REGULAR ARTICLE

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Risk stratification of low-dose cytarabine and venetoclax in patients with AML ineligible for intensive chemotherapy

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Key Points

- Molecular subclassification is relevant for defining treatment outcomes after venetoclax-based therapies.
- Complex karyotype and *TP53* mutation confer adverse prognosis in patients treated with LDAC plus venetoclax.

Prognostic risk categorization aids treatment selection for patients with acute myeloid leukemia (AML). Although the European LeukemiaNet (ELN) classifications (2017 and 2022) for AML have been used to stratify outcomes for patients receiving intensive chemotherapy, their application to patients receiving less intensive therapy, such as azacitidine plus venetoclax, has been less satisfactory. In response, a 4-gene classifier that stratifies older patients with AML unfit for intensive chemotherapy into those with higher benefit (wild type), intermediate benefit (*FLT3*–internal tandem duplication [ITD] or *NRAS*/*KRAS* mutation), or lower benefit (*TP53* mutation) after azacitidine plus venetoclax treatment was developed. We hypothesized that this 4-gene classifier may also have prognostic utility in patients receiving low-dose cytarabine (LDAC) plus venetoclax. Surprisingly, neither the ELN 2022 criteria nor the 4-gene azacitidine-venetoclax classifier model adequately stratified prognosis in a cohort of 139 patients receiving LDAC plus venetoclax. Patients with concurrent *NPM1* and *FLT3*-ITD/*RAS* variants performed

Submitted 6 May 2025; accepted 6 October 2025; prepublished online on *Blood Advances* First Edition 21 November 2025; final version published online 11 February 2026. https://doi.org/10.1182/bloodadvances.2025017083.

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The full-text version of this article contains a data supplement.

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surprisingly well with LDAC plus venetoclax (complete remission [CR]/CR with incomplete blood count recovery [CRi] rate, 92%; median overall survival [OS], 29.67 months). Data-driven (sequential bootstrapping and tree-based) and empirical analyses identified complex karyotype and/or presence of *TP53* mutation as prognostically relevant molecular/cytogenetic risk markers. Patients with complex karyotype and/or *TP53* mutation displayed poor clinical outcomes (CR/CRi, 25%; median OS, 3.48 months). Notably, 74% of the study population lacked these poor prognostic markers and had a 67% CR/CRi rate with a median OS of 14.92 months. Overall, these data support the importance of molecular subclassification in defining treatment outcomes to venetoclax-based therapies. These trials were registered at www.clinicaltrials.gov as #NCT02287233 and #NCT03069352.

Introduction

Acute myeloid leukemia (AML) is a clinically and molecularly heterogeneous disease of the bone marrow that results in the accumulation of immature clonal myeloid progenitors. Older patients with AML often have a higher comorbidity burden, rendering them unsuitable to receive intensive chemotherapy.[1] Historically, treatment options for older patients with AML included lower-intensity therapies with either low-dose cytarabine (LDAC), hypomethylating agents (HMAs), or best supportive care.[2] A phase 1b/2 study of LDAC combined with the highly selective and potent oral BCL-2 inhibitor venetoclax demonstrated a complete remission (CR) plus CR with incomplete blood count recovery (CRi) rate of 54% and a remission duration of 8.1 months, resulting in accelerated approval of this combination for patients with newly diagnosed AML ineligible for intensive chemotherapy.[1] The confirmatory phase 3 trial of LDAC plus venetoclax or placebo (VIALE-C) did not show a statistically significant difference in median overall survival (OS; 7.2 vs 4.1 months, respectively) at the 12-month follow-up mark.[3] However, with 6 months of additional follow-up, LDAC plus venetoclax prolonged median OS compared with the placebo arm (8.4 vs 4.1 months; hazard ratio, 0.70; 95% confidence interval [CI], 0.50-0.99; $P = .04$), confirming its utility in older patient populations with AML.[4]

AML, however, is characterized by diverse chromosomal and genetic abnormalities, contributing to heterogeneous outcomes after therapy.[5] Risk stratification based on genetic factors can inform prognosis and aid in the selection of rational therapeutic approaches. The European LeukemiaNet (ELN) risk classification model is well established for prognostic stratification of patients receiving intensive chemotherapy[6-12]; however, attempts to apply the ELN 2022 risk model to older patients with AML receiving azacitidine plus venetoclax have been unsatisfactory, prompting the development of a new 4-gene classifier (incorporating *FLT3*–internal tandem duplication [ITD], *NRAS*, *KRAS*, and *TP53* mutation status). This tripartite 4-gene classifier stratified patients into those deriving higher, intermediate, and lower benefit from azacitidine plus venetoclax therapy.[13] The mutation status of these 4 genes has also been incorporated into a new ELN 2024 risk classification for older patients receiving less intensive therapy.[14]

The purpose of this analysis is to evaluate the applicability of the ELN 2022 risk stratification or the 4-gene classifier developed for azacitidine plus venetoclax as a prognostic tool for patients treated with LDAC plus venetoclax.

Methods

Patients and study design

To identify molecular determinants relevant for risk stratification of patients receiving LDAC plus venetoclax, participants from the phase 1b/2 M14-387 (ClinicalTrials.gov number NCT02287233) and the phase 3 VIALE-C (ClinicalTrials.gov number NCT03069352) trials[1,3] were pooled and analyzed (supplemental Figure 1). Study design and enrollment criteria for these trials have been described.[1,3]

Per protocol, venetoclax was administered orally at a target dose of 600 mg/d after a 4- to 5-day dose ramp-up (4-day dose ramp-up in VIALE-C; 100 mg on day 1, 200 mg on day 2, 400 mg on day 3, and 600 mg on day 4), and LDAC was administered at 20 mg/m^2 subcutaneously on days 1 to 10 of each 28-day cycle. Dose modifications to venetoclax were allowed, and LDAC reductions were allowed after discussion with the study medical monitor. Patients continued treatment until documented disease progression per investigator assessment, unacceptable toxicity, withdrawal of consent, or patients met other protocol criteria for discontinuation.[1,3] All patients provided written informed consent before enrollment. These studies were approved by the institutional review board or ethics committee at each institution and were conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, and the Declaration of Helsinki.

Outcomes

Responses (CR/CRi) in the M14-387 study were assessed after cycles 1 and 3 and every 3 cycles thereafter until 2 consecutive samples confirmed CR; in VIALE-C, responses were assessed after cycle 1 and every 3 cycles thereafter until 2 consecutive samples confirmed CR or CRi.[1,3] Responses were evaluated per modified International Working Group criteria for AML.[15] OS was defined as the time from randomization to the date of death in VIALE-C and as the number of days from the first dose of the study drug to the date of death in M14-387. In both studies, safety analyses were performed in patients who received $\geq$1 dose of venetoclax or LDAC. Adverse events (AEs) were graded based on the National Cancer Institute Common Terminology Criteria for AEs version 4.03.

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Cytogenetics and next-generation sequencing

Cytogenetic risk analyses were performed locally. DNA was isolated from bone marrow aspirates and collected before the first dose of the study drugs. Genetic mutations specified as ELN molecular determinants for risk stratification were detected centrally using the MyAML next-generation sequencing panel (194 genes; Invivoscribe, San Diego, CA), TruSight Myeloid panel (54 genes; Illumina, San Diego, CA), or FoundationOne Heme panel (405 genes; Cambridge, MA). All sequencing panels included the following molecular determinants: *CEBPA* (biallelic), *NPM1*, *FLT3*-ITD (plus allelic ratio), *TP53*, *RUNX1*, and *ASXL1* for the ELN 2017 analyses, and the list was revised to include *CEBPA* (bZIP), *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2* for the ELN 2022 analyses. Patients treated with LDAC plus venetoclax without prior HMA exposure for myelodysplastic syndrome and for whom both cytogenetic and molecular data were available (62% [139/225]) were included in subsequent analyses (supplemental Figure 1).

Statistical analysis

The association of risk signatures with OS and remission rates was explored. Time-to-event end points (OS) were analyzed using the Kaplan-Meier method, and the corresponding CI was based on the log hazard (log-log transformation of survival). For binary end points, proportions were calculated along with the Wilson CI. Sequential bootstrapping and aggregating thresholds from trees (BATTing)[16] analysis using 27 genetic factors was used to identify a prognostic signature for OS in patients treated with LDAC plus venetoclax. Genetic factors were selected based on those included in the ELN 2017 and 2022 guidelines and those identified as potential sensitivity or resistance markers for venetoclax-based therapies. This analysis identified subgroups with the longest and shortest OS. The *P* value of the hazard ratio was used to compare patient subgroups.

Results

Prognostic utility of ELN 2017 and ELN 2022 classifiers for outcomes after LDAC plus venetoclax

To assess the utility of ELN 2017 and 2022 risk models for outcome determination after lower-intensity therapy with LDAC plus venetoclax, 139 patients without prior HMA exposure for myelodysplastic syndrome were pooled from the M14-387 (n = 53) and VIALE-C (n = 86) studies (supplemental Figure 1). The median age of the combined cohort of patients treated with LDAC plus venetoclax was 76 years (range, 36-92), and 48 patients (35%) had poor cytogenetic risk based on the 2016 National Comprehensive Cancer Network risk criteria (Figure 1A). The ELN 2017 risk model stratified patients treated with LDAC plus venetoclax into 3 distinct cohorts: favorable, intermediate, and adverse (Table 1), with a median OS of 25.26, 13.08, and 6.54 months, respectively (Figure 1B). Separation of these risk groups was less distinct, however, when the ELN 2022 risk criteria were applied, with a median OS of 23.79, 22.01, and 7.69 months for patients with favorable, intermediate, and adverse risk, respectively (Figure 1C). Patients classified as intermediate risk had improved survival using ELN 2022 compared with ELN 2017 risk criteria. The main change associated with the ELN 2022 model was the inclusion of patients with *NPM1* mutation/*FLT3*-ITD low allelic ratio (<0.5) into the intermediate-risk category (n = 6). These patients were previously designated as ELN 2017 favorable. In addition, the ELN 2022 criteria redistributed 20 patients from ELN 2017 intermediate to ELN 2022 adverse risk based on the presence of myelodysplasia-related (MR) gene mutations (involving *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*; supplemental Table 1). CR/CRi rates across prognostic risk categories for patients treated with LDAC plus venetoclax were similar when defined using either ELN 2017 or 2022 criteria (supplemental Figure 2). When examining the pooled rates of any grade, grade ≥3, or serious AEs across the ELN 2017 or 2022 risk classifications, there were also no obvious differences in the safety profile of patients categorized as favorable, intermediate, or adverse risk to explain the differences in outcome (supplemental Tables 2-4). Overall, these analyses demonstrated that the revised ELN 2022 guidelines were not optimal for prognostic stratification of survival after therapy with LDAC plus venetoclax in older, unfit patients with AML.

Evaluation of the 4-gene azacitidine plus venetoclax prognostic risk signature for patients treated with LDAC plus venetoclax

Because ELN 2022 risk criteria failed to optimally segregate survival outcomes after LDAC plus venetoclax, we examined the utility of a 4-gene prognostic risk signature established for azacitidine plus venetoclax therapy.[13] The 4-gene risk signature categorized higher-, intermediate-, and lower-benefit risk groups based on the mutational status of *TP53*, *NRAS*, *KRAS*, and *FLT3*-ITD. The higher-benefit group included patients who were wild type for *TP53* and *NRAS*/*KRAS* and negative for *FLT3*-ITD. The intermediate-benefit group was designated as wild-type *TP53* but positive for the signaling mutations *FLT3*-ITD and/or *NRAS*/*KRAS*. The lower-benefit group was marked by the presence of *TP53* mutation regardless of *FLT3*-ITD or *NRAS*/*KRAS* mutation status. When applying this prognostic signature to the pooled cohort, the shortest median OS was observed for the lower-benefit group (2.83 months; 95% CI, 1.84-6.54). Notably, there was no difference in median OS between the intermediate- (13.96 months; 95% CI, 7.33-20.83) and higher-benefit groups (13.50 months; 95% CI, 10.74-23.56; Figure 2). Therefore, similar to the ELN 2022 risk criteria, the 4-gene azacitidine plus venetoclax signature was not optimal for stratifying patients receiving LDAC plus venetoclax.

Modeling determinants of survival for patients receiving LDAC plus venetoclax

To determine whether an alternative prognostic model could be developed to risk stratify patients receiving LDAC plus venetoclax, we used sequential BATTing analysis to evaluate 27 distinct mutation/cytogenetic factors (supplemental Table 5) as candidate determinates of prognostic outcome. BATTing uses sequential multivariate bootstrapping and aggregation of thresholds from trees[16] to identify molecular factors with prognostic relevance. Surprisingly, complex karyotype was identified as the sole prognostic variable, with no additional factors found to have considerable impact (supplemental Table 5). Absence of complex karyotype defined a higher-benefit group, which constituted 76% of the pooled cohort (106/139), with a median OS of 16.43 months (95% CI, 11.24-21.29). In contrast, patients with

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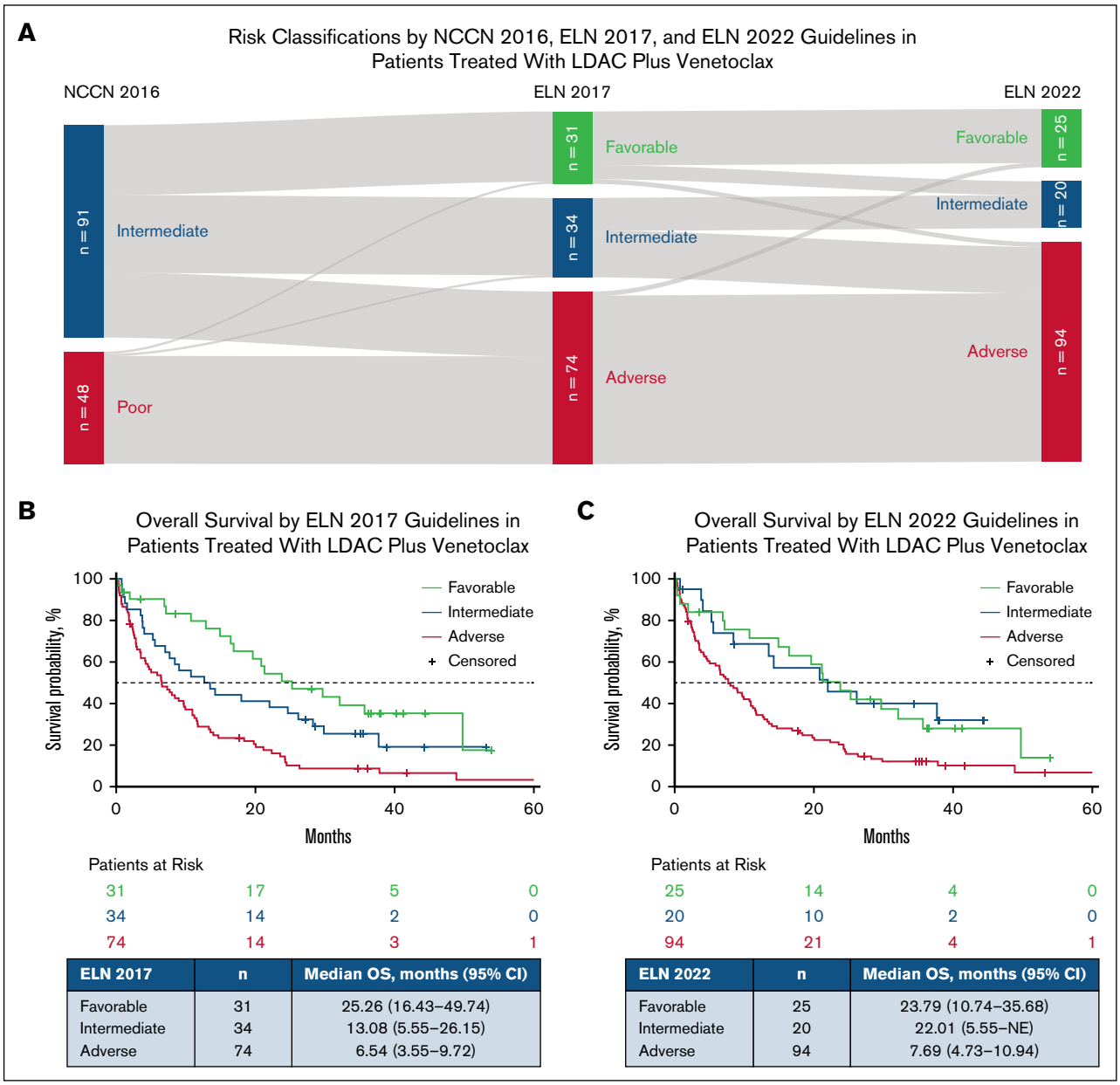

ELN 2017	n	Median OS, months (95% CI)
Favorable	31	25.26 (16.43–49.74)
Intermediate	34	13.08 (5.55–26.15)
Adverse	74	6.54 (3.55–9.72)

ELN 2022	n	Median OS, months (95% CI)
Favorable	25	23.79 (10.74–35.68)
Intermediate	20	22.01 (5.55–NE)
Adverse	94	7.69 (4.73–10.94)

Figure 1. Risk classifications and survival outcomes based on ELN 2017 and ELN 2022 guidelines in patients treated with LDAC plus venetoclax. (A) Sankey plot showing pooled analysis of patients from the VIALE-C and M14-387 clinical trials distributed by ELN 2017 and ELN 2022 criteria. (B-C) Segregation of OS with LDAC plus venetoclax based on prognostic risk determined by ELN 2017 (B) and ELN 2022 criteria (C). NCCN, National Comprehensive Cancer Network.

complex karyotype present defined a lower-benefit group, accounting for 24% of the pooled cohort (33/139), with a median OS of only 3.42 months (95% CI, 1.84-5.88; Figure 3A). Patients in the higher-benefit group lacking complex karyotype also had a higher clinical response rate (67%; CR, 44%; CRi, 23%) than patients in the lower-benefit group with complex karyotype (21%; CR, 3%; CRi, 18%; supplemental Figure 3A).

Among patients with complex karyotype, survival outcomes were poor, regardless of whether *TP53* mutation was present (median OS, 2.83 months; 95% CI, 0.72-4.73) or absent (median OS, 5.88 months; 95% CI, 0.92-8.97; Figure 3B). Moreover, no CRs were observed among patients with complex karyotype in the presence of *TP53* mutation (supplemental Figure 3B). Patients harboring either complex karyotype or *TP53* mutation had a median OS of 3.48 months (95% CI, 1.94-6.44) compared with 14.92 months (95% CI, 10.94-22.01) in patients lacking either feature (Figure 3C). Moreover, patients with either complex karyotype or *TP53* mutation had a response rate of 25% (CR, 8%; CRi, 17%) compared with 67% (CR, 44%; CRi, 23%) in patients with both these poor risk features absent (supplemental Figure 3C). Patient disease characteristics by higher and lower benefit are presented in supplemental Table 6.

To avoid the confounding effect of prior HMA exposure, which was found to be associated with adverse prognostic risk in VIALE-C,

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Table 1. Baseline characteristics of patients treated with LDAC plus venetoclax per ELN 2017 and ELN 2022 favorable-, intermediate-, and adverse-risk groups

	ELN 2017			ELN 2022		
Characteristic	**Favorable (n = 31)**	**Intermediate (n = 34)**	**Adverse (n = 74)**	**Favorable (n = 25)**	**Intermediate (n = 20)**	**Adverse (n = 94)**
Median age, y	76	73	77	76	72	77
Age group, n (%), y						
<75	14 (45)	19 (56)	27 (36)	9 (36)	15 (75)	36 (38)
≥75	17 (55)	15 (44)	47 (64)	16 (64)	5 (25)	58 (62)
AML type, n (%)						
De novo	28 (90)	23 (68)	48 (65)	22 (88)	15 (75)	62 (66)
Secondary	3 (10)	11 (32)	26 (35)	3 (12)	5 (25)	32 (34)
ECOG PS, n (%)						
<2	19 (61)	22 (65)	38 (51)	14 (56)	10 (50)	55 (59)
≥2	12 (39)	12 (35)	36 (49)	11 (44)	10 (50)	39 (41)
Percent blasts, n (%)*						
<30%	5 (16)	11 (33)	27 (36)	4 (16)	6 (30)	33 (35)
≥30% to <50%	4 (13)	10 (30)	14 (19)	3 (12)	2 (10)	23 (25)
≥50%	22 (71)	12 (36)	33 (45)	18 (72)	12 (60)	37 (40)
Cytogenetic risk, n (%)						
Favorable	0	0	0	0	0	0
Intermediate	30 (97)	33 (97)	28 (38)	24 (96)	19 (95)	48 (51)
Poor	1 (3)	1 (3)	46 (62)	1 (4)	1 (5)	46 (49)
Mutations, n (%)						
FLT3	8 (26)	11 (32)	8 (11)	2 (8)	12 (60)	13 (14)
FLT3-ITD low†	6 (19)	2 (6)	7 (9)	0	7 (35)	8 (9)
FLT3-ITD high‡	0	2 (6)	0	0	2 (10)	0
TP53	0	0	25 (34)	0	0	25 (27)
NPM1	22 (71)	2 (6)	2 (3)	16 (64)	8 (40)	2 (2)
NPM1/*FLT3*-ITD negative or low	22 (71)	0	2 (3)	16 (64)	6 (30)	2 (2)
NPM1/*FLT3*-ITD high	0	2 (6)	0	0	2 (10)	0
IDH1/2	10 (32)	9 (26)	11 (15)	7 (28)	4 (20)	19 (20)
ASXL1	3 (10)	0	15 (20)	3 (12)	0	15 (16)
RUNX1	0	0	27 (36)	1 (4)	0	26 (28)
BCOR				1 (4)	0	9 (10)
EZH2				0	0	7 (7)
SF3B1				0	0	10 (11)
SRSF2				5 (20)	1 (5)	24 (26)
STAG2				3 (12)	0	18 (19)
U2AF1				0	0	10 (11)
ZRSR2				1 (4)	0	3 (3)
Biallelic *CEBPA*	8 (26)	0	0			
CEBPA-bZIP				8 (32)	0	0
t(8;21)	0	0	1 (1)	0	0	0

MR genes *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2* were added in ELN 2022.
ECOG PS, Eastern Cooperative Oncology Group performance status; WT, wild type.
*Percentages were calculated based on the number of patients with non-missing values.
†*FLT3*-ITD low is defined as a *FLT3*-ITD to *FLT3*-WT ratio of <0.5.
‡*FLT3*-ITD high is defined as a *FLT3*-ITD to *FLT3*-WT ratio of ≥0.5.

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Table 1 (continued)

Characteristic	ELN 2017			ELN 2022		
	Favorable (n = 31)	Intermediate (n = 34)	Adverse (n = 74)	Favorable (n = 25)	Intermediate (n = 20)	Adverse (n = 94)
t(16;16)	1 (3)	0	0	1 (4)	0	0
t(9;11)	0	2 (6)	0	0	2 (10)	0
t(6;9)	0	0	0	0	0	0
t(11q23)	0	0	0	0	0	0
t(3;3)	0	0	2 (3)	0	0	2 (2)
del(5) or del(7) or del(17)	0	0	39 (53)	0	0	39 (41)
Complex karyotype	0	1 (3)	34 (46)	0	1 (5)	32 (34)

MR genes *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2* were added in ELN 2022.
ECOG PS, Eastern Cooperative Oncology Group performance status; WT, wild type.
*Percentages were calculated based on the number of patients with non-missing values.
†*FLT3*-ITD low is defined as a *FLT3*-ITD to *FLT3*-WT ratio of <0.5.
‡*FLT3*-ITD high is defined as a *FLT3*-ITD to *FLT3*-WT ratio of ≥0.5.

this subgroup was not included in the current molecular prognostic risk score. When examining the excluded 41 patients who had prior exposure to HMA with karyotype and full molecular data available, there were 32 patients classified as higher benefit and 9 with lower benefit. Median OS was poor among patients in both the higher- and lower-benefit groups (5.55 months [95% CI, 3.02-11.24] vs 2.66 months [95% CI, 0.92-5.68]), suggesting that prior HMA exposure is a confounding factor in determining a prognostic signature for LDAC plus venetoclax and supporting the exclusion of these patients from analyses.

Molecular determinants of outcome among patients lacking complex karyotype

We next examined an oncoprint of the higher- and lower-benefit subgroups to allow for the examination of the molecular landscape within each prognostic stratum (supplemental Figure 4A-B). Roughly a third of the patients in the higher-benefit group had mutations in *FLT3*-ITD, *KRAS*, or *NRAS*. Median OS was similar in the presence (14.69 months; 95% CI, 8.44-21.16) or absence (16.43 months; 95% CI, 10.94-24.48) of these kinase-activating mutations (Figure 4A). Similar response rates were also observed for both these subgroups (63% with kinase mutations vs 69% without; supplemental Figure 5A). Analysis of efficacy outcomes using individual molecular markers (*FLT3*-ITD, *NRAS*, and *KRAS*) were inconclusive (supplemental Figure 7). To explore this observation further, there were 26 patients with mutated *NPM1* in the higher-benefit group. Median OS was superior for patients with *NPM1* mutation (29.67 months; 95% CI, 16.43 to not estimable [NE]) compared with patients who were wild type for *NPM1* (12.88 months; 95% CI, 9.03-17.97; Figure 4B). Among the *NPM1*-mutant subgroup, 12 patients had either concurrent *FLT3*-ITD (n = 8) or *NRAS*/*KRAS* variants (n = 4). When considering patients in the higher-benefit group with *NPM1* mutation, survival outcomes were comparable among those with *FLT3*-ITD/*NRAS*/*KRAS* variants present (median OS, 29.67 months; 95% CI, 10.74 to NE) or absent (median OS, 25.26 months; 95% CI, 7.16 to NE; Figure 4C). Similar rates of CR/CRi were also observed for each group (92% with kinase mutations vs 86% without; supplemental Figure 5C). Among patients with *NPM1* mutation, the co-occurrence of *FLT3*-ITD, *NRAS*, or *KRAS* did not separate outcomes further (supplemental Figure 8).

Among patients in the higher-benefit cohort without an *NPM1* mutation, 53 patients were defined as having AML with MR gene mutations. As anticipated, median OS outcomes were lower for those with AML-MR variants present (11.56 months; 95% CI, 7.69-16.89) than those lacking AML-MR (22.01 months; 95% CI, 14.23-32.10; Figure 4D). Among the AML-MR subgroup, 18 had concurrent *FLT3*-ITD (n = 6) or *NRAS*/*KRAS* variants (n = 12). When considering subpopulations within the higher-benefit group with AML-MR, survival outcomes trended inferiorly for those with (median OS, 7.33 months; 95% CI, 2.43-14.69) vs without (median OS, 12.88 months; 95% CI, 10.74-24.48) *FLT3*-ITD/*NRAS*/*KRAS* mutation (Figure 4E).

Median OS in the presence (20.83 months [95% CI, 10.74-32.10]) vs absence (14.69 months; 95% CI, 9.92-21.29) of *IDH1/2* mutation was comparable (supplemental Figure 6A). Similar trends were observed for median OS in the presence (11.24 months; 95% CI, 4.57-21.16) vs absence (19.61 months; 95% CI, 11.56-23.79) of *RUNX1* mutation (supplemental Figure 6C). CR/CRi rates were also comparable among patients with either *IDH1/2*, *NPM1*, *RUNX1* or MR gene mutations (supplemental Figures 5 and 6).

Discussion

In this retrospective, pooled analysis of 2 clinical studies examining LDAC plus venetoclax in newly diagnosed AML unfit for intensive chemotherapy, the prognostic relevance of existing risk stratification criteria were evaluated. Overall, our results confirmed that risk stratification based on ELN 2022 criteria lacked prognostic utility for LDAC plus venetoclax therapy, similar to recent findings observed with azacitidine plus venetoclax.[13,17] Due to the failure of existing risk stratification criteria to adequately distinguish outcomes of patients receiving LDAC plus venetoclax, a sequential BATTing analysis considering 27 recurring genetic/cytogenetic variables in AML was used. Surprisingly, this only led to the identification of complex karyotype dichotomizing patients into lower- (complex karyotype present) or higher-benefit groups (complex karyotype absent). Consistent with previous findings,[18] most patients (67%) with complex karyotype in this analysis harbored a *TP53* mutation. Although patients with complex karyotype in the absence of *TP53* mutation had a nominally better median OS (5.88 months) than patients positive for both complex

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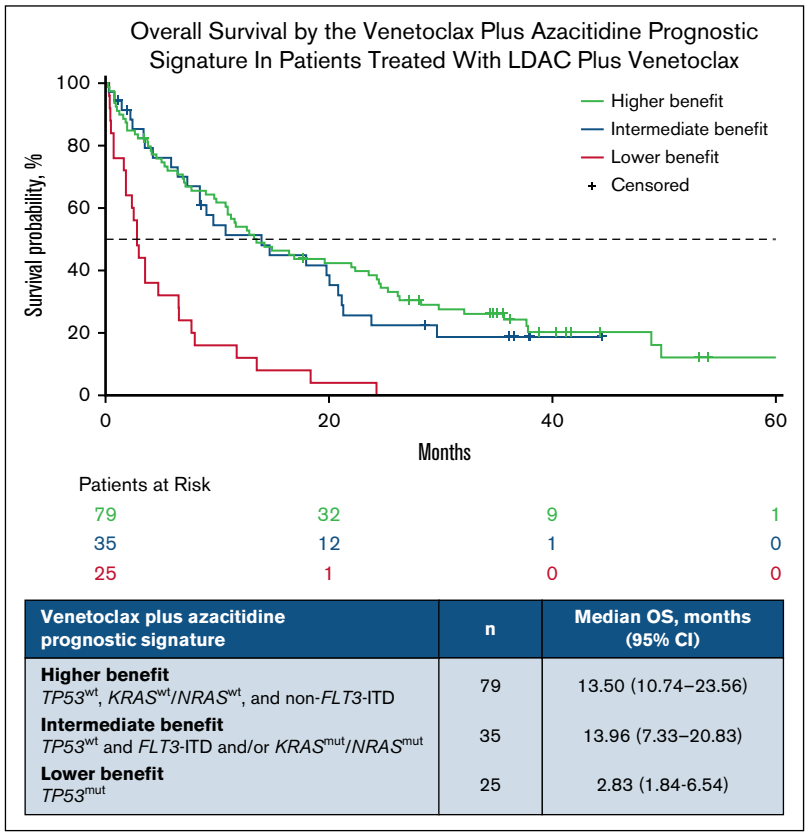

Venetoclax plus azacitidine prognostic signature	n	Median OS, months (95% CI)
Higher benefit *TP53*^{wt}, *KRAS*^{wt}/*NRAS*^{wt}, and non-*FLT3*-ITD	79	13.50 (10.74–23.56)
Intermediate benefit *TP53*^{wt} and *FLT3*-ITD and/or *KRAS*^{mut}/*NRAS*^{mut}	35	13.96 (7.33–20.83)
Lower benefit *TP53*^{mut}	25	2.83 (1.84-6.54)

Figure 2. Survival outcomes based on the azacitidine plus venetoclax prognostic signature in patients treated with LDAC plus venetoclax. mut, mutated; wt, wild type.

karyotype and *TP53* mutation (2.83 months), both subgroups derived low benefit from therapy. When examining the impact of other molecular markers of interest (*FLT3*-ITD, *NRAS*/*KRAS*, MR genes, *IDH1/2*, or *RUNX1*), we observed no clear segregation of risk; thus, the highest benefit of LDAC plus venetoclax was observed in patients lacking complex karyotype or *TP53* mutation (Figure 3C).

Unexpectedly, we found that the 4-gene risk classification model developed for unfit older patients receiving azacitidine plus venetoclax[13] was also suboptimal for distinguishing outcomes after LDAC plus venetoclax. The main reason for this anomaly is explained by the comparable outcomes for patients with or without *FLT3*-ITD or *NRAS*/*KRAS* mutations in the higher-benefit group (Figure 4A). Therefore, in the LDAC plus venetoclax molecular classifier, there was no separation into higher- and intermediate-benefit groups, as had previously emerged from a similar sequential BATTing analysis of patients receiving azacitidine plus venetoclax.

Most patients in the higher-benefit group receiving LDAC plus venetoclax with *FLT3*-ITD or *NRAS*/*KRAS* mutations (n = 32) had either concurrent *NPM1* (n = 12) or MR mutations (n = 18; Figure 4). For patients with *FLT3*-ITD or *NRAS*/*KRAS* and concurrent *NPM1* mutations, the CR/CRi rate was 92% (63% if *FLT3*-ITD or *NRAS*/*KRAS* mutations and wild-type *NPM1*; supplemental Figure 5). Median OS for *FLT3*-ITD or *NRAS*/*KRAS* and *NPM1* mutations was 29.67 months (25.26 months if wild-type *NPM1*; Figure 4C). In prior studies with azacitidine plus venetoclax, patients with *FLT3*-ITD or *NRAS*/*KRAS* and concurrent *NPM1* mutations had a reported CR/CRi rate of 56.5% and a median OS of 9.9 months.[13]

In this study of patients receiving LDAC plus venetoclax, we also analyzed those with MR gene mutations, because *FLT3*-ITD or *NRAS*/*KRAS* variants co-occurred in 34% of patients in this subgroup. Presence of *FLT3*-ITD or *NRAS*/*KRAS* was associated with a trend for inferior CR/CRi (50% vs 69%) and survival (median, 7.33 vs 12.88 months) compared with absence of these kinase-activating variants (Figure 4E; supplemental Figure 5E). Therefore, our study revealed a negative impact for *FLT3*-ITD or *NRAS*/*KRAS* variants in patients with MR gene but not *NPM1* mutations. This was likely a result of the more favorable outcomes for patients with *NPM1* mutation compared with *NPM1* wild-type AML receiving LDAC plus venetoclax within the higher-benefit group (Figure 4B). For patients in the higher-benefit group with *NPM1* mutation receiving LDAC plus venetoclax (n = 26), the median OS was 30 months compared with 13 months for patients who were *NPM1* wild type. Although the favorable outcomes of patients with concurrent *NPM1* and *FLT3*-ITD is intriguing (CR/CRi, 88%; median OS, not reached, with only 2 deaths reported; supplemental Figure 8), it should be noted that there were only 8 patients with this combination genotype; thus, current observations remain exploratory and require confirmation in larger studies.

In addition to the 4-gene risk classifier developed for patients receiving HMA plus venetoclax, the recently published ELN 2024 risk classification model also included specific mention of *NPM1*, *IDH2*, *IDH1*, and *DDX41* mutations within the higher-benefit subgroup.[14] Our current analysis confirmed a survival benefit for

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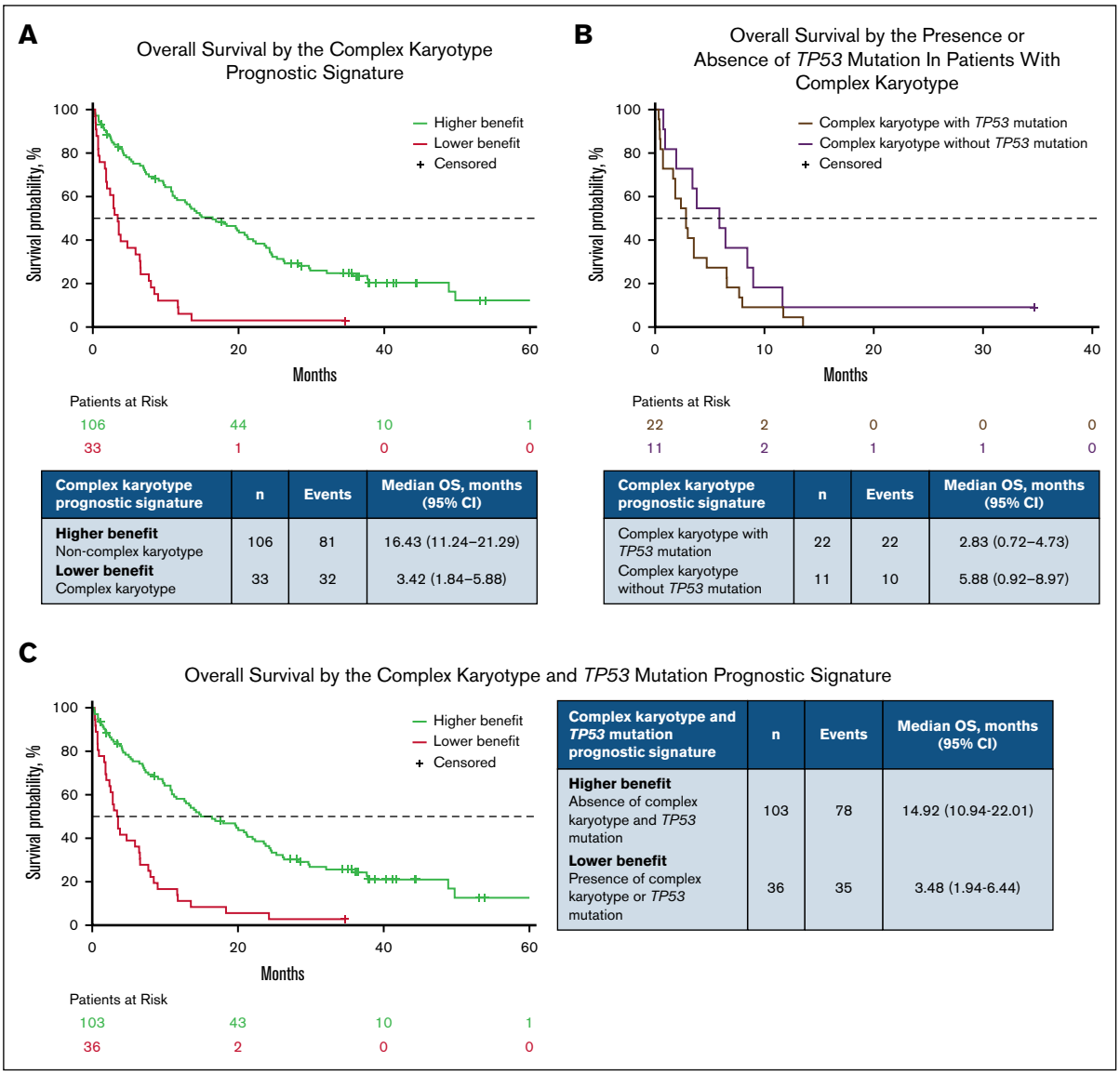

Complex karyotype prognostic signature	n	Events	Median OS, months (95% CI)
Higher benefit Non-complex karyotype	106	81	16.43 (11.24–21.29)
Lower benefit Complex karyotype	33	32	3.42 (1.84–5.88)

Complex karyotype prognostic signature	n	Events	Median OS, months (95% CI)
Complex karyotype with *TP53* mutation	22	22	2.83 (0.72–4.73)
Complex karyotype without *TP53* mutation	11	10	5.88 (0.92–8.97)

Complex karyotype and *TP53* mutation prognostic signature	n	Events	Median OS, months (95% CI)
Higher benefit Absence of complex karyotype and *TP53* mutation	103	78	14.92 (10.94-22.01)
Lower benefit Presence of complex karyotype or *TP53* mutation	36	35	3.48 (1.94-6.44)

Figure 3. Survival outcomes based on the complex karyotype prognostic signature with or without the co-occurrence of *TP53* mutation. OS by the complex karyotype signature (A), with or without *TP53* mutation and complex karyotype (B), and the final prognostic signature inclusive of complex karyotype and *TP53* mutation (C).

patients in the higher-benefit group with *NPM1* mutation (Figure 4B) but not for those with mutated *IDH1/2* (supplemental Figure 6A). The prognostic role of *DDX41* mutation was not examined in this study. In the ELN 2024 recommendations, it was specifically mentioned that the model was not applicable to patients receiving LDAC plus venetoclax–based treatment, because analyses for this patient group were not yet published.[14] It is hoped that the new information from the current manuscript will help refine future iterations of the ELN prognostic risk score for older AML populations.

The clinical management of older patients with *FLT3*-ITD remains controversial. The addition of gilteritinib to azacitidine did not improve survival over azacitidine alone in patients with *FLT3*-mutated AML in the LACEWING study.[19] Although the addition of venetoclax to azacitidine showed enhanced response in patients with *FLT3*-mutated AML, survival was not improved compared with azacitidine monotherapy.[20] Regarding LDAC as an alternative backbone for patients with *FLT3*-ITD, LDAC plus venetoclax in this study was associated with a CR/CRi rate of 71% and a median OS of 13.96 months (supplemental Figure 7). In preliminary results from a randomized study comparing LDAC plus venetoclax and midostaurin vs LDAC plus venetoclax alone (INTERVENE), the triplet combination in a subset analysis of patients with *FLT3*-ITD showed a CR/CRi rate of 82% vs 57% and a median OS of 16.8 vs 9.1 months, with *FLT3*-ITD negativity by the end of cycle 4, assessed by polymerase chain reaction–next-generation sequencing, recorded in 61% of patients treated with LDAC plus venetoclax and midostaurin compared with 0% with LDAC plus venetoclax alone.[21] In a subgroup analysis from another study, patients randomized to LDAC plus quizartinib vs LDAC plus placebo showed improved OS for LDAC combined with quizartinib (median, 13.7 vs 4.2 months) in patients with *FLT3*-ITD.[22] Furthermore, in a separate analysis, cladribine combined with

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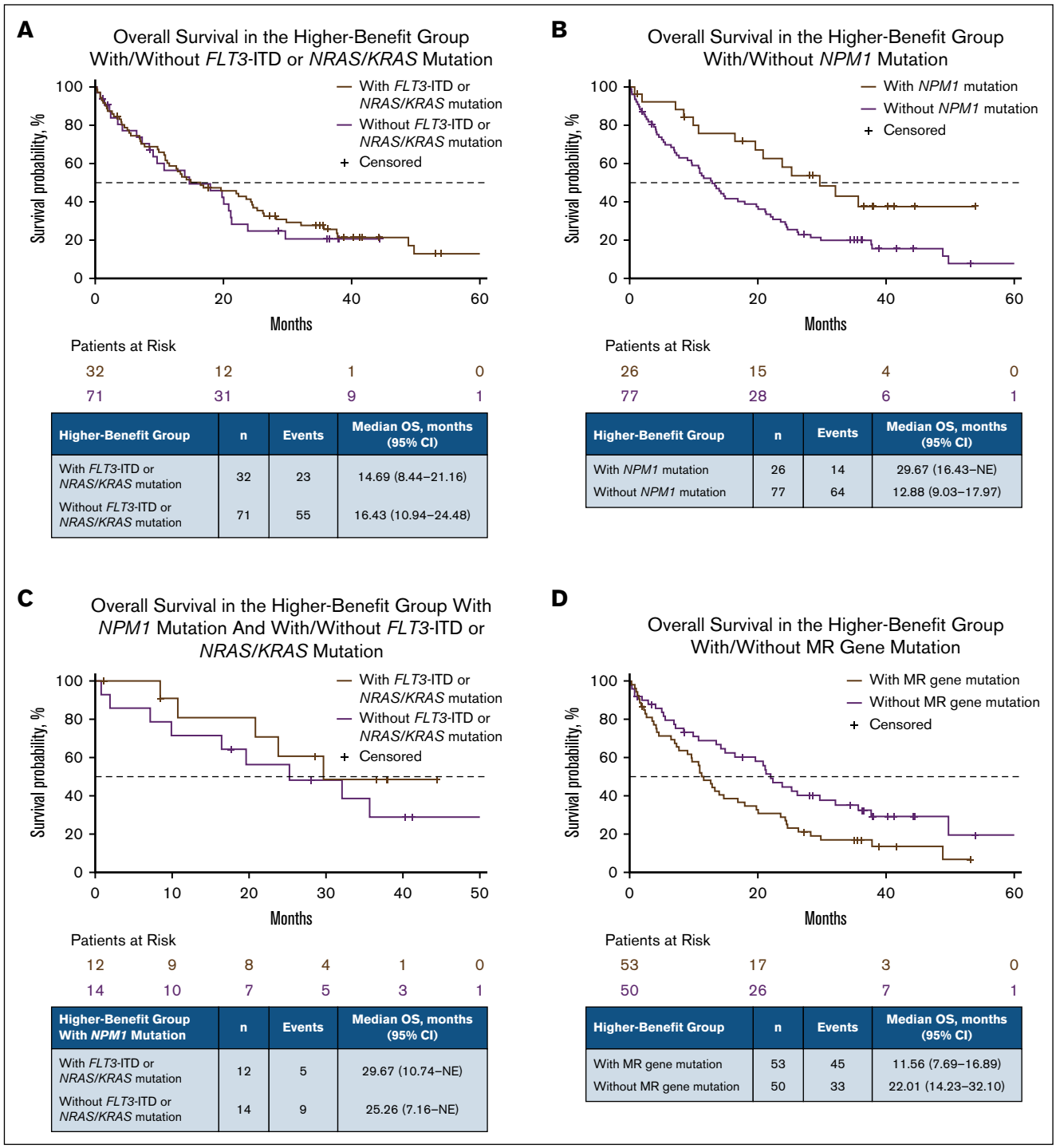

Higher-Benefit Group	n	Events	Median OS, months (95% CI)
With *FLT3*-ITD or *NRAS/KRAS* mutation	32	23	14.69 (8.44–21.16)
Without *FLT3*-ITD or *NRAS/KRAS* mutation	71	55	16.43 (10.94–24.48)

Higher-Benefit Group	n	Events	Median OS, months (95% CI)
With *NPM1* mutation	26	14	29.67 (16.43–NE)
Without *NPM1* mutation	77	64	12.88 (9.03–17.97)

Higher-Benefit Group With *NPM1* Mutation	n	Events	Median OS, months (95% CI)
With *FLT3*-ITD or *NRAS/KRAS* mutation	12	5	29.67 (10.74–NE)
Without *FLT3*-ITD or *NRAS/KRAS* mutation	14	9	25.26 (7.16–NE)

Higher-Benefit Group	n	Events	Median OS, months (95% CI)
With MR gene mutation	53	45	11.56 (7.69–16.89)
Without MR gene mutation	50	33	22.01 (14.23–32.10)

Figure 4. Survival outcomes in the higher-benefit group, characterized by patients without complex karyotype or *TP53* mutation, stratified by molecular markers of interest. OS outcomes in patients with or without *FLT3*-ITD or *NRAS/KRAS* mutations (A), with or without *NPM1* mutation (B), with *NPM1* mutation with or without *FLT3*-ITD or *NRAS/KRAS* mutation (C), with or without MR gene mutation (D), and with MR gene mutations with or without *FLT3*-ITD or *NRAS/KRAS* (E).

LDAC and venetoclax was studied in 30 patients with relapsed/refractory AML, showing an overall response rate after the first cycle of 70% (95% CI, 52.1-83.3), including a high response rate among patients with either *NRAS* mutation (7/9 [77.8%]) or *FLT3*-ITD (3/4 [75%]).[23]

Overall, these results confirm and reinforce the importance of molecular information in stratifying outcomes in patients receiving venetoclax-based therapy for AML. However, these results also suggest that existing AML risk stratification systems cannot be universally applied to all therapies to estimate outcome. Regimen-

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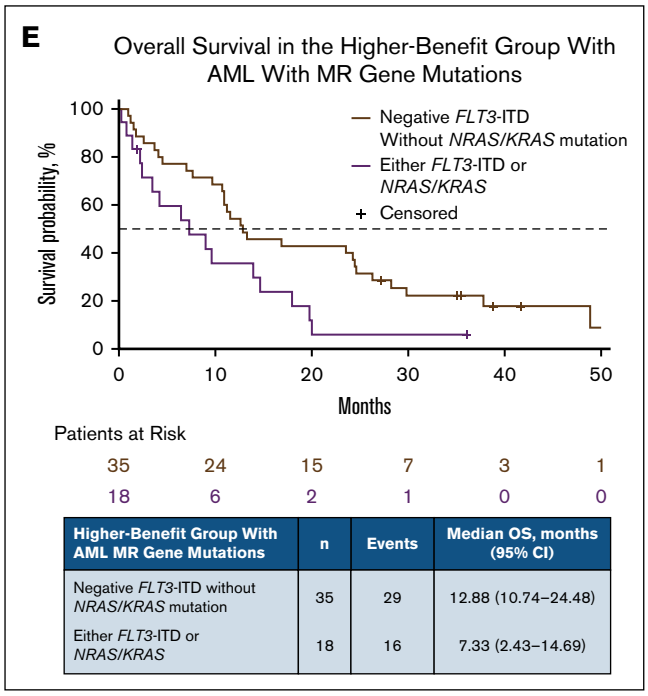

Higher-Benefit Group With AML MR Gene Mutations	n	Events	Median OS, months (95% CI)
Negative *FLT3*-ITD without *NRAS/KRAS* mutation	35	29	12.88 (10.74–24.48)
Either *FLT3*-ITD or *NRAS/KRAS*	18	16	7.33 (2.43–14.69)

Figure 4 (continued)

specific risk classification models are necessary, indicating that novel therapies will need to be individually validated. The limitations of this study need to be acknowledged, including the retrospective nature, small sample size, and the pooling of the phase 1b/2 and phase 3 study populations. In addition, the small numbers of patients across individual mutational subgroups precluded the ability to evaluate the impact of individual mutations in more detail regarding prognostic risk assessment.

Acknowledgments

The authors thank Xiaotong Li for generating heat map figures. Medical writing support was provided by Bio Connections, LLC, and funded by AbbVie.

Venetoclax is being developed in collaboration between AbbVie and Genentech. AbbVie and Genentech funded the M14-387 and VIALE-C studies. AbbVie funded this post hoc analysis and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication.

Authorship

Contribution: B.C., A.H.W., W.M., Y.S., and Z.L. contributed to conception and design; W.F., A.H.W., P.P., P.M., K.L., V.I., I.K., J.N., R.C., M.P., J.B., S.B.T., J.-Z.H., T.Y., J.W., S.A.S., M.R.S., T.L.L., A.E., I.S.T., S.L., G.J.R., and C.D.D. contributed to provision of study materials or patients; B.C., W.M., Y.S., Z.L., Q.J., and R.P. collected and assembled data; and all authors analyzed and interpreted data, wrote the manuscript, had access to relevant data, participated in the drafting, review, and final approval of this publication, and are accountable for all aspects of the work.

Conflict-of-interest disclosure: A.H.W. has served as a consultant for AbbVie, Amgen, Astellas Pharma, Celgene, Janssen, MacroGenics, Novartis, Roche, and Servier; has received research funding from AbbVie, Celgene, Novartis, and Servier; and is employed by the Walter and Eliza Hall Institute of Medical Research, which receives royalties related to venetoclax, and is entitled to a fraction of these payments. P.P. has received grants/research support from AbbVie, Genesis, Novartis, and Roche; and honoraria from AbbVie, Genesis, Gilead, Janssen, Novartis, and Roche. P.M. has received grants/research support from Astellas Pharma, Celgene, Daiichi Sankyo, Janssen, Karyopharm Therapeutics, Novartis, Pfizer, and Teva; has served as a speaker or in an advisory role for AbbVie, Celgene, Daiichi Sankyo, Incyte, Janssen, Karyopharm Therapeutics, Novartis, Pfizer, Teva, and Tolero; and has served as a consultant for Agios, Astellas Pharma, Celgene, Daiichi Sankyo, Oryzon, and Tolero. K.L. has received grants/research support from AbbVie, Novartis, Roche, Sandoz, and Takeda; and personal fees from AbbVie, Astellas Pharma, BeiGene, Celgene, iQone Healthcare Switzerland, Janssen, Novartis, and Sandoz. V.I. has served as an investigator in clinical trials sponsored by AbbVie, Novartis, Astellas, Merck Sharp & Dohme (MSD), Biocad, and Ascentage Pharma; and has participated in educational events for AbbVie, Pfizer, Novartis, Roche, Biocad, and Sotex. I.K. has served as an investigator in clinical trials sponsored by AbbVie. J.N. has served in a consultancy/advisory role for Amgen, Novartis, Pfizer, Roche, and Takeda; and has received travel expenses from Amgen and Janssen. R.C. has participated in speakers' bureaus for Bristol Myers Squibb and AbbVie; and has served on advisory boards for ADC Therapeutics and BeiGene. W.F. reports membership on an entity's board of directors or advisory committee for AbbVie, Amgen, ARIAD/Incyte, Celgene, Jazz Pharmaceuticals, MorphoSys AG, Novartis, Stemline, Clinigen, Otsuka, and Pfizer; has patents and royalties from Amgen; has received support for meeting attendance from Amgen, Daiichi Sankyo, Gilead, Jazz Pharmaceuticals, and Servier; and has received research funding from Amgen, Apis, and Pfizer. M.P. has served as a speaker or in an advisory role for AbbVie, Amgen, Astellas Pharma, Genesis, Janssen, Novartis, AstraZeneca, Bristol Meyers Squibb, Gilead, Sobi, and Pfizer. J.B. has served as a consultant for AbbVie, Servier, Amgen, Astellas Pharma, Bristol Myers Squibb, Jazz Pharmaceuticals, Novartis, Gilead, Palladin, Taiho, and Pfizer; and received travel support from Amgen, Jazz Pharmaceuticals, and Novartis. S.B.T. has served as a consultant for AbbVie and an investigator in clinical trials sponsored by AbbVie. J.-Z.H. has served as an investigator in clinical trials sponsored by AbbVie. T.Y. has received research support/honoraria from and served in an advisory role for AbbVie, Astellas Pharma, Gilead, Janssen, Nippon Shinyaku, Otsuka, Pfizer, Solasia, SymBio, and Takeda. J.W. has served in an advisory role for AbbVie and received research support from Celgene. S.A.S. has served as a consultant and received advisory fees from AbbVie, BerGenBio, Genentech, Senti Bio, and Novartis; and served as a consultant and received advisory fees to institution from AbbVie, BerGenBio, Genentech, Senti Bio, Novartis, Ellipses, Nkarta, Kura Oncology, Sobi, and Syros. M.R.S. has served as a consultant, participated on advisory boards for, and/or received travel expenses from AbbVie, Bristol Myers Squibb, CTI, Forma, Geron, GlaxoSmithKline, Rigel, Taiho, and Treadwell; held equity in and served as a consultant for Empath Biosciences, Karyopharm, and Ryvu; and received research funding from ALX Oncology, Astex, Incyte, and Takeda. A.E. has received honoraria from AbbVie, Astellas, Sanofi, Astex/Otsuka, and Pfizer; and research funding

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from Astex/Otsuka. I.S.T. has received honoraria from Jazz Pharmaceuticals; and participated in speakers' bureaus for Novartis and Pfizer. S.L. is employed by Johnson & Johnson and owns stock and stock options. G.J.R. has served as a consultant for AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Caribou Biosciences, Celgene, Daiichi Sankyo, Ellipses Pharma, Genoptix, Geron, GlaxoSmithKline, Janssen, Jasper Pharmaceuticals, Molecular Partners, Novartis, Pfizer, Oncoverity, OncoPrecision, Rigel, Roche, Syndax, Takeda (IRC Chair), and Telix Pharma; and received research support from Janssen. R.P., Q.J., Z.L., Y.S., and B.C. are employed by AbbVie and may hold stock or stock options. W.M. was formerly employed by AbbVie and is currently employed by Caribou Biosciences and may hold stock or stock options in AbbVie and Caribou Biosciences. C.D.D. has received research support from AbbVie/Genentech, Agios, Bristol Myers Squibb/Celgene, Calithera, Cleave, Daiichi Sankyo, Immune-Onc, and Loxo; served as a consultant or advisory board member for AbbVie, Agios, Aprea Therapeutics, Bristol Myers Squibb/Celgene, Immune-Onc, Kura Oncology, Novartis, Takeda, and Notable Labs. T.L.L. declares no competing financial interests.

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