating agent, venetoclax and a FLT3 inhibitor result in durable remission and encouraging long-term OS in older adults with newly diagnosed *FLT3*-mutated AML. However, better strategies to prevent *FLT3* wild-type relapses and to overcome RAS pathway-mediated resistance are still needed.

Introduction

In older patients with acute myeloid leukemia (AML) who are unfit for intensive chemotherapy, the standard-of-care frontline regimen is a hypomethylating agent (HMA) plus venetoclax.[1] While this regimen significantly improves response rates and overall survival (OS) as compared with azacitidine alone, some molecular features predict for lesser benefit with the HMA plus venetoclax regimen. The presence of *FLT3*-internal tandem duplications (ITD), *NRAS*, *KRAS*, and/or *TP53* mutations has been shown to be associated with both primary and secondary resistance to this regimen.[2,3] In a subgroup analysis of the VIALE-A trial, patients with *FLT3*-ITD-mutated AML did not appear to derive significant clinical benefit from the addition of venetoclax to azacitidine, and the median OS in this population was approximately 10 months.[2] These relapses are largely driven by expansion of the *FLT3*-ITD-mutated subclone.[3] While "doublet" therapies evaluating an HMA plus a FLT3 inhibitor have been explored, the durability of remissions with these regimens is modest.[4-7] In a randomized phase III trial, azacitidine plus gilteritinib resulted in higher response rates as compared with azacitidine alone in older adults with newly diagnosed *FLT3*-mutated AML but did not significantly improve OS.[7] To overcome the observed *FLT3*-mediated resistance to an HMA plus venetoclax, novel "triplet" regimens consist-

ing of an HMA, venetoclax and a FLT3 inhibitor have been developed.[4] In a phase I/II study of azacitidine, venetoclax and gilteritinib in older adults with *FLT3*-mutated AML, the composite complete remission (CR) and CR with incomplete hematologic recovery (CRi) rate was 96%, and the estimated 18-month OS was 72%, which compares favorably to historical expectations with azacitidine plus venetoclax in *FLT3*-mutated AML.[8] In a similar study of frontline decitabine, venetoclax and quizartinib, the CR/CRi rate was 92%, and the median OS had not yet been reached.[9] However, despite these encouraging early data, the follow-up is limited, and the long-term efficacy of these regimens is therefore not well-established. The predictors of long-term outcomes and mechanisms of relapse with these novel FLT3 inhibitor-containing triplet regimens have also not been comprehensively evaluated.

Methods

Study design and participants

We retrospectively evaluated the long-term outcomes and patterns of relapse in adults with newly diagnosed *FLT3*-mutated AML who received a triplet regimen consisting of an HMA, venetoclax and a FLT3 inhibitor. Only patients with *FLT3*-ITD or *FLT3*-tyrosine kinase domain (TKD) mutations (e.g., D835/D836) with variant allelic frequency (VAF) ≥1% were included in this analysis. All patients were treated on prospective clinical trials (NCT03404193, NCT03661307, NCT04140487, NCT05010122 and NCT05520567). The details of the specific treatment regimens have been previously published.[8-12] This study was conducted at a single academic center (The University of Texas MD Anderson Cancer Center [UTMDACC]). This study was approved by the Institutional Review Board of UTMDACC and was conducted in accordance with the Declaration of Helsinki.

Baseline molecular testing

Mutational analysis was prospectively performed at diagnosis and at relapse using an 81-gene next-generation sequencing (NGS) panel, with a sensitivity of 2% VAF (*Online Supplementary Table S1*).[13,14] Multiplex polymerase chain reaction (PCR) for *FLT3*-ITD or the *FLT3* kinase domain (D835/D836), which has a sensitivity of 1%, was performed at diagnosis and relapse.

Response and outcomes definitions

Responses were determined according to the European LeukemiaNet (ELN) 2022 guidelines.[15] Multiparameter flow cytometry with a sensitivity of 0.1-0.01% was performed on bone marrow samples for measurable residual disease (MRD) assessment.[16,17] Error-corrected NGS-based MRD assessment for *FLT3*-ITD was retrospectively performed on bone marrow samples. Molecular barcode-tagged primers were utilized to perform PCR amplification for the detection of the *FLT3*-ITD. Bidirectional paired-end NGS of the PCR products was performed on an Illumina MiSeq Sequencer. The genomic reference sequence used was genome GRCh37/hg19. Illumina Experiment Manager 1.19.1, MiSeq Control Software 4.1.0.656, Sequence Analysis Viewer 2.4.7, MiSeq Reporter 2.5.1, Invivoscribe dockerized MRD software (Invivoscribe®, San Diego, CA) were utilized in the experimental setup and data analysis. This assay has an analytical sensitivity of 5×10^{-5} mutant alleles per total alleles (VAF 0.005%). The analytical sensitivity of this assay was validated for an ITD length of 30 bp. While the maximum ITD length detectable by this assay is 252 bp, the detectable size and sensitivity vary depending on the insertion location and sequence of the ITD. NGS MRD negativity was defined as *FLT3*-ITD <0.005%. Relapse-free survival (RFS) was calculated from time of response until relapse or death, censored if alive at last follow-up. OS was calculated from time of treatment initiation until death, censored if alive at last follow-up.

Statistical methods

The patients' characteristics were summarized using the median (range) for continuous variables and frequencies (percentages) for categorical variables. To compare two groups with continuous variables, the Wilcoxon rank-sum test was performed. The Kaplan-Meier method was used to estimate the probabilities of RFS and OS and differences between groups were evaluated with the log-rank test. All statistical analyses were performed using GraphPad Prism 9.

Results

Baseline characteristics

The baseline characteristics of the study population (N=73) are shown in Table 1. The median age was 70 years (range, 18-88 years), and 26 patients (36%) were ≥75 years of age. Fifty-eight patients (80%) had only a *FLT3*-ITD mutation, 14 patients (19%) had only a *FLT3*-TKD mutation, and one patient (1%) had both *FLT3*-ITD and TKD mutations. The most common FLT3 inhibitors used were gilteritinib (N=49, 67%) and quizartinib (N=18, 25%). Patients with *FLT3*-TKD-mutated AML only received gilteritinib (N=13) or midostaurin (N=1). The median *FLT3* VAF for ITD mutations was 23% (range, 1-80%) and for TKD mutations was 19% (range, 2-57%). The most common co-mutations were *DNMT3A* and *NPM1*, present in 47% of patients each. A RAS pathway mutation (defined as *KRAS*, *NRAS*, *PTPN11*, *CBL*, *NF1* and/or *BRAF*) was detected in 19 patients (26%). The rate of RAS pathway mutations in *FLT3*-ITD and *FLT3*-TKD-mutated AML was similar (25% [15/59] and 29% [4/14], respectively).

Dose intensity

The median number of cycles received was 3 (range, 1-36 cycles). The median durations of the HMA, venetoclax and FLT3 inhibitor in cycle 1 were 7 days (range, 2-10 days), 14 days

(range, 2-28 days), and 14 days (range, 2-28 days), respectively. In cycle 4, the median durations were 5 days (range, 2-5 days), 7 days (range, 3-21 days), and 21 days (range, 7-28 days), respectively. Granulocyte-colony stimulating factor was given to 58% of responders (42/72) in cycle 1 and to 36% (10/28) in cycle 4.

Response rates

Sixty-nine patients (82%) achieved CR and eight patients (11%) achieved CRi, for a CR/CRi rate of 93%. (*Online Supplementary Table S2*). An additional four patients (6%) achieved a morphological leukemia-free state. There was one early death. Among 59 evaluable responders, 48 (81%) achieved MRD negativity by multiparameter flow cytometry as their best response. Multiparameter flow cytometry MRD negativity was achieved in 48% (20/42) after cycle 1, 63% (19/30) after cycle 2, 70% (14/20) after cycle 3, and 69% (9/13) after cycle 4. Among *FLT3*-ITD-mutated patients, *FLT3* NGS MRD negativity at 0.005% sensitivity was achieved in 6% (1/17) after cycle 1, 60% (11/17) after cycle 2, 82% (9/11) after cycle 3, and 90% (9/10) after cycle 4. Rates of *FLT3*-ITD NGS MRD negativity after each cycle and cumulatively are shown in Figure 1.

Disposition

The disposition of the 73 patients is shown in *Online Supplementary Figure S1*. Among the 72 responders, 30 (42%) underwent allogeneic stem cell transplant (alloSCT) in first remission at a median of 4.5 months after the start of treatment and after a median of 3 cycles of protocol therapy. Among the 30 transplanted patients, 12 subsequently died (6 from alloSCT-related complications and 6 due to relapsed AML) and the remaining are alive and in remission at last follow-up. Seventeen transplanted patients (57%) received a post-alloSCT FLT3 inhibitor. Thirteen patients (18%) relapsed in the absence of alloSCT, six (8%) died in remission (3 from infection, 2 from unknown causes, and 1 from aortic dissection), and 23 (32%) are in ongoing remission without alloSCT.

Survival outcomes

The median follow-up was 26 months (range, 1-56 months). For the entire cohort, the median RFS and OS were 28.8 months and 38.5 months, respectively, and the estimated 3-year RFS and OS rates were 46% and 52%, respectively (*Online Supplementary Figure S2*). For patients with a *FLT3*-ITD mutation, the median RFS and OS were 16.7 months and 28.1 months, respectively, and the 3-year RFS and OS rates were 38% and 45%, respectively (Figure 2A, B). For patients with *FLT3*-TKD mutation only, the median RFS and OS were 36.6 months and 39.3 months, respectively, and the 3-year RFS and OS rates were both 76% (Figure 2A, B).

Table 1. Baseline characteristics of the study population.

Characteristic, N=73	Values
Age, years	
Median (range)	70 (18-88)
≥75 years, N (%)	26 (36)
Cytogenetics, N (%)	
Diploid	36 (49)
Adverse	10 (14)
Others	22 (30)
Insufficient	5 (7)
ELN 2022 risk stratification, N (%)	
Favorable	9 (12)
Intermediate	28 (38)
Adverse	36 (49)
FLT3 subtype, N (%)	
ITD	58 (80)
TKD	14 (19)
ITD+TKD	1 (1)
FLT3 VAF, median (range)	
ITD	23 (1-80)
TKD	19 (2-57)
FLT3 inhibitor, N (%)	
Gilteritinib	49 (67)
Quizartinib	18 (25)
Sorafenib	5 (7)
Midostaurin	1 (1)
Hypomethylating agent, N (%)	
Azacitidine	35 (48)
Decitabine	38 (52)
Non-*FLT3* mutations, N (%)†	
DNMT3A	34 (47)
NPM1	34 (47)
RUNX1	18 (25)
TET2	15 (21)
WT1	15 (21)
IDH2	12 (16)
BCOR	10 (14)
SRSF2	7 (10)
CEBPA	6 (8)
PTPN11	6 (8)
U2AF1	6 (8)
ASXL1	5 (7)
BCORL1	5 (7)
IDH1	5 (7)
NRAS	5 (7)
RAD21	5 (7)
SF3B1	5 (7)
STAG2	5 (7)
SMC1A	4 (5)
RAS pathway mutation*, N (%)	19 (26)

†Mutations detected in ≥5% of patients. *Includes *KRAS*, *NRAS*, *PTPN11*, *CBL*, *NF1* and/or *BRAF* mutations. ELN: European LeukemiaNet; ITD: internal tandem duplication; TKD: tyrosine kinase domain; VAF: variant allele frequency.

Predictors of survival

When stratified by age <75 *versus* ≥75 years, outcomes were similar (3-year OS: 53% and 49%, respectively; *P*=0.99) (*Online Supplementary Figure S3*). Age also did not impact outcomes in either the *FLT3*-ITD or *FLT3*-TKD-mutated subgroups (<75 *vs*. ≥75 years; *P*=0.73 for ITD and *P*=0.43 for TKD) (*Online Supplementary Figure S4*). Neither *NPM1* co-mutation status nor ELN 2022 risk stratification impacted OS (*P*=0.85 for *NPM1* mutated *vs*. wild-type; *P*=0.91 for adverse *vs*. favorable/intermediate risk) (*Online Supplementary Figure S5*). Patients with *FLT3*-ITD, *NPM1*, and *DNMT3A* "triple" mutations had numerically worse OS than those who were *FLT3*-ITD and *NPM1*-mutated but *DNMT3A* wild-type (3-year OS: 36% *vs*. 66%, respectively; *P*=0.35), although this difference was not statistically significant (*Online Supplementary Figure S6*). The strongest predictor for survival outcomes was a baseline RAS pathway mutation. Presence of a baseline RAS pathway mutation was associated with a trend towards worse survival (3-year OS: 22% *vs*. 63% in those with no RAS pathway mutation; *P*=0.07) (Figure 3). RAS pathway mutations were associated with poor outcomes in both *FLT3*-ITD and *FLT3*-TKD-mutated AML (3-year OS of 15% and 38%, respectively).

A landmark analysis was performed to evaluate the impact of alloSCT in first remission. The baseline characteristics of the transplanted and non-transplanted groups are shown in *Online Supplementary Table S3*. As expected, patients who underwent alloSCT in first remission were significantly younger than those who did not undergo alloSCT (median age: 67 years *vs*. 72 years; *P*=0.001). The relapse rate in patients who underwent alloSCT was 20% *versus* 28% in those who did not undergo alloSCT (*P*=0.45). The rates of death in remission for patients who underwent alloSCT and those who did not were 20% and 13%, respectively (*P*=0.42). Survival outcomes were similar regardless of alloSCT consolidation (3-year OS: 55% for alloSCT *vs*. 61%

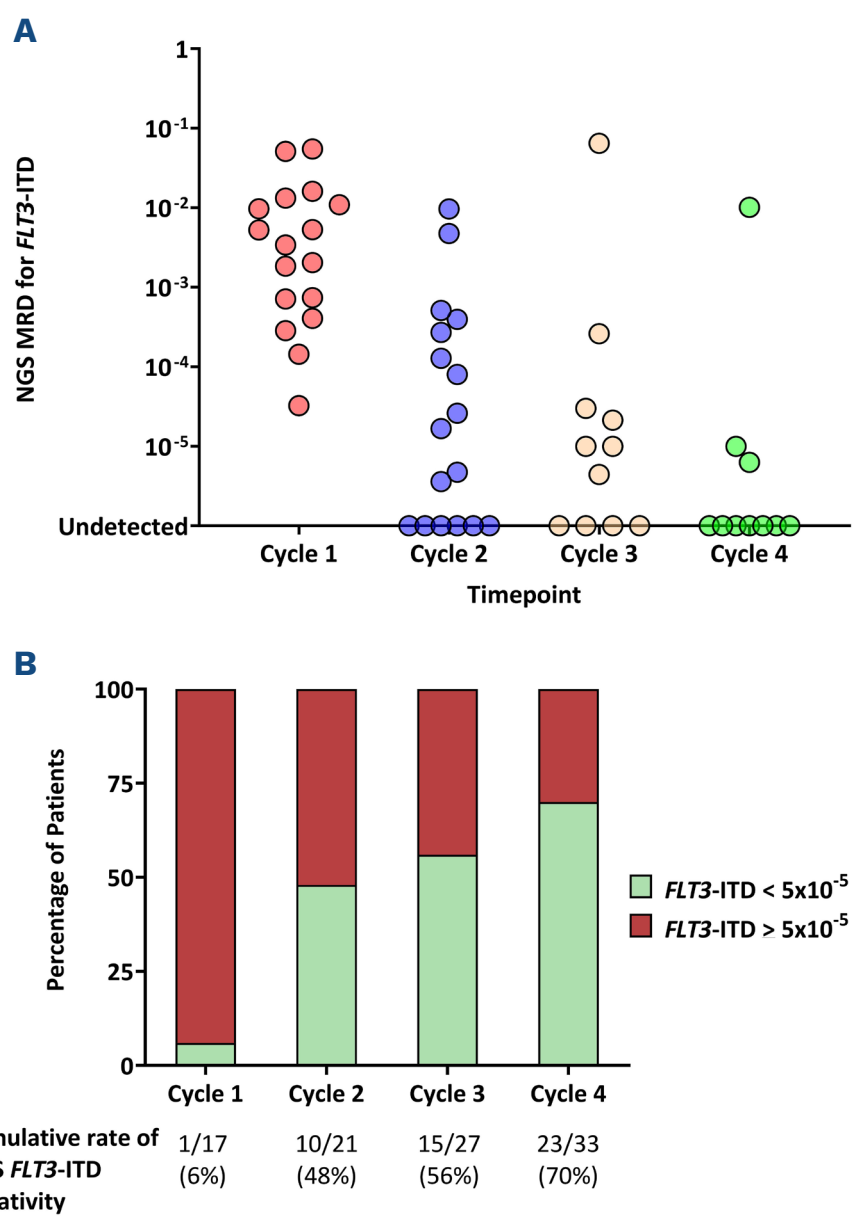

Figure 1. Measurable residual disease as determined by next-generation sequencing for the *FLT3*-ITD. Measurable residual disease (MRD) negativity was defined as *FLT3*-ITD <5x10^{-5} (0.005%). (A) MRD after cycles 1-4. (B) Cumulative rates of MRD negativity. NGS: next-generation sequencing; ITD: internal tandem duplication.

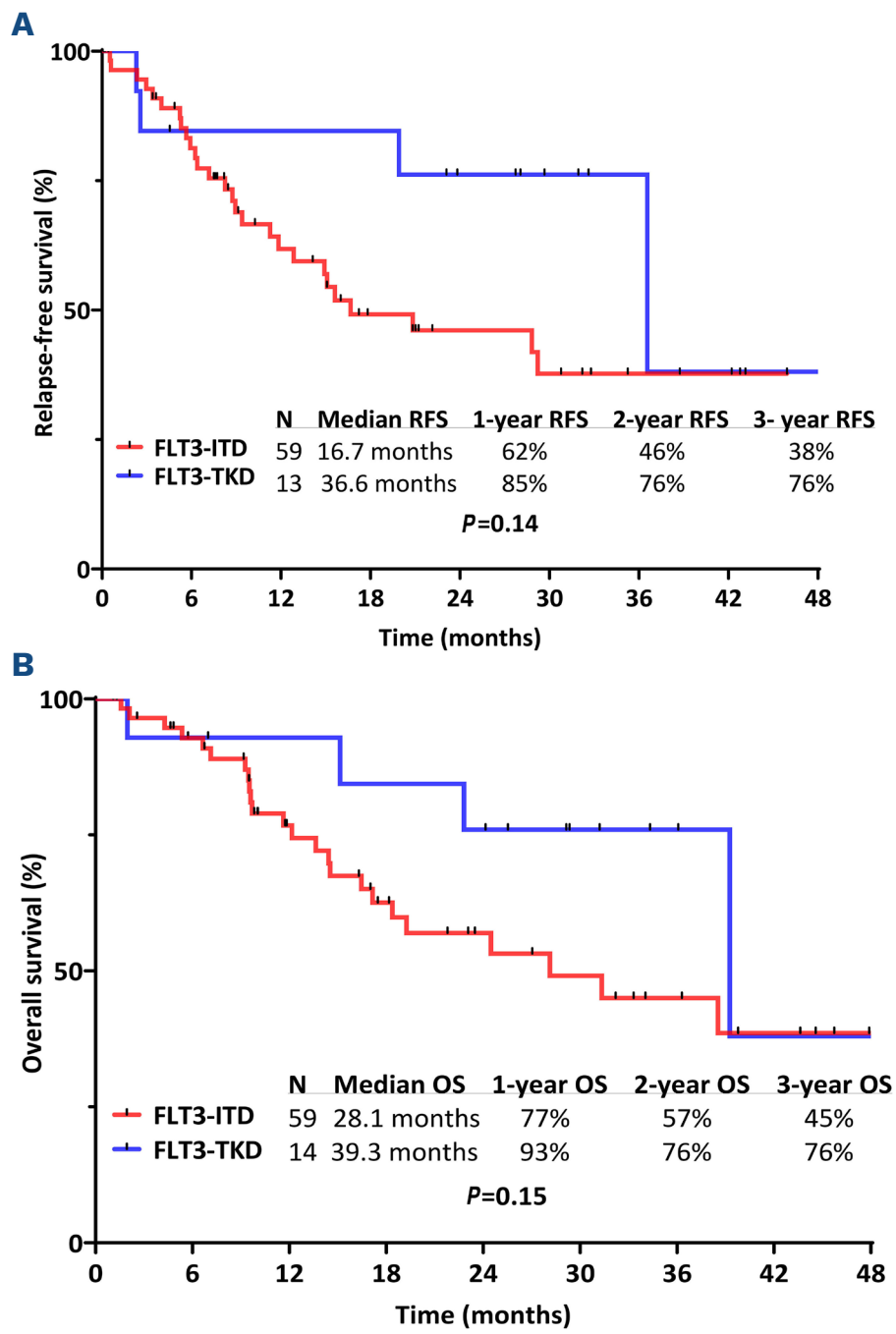

Figure 2. Outcomes by *FLT3* mutation subtype. (A) Relapse-free survival. (B) Overall survival. RFS: relapse-free survival; ITD: internal tandem duplication; TKD: tyrosine kinase domain; OS: overall survival.

for no alloSCT; *P*=0.49) (*Online Supplementary Figure S7*). Similarly, no impact of alloSCT was observed in patients <75 years of age (*P*=0.32), those with *FLT3*-ITD-mutated AML (*P*=0.71), nor in those with ELN 2022 adverse-risk disease (*P*=0.72) (*Online Supplementary Figures S8-10*). Among non-transplanted patients with *FLT3*-ITD-mutated AML, those who achieved high-sensitivity *FLT3* NGS MRD negativity by the end of cycle 4 had superior outcomes compared to those who remained MRD-positive (3-year OS: 61% *vs.* 0%, respectively; *P*=0.02) (Figure 4A, B). Among evaluable transplanted patients, three of four (75%) who were *FLT3* NGS MRD-positive prior to alloSCT subsequently relapsed, compared with two of 11 (18%) who were MRD-negative (*P*=0.04), although no difference in OS was observed. In transplanted patients, the number of cycles received prior to alloSCT (<3 *vs.* ≥3) did not have an impact on post-alloSCT relapse rates (15% *vs.* 24%, respectively; *P*=0.58).

Relapse characteristics

Overall, 19 patients relapsed (26% of responders), and the median duration of response in the relapsed patients was 9.4 months (range, 2.3-26.6 months). One relapse was only extramedullary (cerebrospinal fluid and skin). Seventeen patients underwent repeat cytogenetic and molecular sequencing at relapse to evaluate for clonal evolution. Using the *FLT3* PCR assay (sensitivity 1%), the *FLT3* mutation was no longer detected at relapse in 11 patients (65% of evaluable relapses), and these patients constitute the "*FLT3* wild-type relapse" group for subsequent analyses. The rate of *FLT3* wild-type relapse was similar in patients with pretreatment *FLT3*-ITD or *FLT3*-TKD mutations (62% [8/13] and 75% [3/4], respectively; *P*=0.62). To evaluate for the presence of low-level *FLT3*-mutated subclones in patients with *FLT3* wild-type relapse as assessed by conventional PCR, the high-sensitivity *FLT3*-ITD NGS MRD assay was retrospectively performed on seven relapse samples with available bone marrow material. In five of these relapse samples *FLT3*-ITD was undetectable with the high-sensitivity NGS MRD assay and two had low-level *FLT3*-ITD detected at 0.01% and <0.001% VAF.

Twelve of the 17 evaluable patients (71%) had new cytogenetic or molecular abnormalities at relapse (*Online Supplementary Table S4*). The most common newly emergent mutations detected at the time of relapse were RAS pathway mutations, which were identified in four patients (24%; *KRAS/NRAS*, N=2; *PTPN11*, N=1; *CBL*, N=1). The median VAF of these RAS pathway mutations was 14% (range, 4-37%). Other mutations newly detected at relapse included *GATA2* in three patients (18%), spliceosome mutations in two patients (12%; *SF3B1*, N=1; *ZRSR2*,

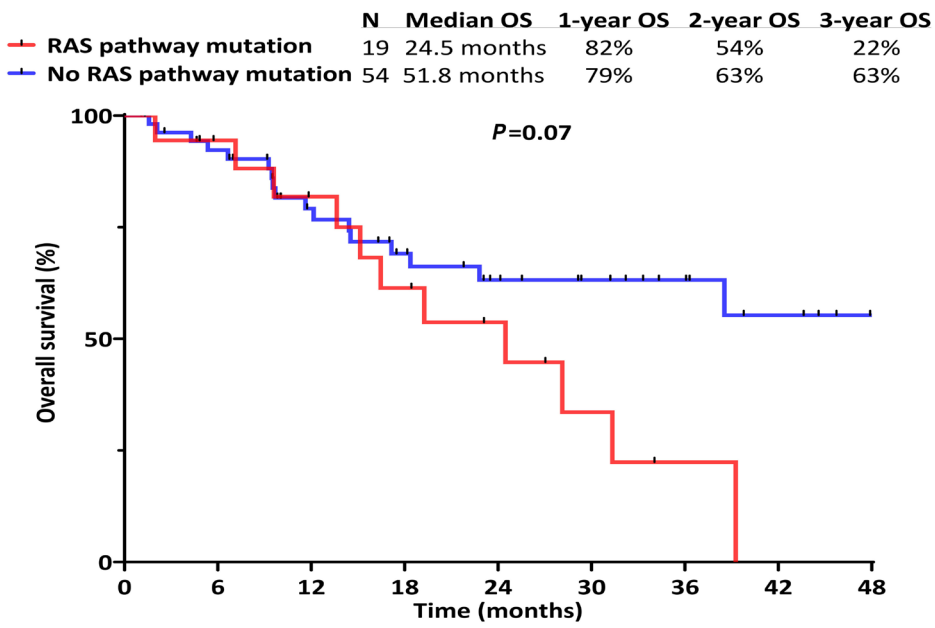

Figure 3. Overall survival by RAS pathway mutation status. OS: overall survival.

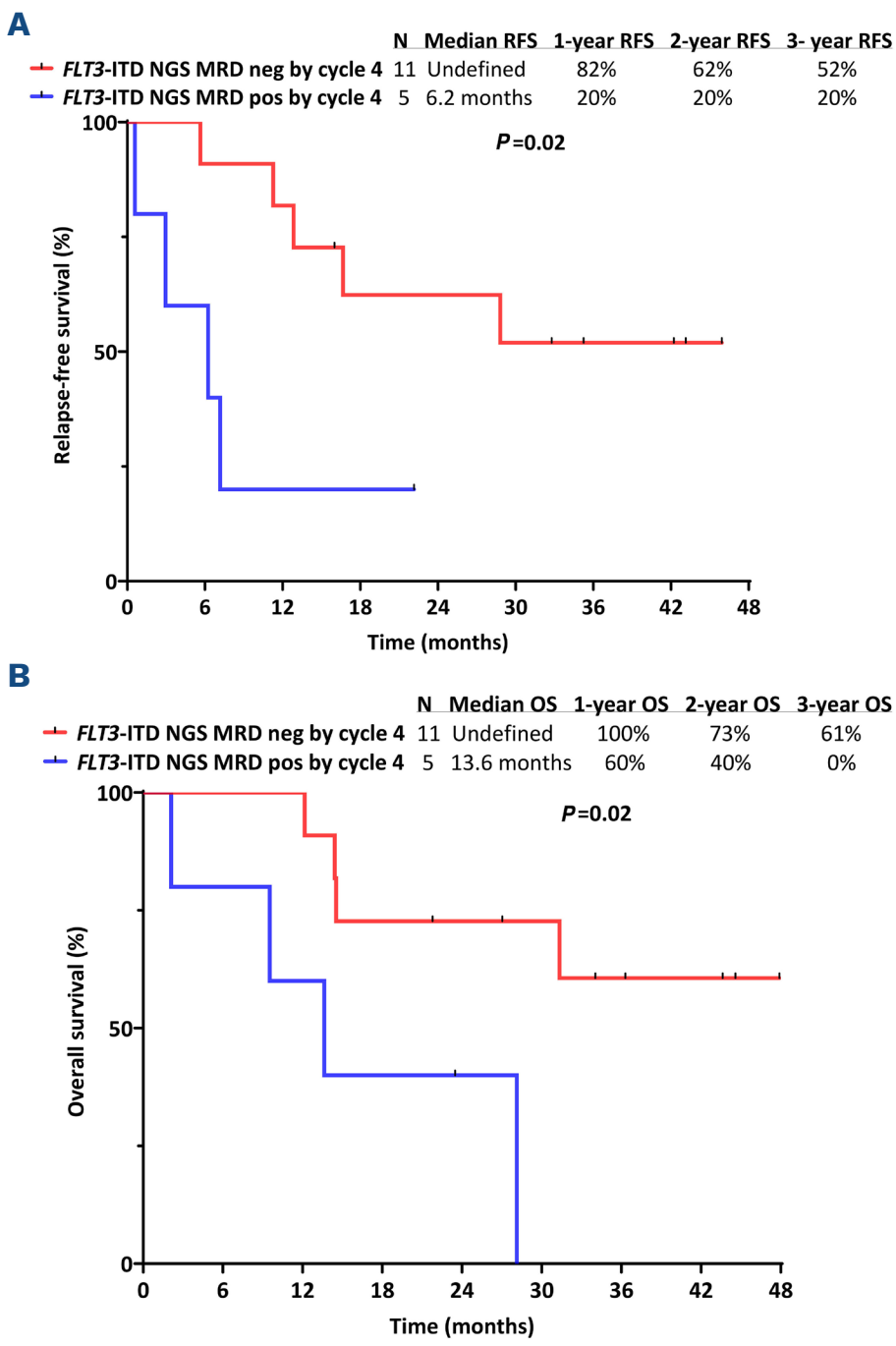

Figure 4. Outcomes of the study cohort stratified by *FLT3*-ITD measurable residual disease negativity, assessed by next-generation sequencing, within 4 cycles. Measurable residual disease negativity was defined as *FLT3*-ITD <5x10^{-5} (0.005%). (A) Relapse-free survival. (B) Overall survival. ITD: internal tandem duplication; NGS: next-generation sequencing; MRD: measurable residual disease; neg: negative; pos: positive; RFS: relapse-free survival; OS: overall survival.

N=1), *IKZF1* in two patients (12%), and *FLT3*-TKD mutation (VAF 5%) in one patient (6%).

Outcomes after relapse

Outcomes after relapse were poor. Among the 18 patients who received salvage therapy, the CR/CRi rate to first salvage was 22%. The median OS from relapse was only 6.1 months, with a 1-year OS of 28% (*Online Supplementary Figure S11*). Outcomes were inferior in those with persistently detectable *FLT3* mutation by PCR as compared with those with *FLT3* wild-type relapse (1-year OS: 0% *vs*. 45%, respectively; *P*=0.03) (*Online Supplementary Figure S12*).

Discussion

Our data suggest that triplet regimens consisting of an HMA, venetoclax and a FLT3 inhibitor are an effective strategy for older patients with *FLT3*-mutated AML, resulting in a CR/CRi rate of 93% and median OS for *FLT3*-ITD and *FLT3*-TKD-mutated AML of 28.1 and 39.3 months, respectively. In contrast, the reported median OS with azacitidine plus venetoclax from VIALE-A in these subgroups was 9.9 and 19.2 months, respectively.[2] The high response rates and durable remissions observed with these triplet regimens suggest a possible benefit compared with conventional doublet therapy and support the continued clinical development and dose optimization of these HMA, venetoclax and FLT3 inhibitor combinations.

Among patients treated with these triplet regimens, long-term outcomes were not impacted by age, *NPM1* co-mutation status, nor ELN 2022 risk. Importantly, even in patients ≥75 years old (a subgroup easiest to compare with patients in VIALE-A[1]), a median OS of 28.1 months and an estimated 3-year OS rate of 49% were observed, suggesting that these triplet regimens can be delivered safely and were highly effective even in an older, less fit population. These triplet regimens may also be a reasonable frontline option for relatively fit patients 60-74 years of age with *FLT3*-mutated AML, including those planned for alloSCT in first remission. Of note, in a subgroup of patients >60 years of age who were enrolled in the QuANTUM-First study (all of whom were *FLT3*-ITD-mutated and were deemed suitable candidates for intensive chemotherapy), there was no clear benefit of the addition of quizartinib to intensive chemotherapy, possibly due to additional toxicity in the experimental arm.[18] Among older patients who were randomized to receive intensive chemotherapy plus quizartinib, the median OS was 17.5 months and the 3-year OS was approximately 35%. While challenging to compare across studies, it is notable that we observed a median OS of 31.3 months and a 3-year OS of 46% in patients <75 years old with *FLT3*-ITD-mutated AML, suggesting comparable, or perhaps even superior, outcomes with the triplet regimen in a similar population. Randomized studies comparing these approaches (e.g., a FLT3 inhibitor in combination with intensive chemotherapy or with HMA plus venetoclax) in younger, alloSCT-eligible patients with *FLT3*-ITD mutated AML are planned and may shape our future approach to *FLT3*-mutated AML.

No difference in OS was observed based on alloSCT consolidation. AlloSCT in first remission improves OS in patients with *FLT3*-ITD-mutated AML and is generally recommended for younger, fit patients.[15] The lack of benefit of alloSCT in our study (including in the *FLT3*-ITD-mutated subgroup) may be related in part to the higher rate of transplant-related mortality (20%) in this older population. While alloSCT may still be appropriate for carefully selected older adults with *FLT3*-ITD-mutated AML, recent data also suggest that high-sensitivity NGS-based MRD testing may help to identify patients in whom alloSCT may potentially be deferred with careful serial NGS MRD monitoring.[19,20] We observed that patients who achieved *FLT3*-ITD NGS MRD negativity within four cycles of the triplet regimen had relatively favorable long-term survival (3-year OS, 61%), although there were not enough patients to evaluate the interaction of NGS MRD status and alloSCT. Thus, whether and how *FLT3*-ITD NGS MRD dynamics should impact decisions about alloSCT in patients receiving these triplet regimens remains unknown.

Baseline RAS pathway mutations were associated with worse long-term OS and were also the most common new mutations detected at relapse (newly detected in 24% of relapses). RAS pathway mutations have been previously described as mechanisms of resistance to both HMA plus venetoclax, to FLT3 inhibitors, and to venetoclax plus FLT3 inhibitors.[21-23] While inhibitors of key proteins in RAS signaling (e.g., MEK inhibitors such as trametinib) have been evaluated in AML, their efficacy has been largely disappointing.[24,25] Strategies using low-dose cytarabine-based regimens in combination with venetoclax may help to overcome RAS-mediated resistance mechanisms,[26] although the safety of adding FLT3 inhibitors to these regimens is not yet established.

Sixty-five percent of relapses in our study were driven by *FLT3* wild-type clones, suggesting clonal escape as a major mechanism of secondary resistance to these regimens. The proportion of *FLT3* wild-type relapses observed with these triplet regimens appears numerically higher than what has been reported with intensive chemotherapy plus a FLT3 inhibitor. For example, in younger patients with *FLT3*-mutated AML receiving frontline intensive chemotherapy plus midostaurin, 46% of relapses were *FLT3* wild-type.[27] Whether this is reflective of meaningfully different patterns of relapse with these two approaches will need to be confirmed with larger datasets.

A notable limitation of our study is the heterogeneous pooled analysis from several clinical trials using different FLT3 inhibitors and dosing schedules. For example, 67% of patients in our analysis received frontline gilteritinib, and therefore the generalizability of our findings to triplet regimens with other FLT3 inhibitors is uncertain. Furthermore,

as some of these studies are ongoing and have not yet been published, we were unable to provide outcome data by specific FLT3 inhibitors (e.g., gilteritinib *vs*. quizartinib). Despite these limitations, the pooled nature of our analysis provided a relatively large sample size (N=73), allowing for important subgroup analyses that are not feasible with the modest number of patients enrolled in the individual studies. Randomized studies are needed for a more formal assessment of the potential superiority of a FLT3 inhibitor-containing triplet regimen *versus* the standard azacitidine and venetoclax doublet in *FLT3*-mutated AML (e.g., the ongoing MyeloMATCH trial: NCT06317649).

In summary, triplet regimens with an HMA, venetoclax and a FLT3 inhibitor are effective in older adults with newly diagnosed *FLT3*-mutated AML, with response durations and survival outcomes that compare favorably to historical expectations of azacitidine plus venetoclax in a similar *FLT3*-mutated population. To further improve outcomes with these triplet regimens, novel strategies that address both *FLT3* wild-type clonal escape and RAS-mediated resistance are needed.

Disclosures

NJS has received consulting fees from Amgen, Pfizer Inc., GSK, Adaptive Biotechnologies, Autolus, and Sanofi; research funding from Takeda Oncology, Astellas Pharma Inc., Xencor, GSK, NextCure, Ascentage, Novartis, Hemogenyx, and Vironexis; and honoraria from Adaptive Biotechnologies, Novartis, Amgen, Takeda Oncology, Pfizer Inc., Astellas Pharma Inc., and Sanofi. SL declares research support from Amgen and Astellas and consulting fees from AbbVie, Arima, Blueprint Medicine, BMS, Caris Diagnostics, Daiichi-Sankyo, Immunogen, Kura Oncology, Recordati, Servier, Stemline, Syndax, and Tempus AI. MK is a member of the advisory boards of AbbVie, Auxenion, Dark Blue Therapeutics, Legend, MEI Pharma, and Menarini/Stemline Therapeutics; has received consulting fees from AbbVie, Adaptive, Curis, Intellisphere, Janssen, Menarini/Stemline Therapeutics, Novartis, Sanofi Aventis, Servier, Syndax, and Vincerx; and has received research funding from AbbVie, Janssen, and Klondike Biopharma. ND has received research funding from Astellas Pharma, AbbVie, Genentech, Daiichi Sankyo, Gilead Sciences, ImmunoGen, Pfizer, Bristol Myers Squibb, Trovagene, Servier, Novimmune, Incyte, Hanmi Pharm, Fate Therapeutics, Amgen, Kite Pharma, Novartis, Astex Pharmaceuticals, KAHR, Sumitomo, Shattuck, Sobi, Arcellx, Nerviano, Avencell, SOBI, AstraZeneca, Vincerx, Caribou, and Trillium; has been an advisor for Astellas Pharma, AbbVie, Genentech, Daiichi Sankyo, Novartis, Jazz Pharmaceuticals, Amgen, Servier, Karyopharm Therapeutics, Trovagene, Trillium, Syndax, Gilead Sciences, Pfizer, Bristol Myers Squibb, Kite Pharma, Actinium Pharmaceuticals, Arog Pharmaceuticals, ImmunoGen, SOBI, Arcellx, Caribou, Avencell, Dark Blue, Charm, Merrill life, Vincerx, AstraZeneca, and Shattuck labs; and has been a data monitoring committee member for Kartos Therapeutics, KEROS, and Jazz Pharmaceuticals. The rest of the authors have no relevant conflicts of interest to disclose.

Contributions

NJS conceptualized the study, collected and analyzed the data, treated patients and wrote the first draft of the manuscript. SL collected and analyzed the data and performed the pathology analysis and interpretation. MY, CDD, TMK, GB, GCI, BO, EJS, UP, MK, FR, and HK treated patients. KPP and MR performed pathology analysis and interpretation. OK, JJ, KK, and MM collected and analyzed the data and performed statistical analyses. ND conceptualized the study and treated patients. All authors reviewed and edited the manuscript and approved the final version.

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Data-sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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