Hypomethylating agents plus venetoclax *versus* intensive chemotherapy in acute myeloid leukemia with chromosome 5 and 7 abnormalities

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Abstract

Abnormalities in chromosomes 5 and 7 are frequently identified in acute myeloid leukemia, are particularly enriched in therapy- and myelodysplasia-related disease, and confer an adverse prognosis. Given the high risk of relapse, allogeneic stem cell transplant (allo-SCT) is typically recommended for patients achieving complete remission following induction chemotherapy. We currently lack prospective data to decide whether intensive chemotherapy (IC) or a hypomethylating agent + venetoclax (HMA+ven) is the superior frontline treatment approach for these patients. Hence, we performed a retrospective study in a large cohort of patients with acute myeloid leukemia and deletion 7 (-7) and/or deletion 5 or 5q (-5/del5q) comparing outcomes between patients treated with IC or HMA+ven. Remission rates after IC and HMA+ven were found to be comparable (43% *vs*. 52%, *P*=0.2). When adjusting for patient and disease characteristics in multivariable analysis, treatment with IC *vs*. HMA+ven did not significantly impact overall survival (hazard ratio [HR]=1.02, *P*=0.9202), while age at diagnosis (HR=1.02, *P*=0.0324), prior myeloid disease (HR=1.42, *P*=0.0266), monosomal karyotype (HR=1.48, *P*=0.029), complex karyotype (HR=1.61, *P*=0.0156), and *KRAS* mutations (HR=2.21, *P*=0.0063) were associated with inferior survival. There was also no difference in overall survival in patients age 60-75 years by treatment strategy (7.8 *vs*. 6.4 months, *P*=0.56), motivating future randomized trials of IC *versus* HMA+ven in this older population to inform optimal therapy. Importantly, overall survival was significantly improved in patients undergoing allo-SCT irrespective of frontline therapy, and allo-SCT consolidation was the most important predictor of long-term survival in multivariable analysis (HR=0.36, *P*<0.0001).

Introduction

Abnormalities in chromosomes 5 and 7 occur frequently in myeloid malignancies and confer an unfavorable prognosis in patients with acute myeloid leukemia (AML).[1-4] These chromosome aberrations are present in 5-15% of cases of *de novo* AML and are enriched in patients with therapy-related AML (20-30%),[2,5-7] or a history of an antecedent myelodysplastic syndrome.[8] A chromosome 7 deletion (-7) is the most common individual cytogenetic abnormality conferring adverse risk in AML, and both -7 and -5/del5q are designated as adverse risk by the European LeukemiaNet (ELN) 2022 recommendations.[1,9] As these alterations are associated with inferior outcomes,

allogeneic stem cell transplant (allo-SCT) is recommended for patients who achieve a complete remission (CR) following induction therapy. However, the optimal upfront treatment strategy to achieve CR prior to allo-SCT remains unclear. Induction with intensive chemotherapy (IC), consisting of 7 days of cytarabine and 3 days of daunorubicin (7+3 regimen), has been the mainstay of upfront therapy for AML for over half a century.[10] IC with liposomal cytarabine and daunorubicin (CPX-351) was recently approved for AML with myelodysplasia-related changes and has been shown to give a superior overall survival (OS) when compared to the standard 7+3 regimen.[11] More recently, a combination of a hypomethylating agent (HMA) plus venetoclax (HMA+ven) has emerged as a successful therapeutic approach in older and frail patients given its favorable toxicity profile compared to that of IC.[12-14] Numerous studies have explored the prognostic and predictive impact of mutations on treatment response and survival with IC *versus* HMA+ven.[15-17] However, using individual cytogenetic abnormalities to help select the upfront treatment strategy in AML has been explored less and it remains unclear what the optimal frontline treatment approach in AML patients with -7 and/or -5/del5q should be. Furthermore, the association of chromosome 5 and 7 abnormalities with genomic complexity, such as complex and monosomal karyotype, as well as *TP53*-mutated AML portends a poor response to induction chemotherapy with either IC or HMA+ven and it is unclear whether IC has any advantage over HMA+ven in this subgroup of patients.[8,18-21] Hence, we sought to collect comparative outcome data in AML patients with -7 and/or -5/del5q chromosomal abnormalities to help guide clinical management and inform future clinical trial design.

Methods

Study population

The aim of this study was to examine and compare the relative impact of frontline treatment in newly diagnosed patients with AML harboring -7 and/or -5/del5q and treated with IC or HMA+ven. We included consecutive patients age ≥18 years with AML with -7 and/or -5/del5q diagnosed between April 2014 and May 2024 who were treated at Memorial Sloan Kettering Cancer Center, Dana-Farber Cancer Institute, Yale Cancer Center, Institut Paoli-Calmettes, and Vilnius University Hospital Santaros Klinikos. The distribution of the patients by center is detailed in *Online Supplementary Table S1*. Patients were treated with upfront IC, either the 7+3 regimen or CPX-351, or a HMA (decitabine or azacitidine) plus venetoclax. Detection of -7 and/or -5/del5q was achieved by conventional cytogenetic testing at the participating centers according to local standards, including karyotyping and fluorescence *in situ* hybridization (FISH), with karyotype performed and utilized for all patients and additional FISH data included if available. Data including patient and treatment characteristics, other concurrent cytogenetic abnormalities, and mutational alterations (full list evaluated provided in *Online Supplementary Table S2*) were also collected. The molecular ontogeny of AML was defined as previously described.[22] A complex karyotype was defined as three or more unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities, excluding hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities. A monosomal karyotype was defined as the presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML). Both transplant-eligible and transplant-ineligible patients were included in the study. There were no specific protocol treatment guidelines and therapy was selected at the discretion of the treating physician. Institutional review board approval at all participating institutions was obtained before study initiation.

Clinical outcomes

Assessment of response as per the ELN 2017 criteria was completed following induction for patients in the IC-treated group and at the time of best response for those in the group treated with HMA+ven.[23] Minimal residual disease (MRD) status was assessed by flow cytometry. OS was calculated from the time of starting induction therapy to death from any cause or last follow-up. Patients who were lost to follow-up were censored on the date of last known follow-up. Subgroup analysis was performed in patients 60-75 years old, patients who received an allo-SCT, patients with a concurrent complex karyotype and patients having *TP53*-mutated AML according to the definition of the International Consensus Classification (presence of a *TP53* mutation with variant allele frequency ≥10%).[24]

Statistical analysis

Descriptive statistics were summarized for categorical and continuous variables. Categorical variables were tabulated as counts and percentages, and comparisons of counts were made by Fisher exact tests. Continuous variables were summarized with median and range and compared with Wilcoxon rank sum tests. Unless otherwise noted, two-sided 95% confidence intervals (95% CI) were provided for both categorical and continuous estimates. The method of Kaplan and Meier was used to estimate OS with 95% CI from the log method. Landmark analysis was used to evaluate post-transplant survival outcomes. Log-rank tests were employed for the comparison of time-to-event outcomes. For all these analyses, a two-sided P value <0.05 was considered statistically significant.

To assess the hazard of various covariates on OS, Cox proportional hazards models were constructed. Univariable regression models were first constructed to select

significant covariates with a *P* value <0.10, and the selected covariates were further evaluated in multivariable regression models in a backward elimination approach together with treatment (HMA+ven *vs*. IC) as a pre-defined covariate. Of note, time to transplant was used as a time-varying covariate.

Results

Baseline demographic and disease characteristics in patients treated with intensive chemotherapy or a hypomethylating agent plus venetoclax

A total 246 AML patients were found to have -7 and/or -5/del5q and received frontline treatment with either IC or HMA+ven. The baseline demographic and clinical characteristics of all patients are summarized in Table 1. A total of 121 (49%) patients had -5/del5q, 74 (30%) had -7, and 51 (21%) had both -5 or del(5q) and -7. A total of 85 (35%) patients received IC and 161 (65%) patients received HMA+ven as frontline treatment. The median age of the whole cohort was 69 years: patients in the group treated with HMA+ven were significantly older than those in the IC-treated group, with a median age of 73 years (range, 22-92) compared to 62 years (range, 33-79), respectively (*P*<0.001). The distribution of female and male patients was similar across groups. Approximately one-third of patients had a prior diagnosis of a myeloid malignancy in both groups. Therapy-related AML was diagnosed in 20% of IC-treated and 31% of HMA+ven-treated patients. Prior HMA exposure for an antecedent myelodysplastic syndrome was more common in patients treated with IC than in those treated with HMA+ven (19% *vs*. 8%, *P*=0.021).

The molecular ontogeny of most of the cases of AML was defined as *TP53*-mutated (61%), followed by secondary ontogeny (22%) and *de novo* ontogeny (16%). *TP53* mutations (73% *vs*. 40%, *P*<0.001), complex karyotype (83% *vs*. 64%, *P*=0.002), and deletion 17p (35% *vs*. 18%, *P*=0.005) were more common in patients treated with HMA+ven than in those treated with IC. In contrast, *de-novo* ontogeny, secondary ontogeny, RAS pathway mutations (*KRAS, NRAS, PTPN11,* and/or *CBL*), and *RUNX1* mutations were seen less frequently with HMA+ven that with IC (10% *vs*. 28%, *P*<0.001; 17% *vs*. 32%, *P*<0.001; 17% *vs*. 37%, *P*<0.001; and 9% *vs*. 25%, *P*=0.002, respectively).

Although the use of IC and HMA+ven is common in patients with AML who are age <60 years old or >75 years old, respectively, the optimal therapeutic approach in the

Table 1. Baseline demographic and disease characteristics for patients with -7 and -5/del5q by overall group, those treated with intensive chemotherapy and those treated with a hypomethylating agent plus venetoclax.

Characteristics	Overall N=246	IC N=85 (35%)	HMA+ven N=161 (65%)	*P*
Chromosome 5 and 7 abnormalities, N (%)				
-5/del5q	121/246 (49)	41/85 (48)	80/161 (50)	-
-7	74/246 (30)	32/85 (38)	42/161 (26)	0.071
Both -5/del5q and -7	51/246 (21)	12/85 (14)	39/161 (24)	-
Patient and treatment characteristics				
Age, years, median (range)	69 (22-92)	62 (33-79)	73 (22-92)	<0.001
Male sex, N (%)	138/246 (56)	52/85 (61)	86/161 (53)	0.28
Prior myeloid malignancy, N (%)	79/246 (32)	29/85 (34)	50/161 (31)	0.67
Therapy-related, N (%)	67/246 (27)	17/85 (20)	50/161 (31)	0.072
Prior hypomethylating agent, N (%)	29/246 (12)	16/85 (19)	13/161 (8)	0.021
Concomitant cytogenetic and molecular abnormalities, N (%)				
Complex karyotype	187/246 (76)	54/85 (64)	133/161 (83)	0.002
Monosomal karyotype	181/246 (74)	57/85 (67)	124/161 (77)	0.10
Deletion 17p	71/246 (29)	15/85 (18)	56/161 (35)	0.005
RAS pathway	55/236 (23)	28/75 (37)	27/161 (17)	<0.001
ASXL1	24/246 (10)	7/85 (8)	17/161 (11)	0.66
DNMT3A	35/246 (14)	12/85 (14)	23/161 (14)	>0.99
IDH1 or *IDH2*	19/246 (8)	7/85 (8)	12/161 (8)	0.81
RUNX1	36/246 (15)	21/85 (25)	15/161 (9)	0.002
TET2	29/246 (12)	5/85 (6)	24/161 (15)	0.039
Splicing factor mutation	45/233 (19)	23/75 (31)	22/158 (14)	0.004
Ontogeny as defined by co-occurring mutations, N (%)				
De novo	40/246 (16)	24/85 (28)	16/161 (10)	-
Secondary	55/246 (22)	27/85 (32)	28/161 (17)	<0.001
TP53-mutated	151/246 (61)	34/85 (40)	117/161 (73)	-

P values <0.05 are considered statistically significant. IC: intensive chemotherapy; HMA+ven: hypomethylating agent plus venetoclax.

population aged 60-75 years is unclear. Therefore, we also examined the demographic and clinical characteristics of a total of 130 patients aged 60-75 years old with chromosome 5 and/or 7 abnormalities receiving IC or HMA+ven (*Online Supplementary Table S3)*. In total, 60 (46%) had -5/del5q, 44 (34%) had -7, and 26 (20%) had both -5 or del(5q) and -7. Of the 130 patients, 42 (32%) patients received IC and 88 (68%) received HMA+ven. The median age of this cohort was 69 years, with the HMA+ven group being older than the IC group (70 *vs*. 66 years, respectively, *P*<0.001). In the cohort aged 60-75 years, there were similar rates of complex karyotype, deletion 17p, and RAS pathway mutations in both the IC- and HMA+ven-treated groups, with complex karyotype in 64% *vs*. 76% (*P*=0.21), deletion 17p in 32% *vs*. 19% (*P*=0.15), and RAS pathway mutations in 18% *vs*. 26% (*P*=0.35) of patients. The distribution of ontogeny defined based on co-occurring mutations varied between the IC- and HMA+ven-treated groups in the population 60-75 years old, although this did not reach statistical significance: *de novo* ontogeny was identified in 26% *vs*. 14%, secondary ontogeny in 29% *vs*. 20%, and TP53 mutations in 45% *vs*. 66% of patients (*P*=0.061).

Treatment characteristics and response rates in patients treated with intensive chemotherapy or a hypomethylating agent plus venetoclax

Treatment characteristics and clinical outcomes for all 246 patients with chromosome 5 and/or 7 abnormalities treated with IC or HMA+ven are summarized in Table 2. In the IC group, 54 (64%) patients were treated with the 7+3 regimen and 31 (36%) were treated with CPX-351. Of those treated with the 7+3 regimen, nine received an additional agent (2 midostaurin, 1 ivosidenib, 1 venetoclax, and 5 other or unknown). In the HMA+ven group, 96 (60%) were treated with decitabine plus venetoclax and 65 (40%) were treated with azacitidine plus venetoclax, with a median number of two cycles of treatment among 120 patients with information available on the number of cycles administered (range, 1-19). There was no difference in rates of CR or CR with incomplete count recovery (CRi) between IC- and HMA+ven-treated patients (43% *vs*. 52%, *P*=0.20). Among those who had MRD assessed by flow cytometry, MRD-negative rates were similar in patients treated with HMA+ven and those treated with IC (43% [16/37] *vs*. 50% [9/18], *P*=0.77). The number of patients proceeding to transplant was 76 (31%), with a significantly higher number in the IC-treated group than in the group treated with HMA+ven (54% vs. 19%, *P*<0.001). We also evaluated 30- and 60-day mortality after treatment initiation, with comparable rates among IC- and HMA+ven-treated patients (2% *vs*. 4%, *P*=0.72; 8% *vs*. 16%, *P*=0.11).

We also assessed the clinical outcomes for the subgroup of 130 patients 60-75 years old with chromosome 5 and 7 abnormalities treated with IC or HMA+ven (*Online Supplementary Table S4*). There was no difference in rates of CR/CRi between IC- and HMA+ven-treated patients in this older group (44% *vs*. 49%, *P*=0.69). MRD-negative rates were similar in older HMA+ven-treated patients and in those treated with IC (56% *vs*. 56%, *P*>0.99). The number of patients proceeding to allo-SCT in this group aged 60-75 years old was 43 (33%), and IC-treated patients were significantly more likely to proceed to allo-SCT compared to HM+ven-treated patients (48% *vs*. 26%, *P*=0.018). Rates of 30- and 60-day mortality after IC and HMA+ven initiation were comparable in this subset (2% *vs*. 5%, *P*>0.99; 10% *vs*. 16%, *P*=0.42).

Overall survival is not different in patients treated with intensive chemotherapy or a hypomethylating agent plus venetoclax who are 60-75 years old

We next examined survival outcomes in patients with chromosome 5 and 7 abnormalities treated with IC or HMA+ven. In an unadjusted analysis, patients treated with IC had better OS with a median of 11 months (95% CI: 8.1-16) com-

Table 2. Treatment characteristics and rates of remission, minimal residual disease-negativity, and transplantation in patients with -7 and/or -5/del5q by overall group, those treated with intensive chemotherapy and those treated with a hypomethylating agent plus venetoclax.

Treatment and outcomes	Overall N=246	IC N=85 (35%)	HMA+ven N=161 (65%)	*P*
Treatment, N (%)	-	7+3 regimen: 54/85 (64) CPX-351: 31/85 (36)	Aza/Ven: 96/161 (60) Dec/Ven: 65/161 (40)	-
Clinical outcome, N (%)				
CR/CRi	100/206 (49)	34/80 (43)	66/126 (52)	0.20
MRD negativity	25/55 (45)	9/18 (50)	16/37 (43)	0.77
Proceeded to transplant	76/246 (31)	46/85 (54)	30/161 (19)	<0.001
30-day mortality	9/246 (4)	2/85 (2)	7/161 (4)	0.72
60-day mortality	33/246 (13)	7/85 (8)	26/161 (16)	0.11

P values <0.05 are considered statistically significant. IC: intensive chemotherapy; HMA+ven: hypomethylating agent plus venetoclax; Aza/Ven: azacitidine plus venetoclax; Dec/Ven: decatibine plus venetoclax; CR: complete response; CRi: complete response with incomplete count recovery; MRD: minimal residual disease.

pared with 6.3 months (95% CI: 5.7-7.8) for patients treated with HMA+ven (*P*=0.0013) (Figure 1A). However, limiting the analysis to the subgroup of patients 60-75 years old, there was no significant difference in OS between the two groups (Figure 1B). IC-treated patients had a median OS of 7.8 months (95% CI: 5.8-12) compared with 6.4 months (95% CI: 5.7-9.4) in the HMA+ven-treated group (*P*=0.56). Among all patients in CR/CRi after initial therapy who had MRD assessment performed, the median OS was 25 months (95% CI: 17-45) in the MRD-negative group and 17 months (95% CI: 8-not reached) in the MRD-positive group (*P*=0.65).

Overall survival is improved with allogeneic stem cell transplantation independent of frontline treatment strategy

To assess the impact of transplant on patients with chromosome 5 and 7 abnormalities and avoid immortal-time bias, we performed a landmark analysis on transplant using a median transplant time of 4 months as the landmark time. A significantly longer median OS was demonstrated in patients who proceeded to allo-SCT compared to that in patients who did not (21 months [95% CI: 16-42] *vs*. 3.8 months [95% CI: 3.2-6.1], *P*<0.0001) (Figure 2A).

We next assessed what the impact of allo-SCT on OS outcomes was in patients treated with either IC or HMA+ven among those patients who proceeded to transplant, again using a median transplant time of 4 months as the landmark time. In patients treated with IC the median OS of transplant recipients was 20 months (95% CI: 12-47) compared with 2.8 months (95% CI: 1.8-6.1) in those not receiving an allo-SCT (*P*<0.0001) (Figure 2B). Comparison of IC subgroups (7+3 regimen *vs*. CPX-351) was not evaluated given limitations in sample size. In patients treated with HMA+ven as frontline therapy the median OS in transplanted patients was 21 months (95% CI: 16-not reached) compared with 5.0 months (95% CI: 3.6-9.8) in those not receiving an allo-SCT (*P*<0.0001) (Figure 2C).

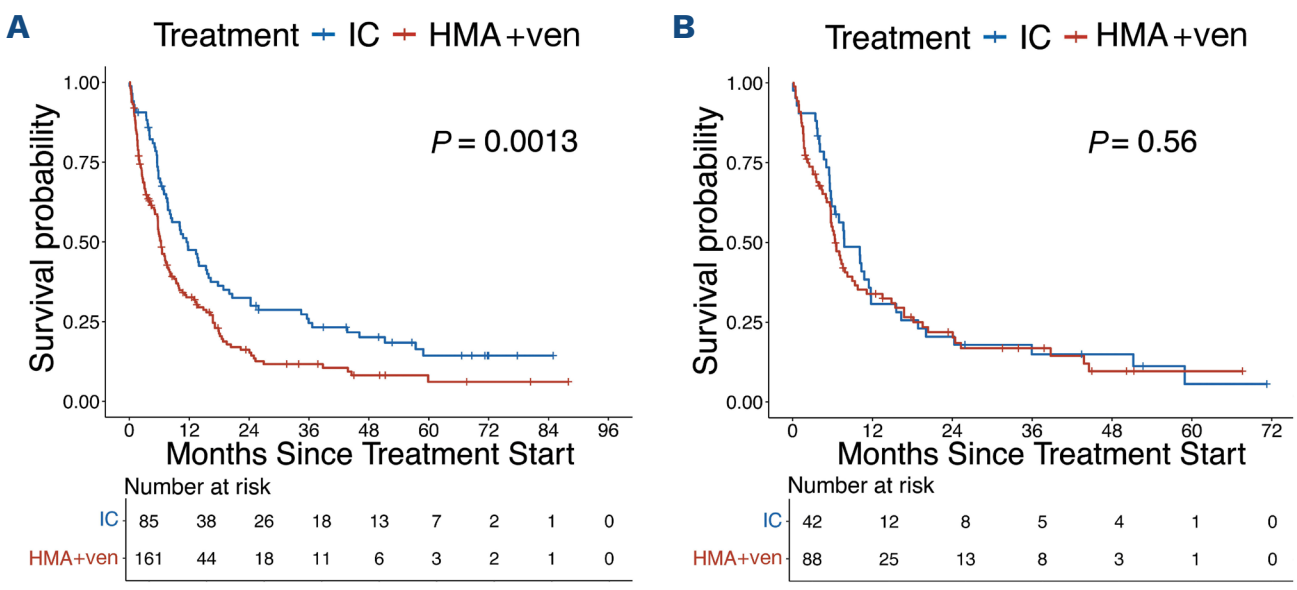

Figure 1. Survival outcomes in patients with -7 and/or -5/del5q stratified by therapy. (A) Overall survival in all patients with -7 and -5/del5q treated with intensive chemotherapy (IC) or a hypomethylating agent plus venetoclax (HMA+ven). (B) Overall survival in patients aged 60-75 years treated with IC *vs*. HMA+ven.

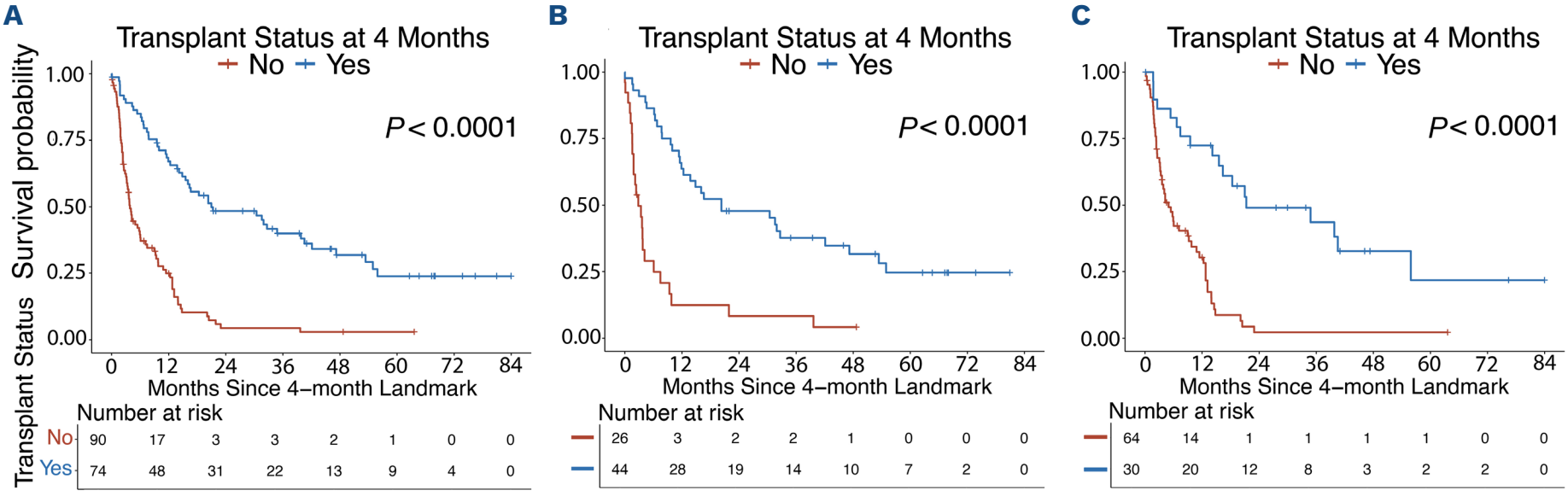

Figure 2. Landmark analysis in patients with -7 and/or -5/del5q who proceeded or did not proceed to transplant using the median transplant time of 4 months as the landmark. (A) All patients with -7 and -5/del5q. (B) Patients with -7 and -5/del5q who received intensive chemotherapy. (C) Patients with -7 and -5/del5q who received a hypomethylating agent plus venetoclax.

The presence of a complex karyotype negatively affects overall survival in patients treated with intensive chemotherapy

Given the frequent co-occurrence of a complex karyotype and mutations in *TP53*, we analyzed response and survival outcomes based on the presence or absence of a complex karyotype and mutations in *TP53* with a variant allele frequency of at least 10%. Among those with a complex karyotype, the rate of CR/CRi was 52% and 44% in those treated with HMA+ven and IC, respectively (*P*=0.037). Among those who did not have a complex karyotype, the rate of CR/CRi was 52% and 40% in those treated with HMA+ven and IC, respectively (*P*=0.17). Those with *TP53* mutations had CR/CRi rates of 55% and 50% after HMA+ven and IC, respectively (*P*=0.44), and those without *TP53* mutation had CR/CRi rates of 46% and 38% after HMA+ven and IC, respectively (*P*=0.016).

Among IC-treated patients, the median OS was superior in patients without a complex karyotype compared to that in patients with a complex karyotype (14 months [95% CI: 10-not reached] *vs*. 9.3 months [95% CI: 7.0-16], *P*=0.019) (Figure 3A). In contrast, in patients treated with HMA+ven, the OS did not differ significantly between the subgroups without or with a complex karyotype (median OS 6.4 months [95% CI: 5.6-7.8] vs. 6.2 months [95% CI: 3.9-20]; *P*=0.66) (Figure 3B). Next, patients with and without a *TP53* mutation receiving either IC (Figure 3C) or HMA+ven (Figure 3D) were assessed. In patients treated with IC, the median OS was 14 months (95% CI: 7.7-26) in those without a *TP53* mutation compared to 10 months (95% CI: 7.4-16) in those with a *TP53* mutation (*P*=0.37). Among patients treated with HMA+ven, the median OS was 8.2 months (95% CI: 5.7-20) in those without a *TP53* mutation compared to 5.8 months (95% CI: 4.2-7.6) in those with a *TP53* mutation (*P*=0.059).

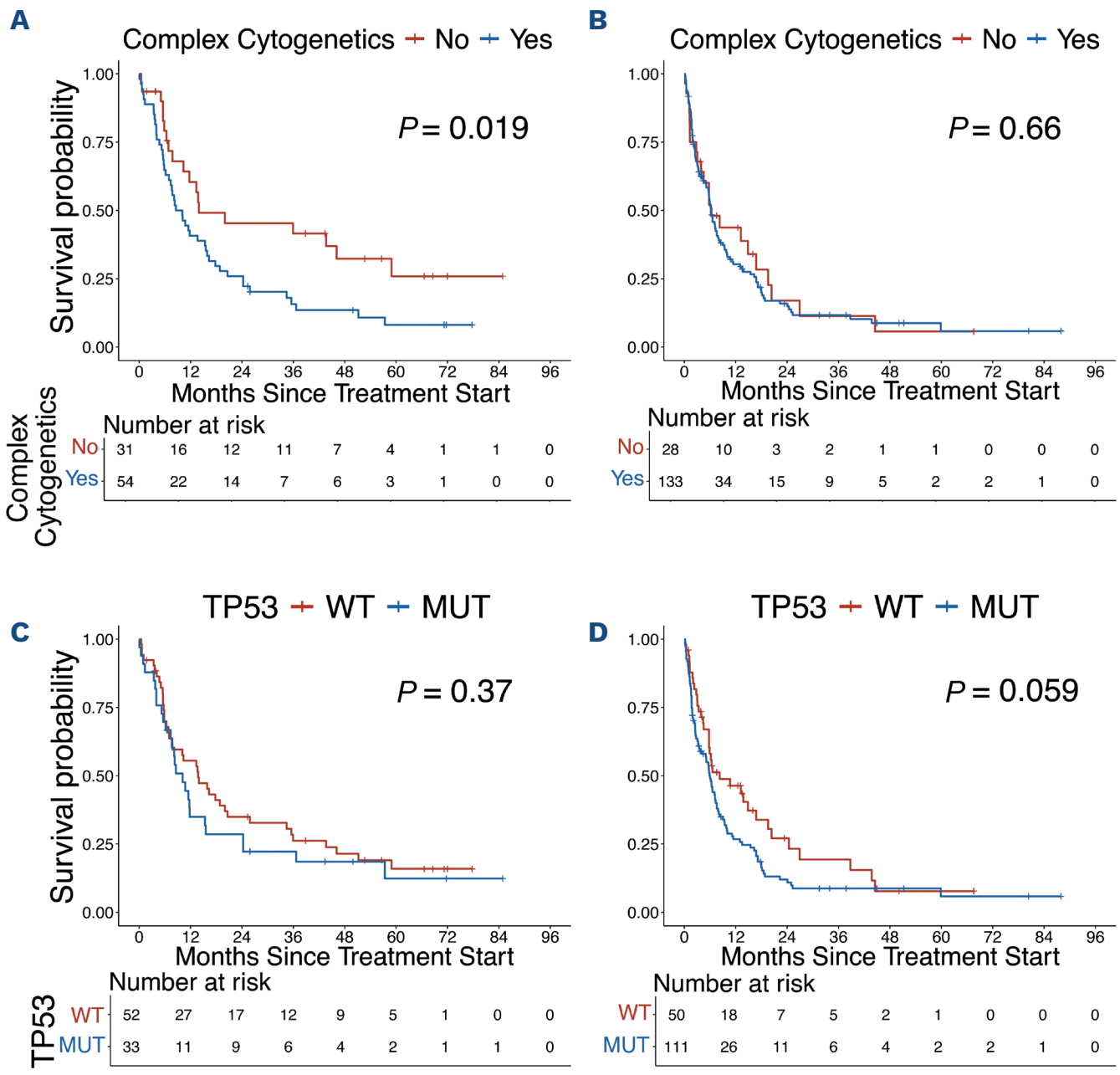

Figure 3. Overall survival in patients with -7 and/or -5/del5q with a concurrent complex karyotype or *TP53* co-mutation treated with intensive chemotherapy or a hypomethylating agent plus venetoclax. (A) Overall survival (OS) in all patients with or without a complex karyotype treated with intensive chemotherapy (IC). (B) OS in all patients with or without a complex karyotype treated with a hypomethylating agent plus venetoclax (HMA+ven). (C) OS in all patients with or without a *TP53* co-mutation with a variant allele frequency ≥10% treated with IC. (D) OS in all patients with or without a *TP53* co-mutation with a variant allele frequency ≥10% treated with HMA+ven. WT: wild-type; MUT: mutated.

Response and survival outcomes in demographic and mutational subgroups

We evaluated response and survival outcomes in younger patients in the cohort. Of the 246 patients, 59 were <60 years old at diagnosis, comprising 39 and 20 treated with IC and HMA+ven, respectively. The CR/CRi rates were comparable at 46% after IC and 42% after HMA+ven (*P*>0.99). The median OS among these IC-treated patients was 21 months (95% CI: 14-46) *versus* 7.6 months (95% CI: 4.2-22) in the HMA+ven-treated group (*P*=0.028).

The rate of CR/CRi among 34 patients with *NRAS* and/or *KRAS* co-mutation was 31% overall and 31% in both the HMA+ven- and IC-treated groups. The median OS of these patients was 13 months (95% CI: 7.8-not reached) in the IC group and 6.3 months (95% CI: 2.8-not reached) in the HMA+ven group (*P*=0.059). Among 22 patients with splicing factor mutations, including *SF3B1, SRSF2, U2AF1*, and *ZRSR2*, the CR/CRi rate was 55% after initial therapy compared with 53% in those without such mutations (*P*>0.9). The median OS was 5.7 months (95% CI: 3.3-20) among those with splicing factor mutations and 6.3 months (95% CI: 5.2-7.6) among those without (*P*=0.64).

We also analyzed outcomes after HMA+ven by the ELN 2024 risk classification for patients receiving less-intensive therapies.[25] Among this cohort, seven patients had favorable-risk, 36 had intermediate-risk, and 118 had adverse-risk disease. The rates of CR/CRi were 100%, 46%, and 51% in the favorable-, intermediate-, and adverse-risk cohorts, respectively (favorable *vs*. intermediate, *P*=0.072; favorable *vs*. adverse, *P*=0.089; intermediate *vs*. adverse, *P*>0.9). The median OS was 20 months (95% CI: 4.5-not reached), 6.4 months (95% CI: 3.9-24), and 6.1 months (95% CI: 5.1-7.6) in the favorable-, intermediate-, and adverse-risk cohorts, respectively (favorable *vs*. intermediate, *P*=0.55; favorable *vs*. adverse, *P*=0.36; intermediate *vs*. adverse, *P*=0.36).

Induction treatment choice has no impact on overall survival in acute myeloid leukemia patients with chromosome 7 or 5 abnormalities when adjusted for other patient and treatment characteristics

Finally, we performed univariable and multivariable analyses to determine which patient, disease, and treatment characteristics affected survival outcomes. In univariable analysis (*Online Supplementary Table S5*), several features were found to be associated with significantly inferior survival, including age at diagnosis, prior myeloid malignancy, monosomal or complex karyotype, *TP53* or *TET2* co-mutations, and treatment with HMA+ven. Prior HMA exposure and *KRAS* co-mutation were associated with a trend toward inferior survival with borderline significance (*P*=0.070 and *P*=0.059, respectively). Time-varying transplant was associated with significantly improved survival. Next, multivariable analysis was performed to identify independent predictors of survival for patients with chromosome 5 and 7 abnormalities treated with IC or HMA+ven. Age at diagnosis, prior myeloid disease, monosomal karyotype, complex karyotype, treatment with HMA+ven *versus* IC, *KRAS* mutation, and time-varying transplant were covariates in the final model. Age at diagnosis (HR=1.02, 95%

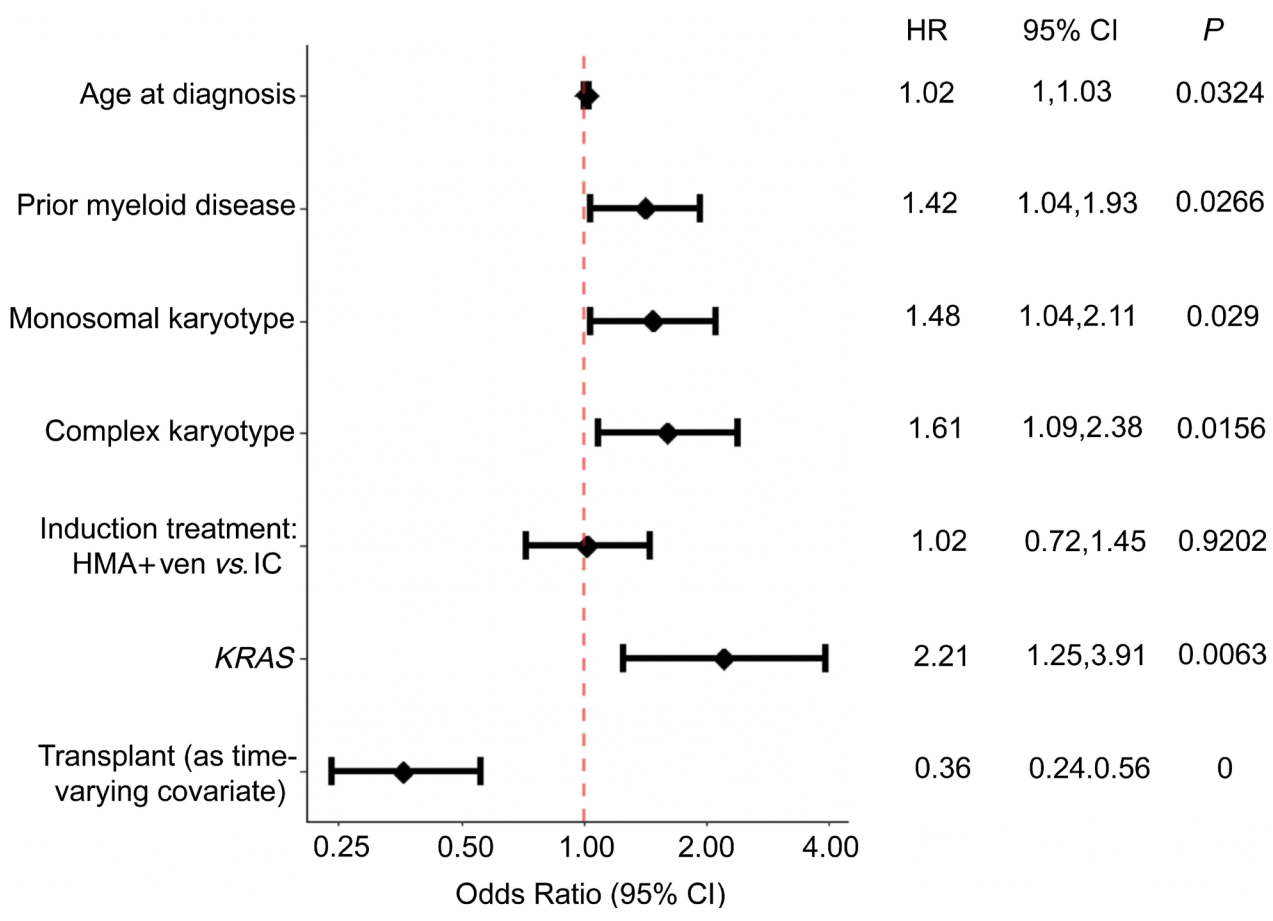

Figure 4. Multivariable analysis of predictors of overall survival in patients with -7 and -5/del5q. HR: hazard ratio; 95% CI: 95% confidence interval; HMA+ven: hypomethylating agent plus venetoclax; IC: intensive chemotherapy.

CI: 1-1.03; *P*=0.0324), prior myeloid disease (HR=1.42, 95% CI: 1.04-1.93; *P*=0.0266), monosomal karyotype (HR=1.48, 95% CI: 1.04-2.11; *P*=0.029), complex karyotype (HR=1.61, 95% CI: 1.09-2.38; *P*=0.0156), and *KRAS* mutation (HR=2.21, 95% CI: 1.25-3.91; *P*=0.0063) were all associated with inferior survival. Allo-SCT as a time-varying covariate was associated with a significant improvement in OS (HR=0.36, 95% CI: 0.24-0.56; *P*<0.0001). Importantly, induction treatment choice with HMA+ven *versus* IC had no impact on OS in multivariable analysis (HR=1.02, 95% CI: 0.72-1.45; *P*=0.9202).

Discussion

The present study retrospectively analyzed the response and comparative survival outcomes of 246 newly diagnosed AML patients with chromosome 5 and 7 abnormalities treated with IC or HMA+ven. While numerous investigations have examined the importance of mutations in predicting response to treatment and clinical outcomes, the value of classical cytogenetic markers in guiding selection between IC and HMA+ven as the preferred induction regimen has not been analyzed.[15-17] We focused on -5/del5q and -7 as these are commonly seen in patients with AML, particularly those with therapy-related AML or an antecedent myelodysplastic syndrome, and are associated with poor outcomes.[2,3] In our analysis, we observed that the receipt of allo-SCT was important for long-term survival, independently of the preceding treatment strategy. Importantly, in older adults (age 60-75) with AML and -5/del5q and/or -7, remission and survival outcomes were comparable in patients treated with IC and HMA+ven. Lastly, although OS was superior with IC than with HMA+ven in the overall cohort, this likely reflects the younger age and greater fitness of the IC-treated group. When rigorously adjusting for patient and treatment characteristics in multivariable analysis, we conclude that the upfront treatment approach with IC or. HMA+ven did not significantly impact OS outcomes in AML patients with -5/del5q and -7.

It is important to note that this was not a randomized study, and established patient and disease characteristics with known impact on clinical outcomes likely influenced treatment decisions. Some examples which illustrate this include the following. Older patients were more likely to be treated with HMA+ven than with IC (median age 73 years *vs*. 62 years) as this regimen is a well-established therapeutic approach in previously untreated AML in older patients ineligible for IC based on the results of the VIALE-A trial.[14] Patients with prior HMA exposure were more likely to be treated with IC, both in the overall cohort (19% *vs*. 8%) and among patients aged 60-75 (26% *vs*. 7%). Patients with a concomitant complex karyotype or mutations in *TP53* were more likely to be treated with HMA+ven than with IC (83% *vs*. 64% and 73% *vs*. 40%, respectively), likely given the limited responses and poor prognosis historically observed with IC in this population.[18,19,26] In contrast, among those with RAS pathway co-mutations, treatment with IC was more common than treatment with HMA+ven (37% *vs*. 17%), presumably given the association of RAS-mutant leukemia stem cells with venetoclax resistance.[15]

However, despite these clear differences in the patient and disease characteristics between IC-and HMA+ven-treated patients, rates of CR/CRi were comparable. OS was superior in IC-treated patients, and this group was more likely to proceed to transplant, likely reflecting younger age and increased fitness as compared to the patients treated with HMA+ven. This is further underscored by the absence in a difference in OS between IC- and HMA+ven-treated older patients (60-75 years). Given these findings, we strongly advocate for randomized trials in this patient population, comparing IC and HMA+ven, to examine whether HMA+ven leads to fewer adverse events and should indeed be prioritized in older patients. Furthermore, 30- and 60-day mortality rates after treatment initiation were low among both IC- and HMA+ven-treated patients and comparable across groups. Given that patients in this study were all treated at tertiary care centers with significant experience in the complex care of AML patients, the understanding of the comparative impact of these therapies on 30- and 60-day mortality in community practice settings is limited. In addition to the choice of upfront treatment strategy, allo-SCT was the most critical factor determining long-term OS, with those undergoing allo-SCT having a significantly longer median OS compared to those who did not. Notably, when comparing survival outcomes by transplant status, IC- and HMA+ven-treated patients undergoing transplant had nearly identical median OS (20 *vs*. 21 months). Furthermore, multivariable analysis demonstrated that upfront treatment choice did not affect OS, in contrast to allo-SCT, which was associated with a significant improvement in OS.

When analyzing the impact of concomitant cytogenetic and molecular features on survival outcomes, a complex karyotype or *TP53* co-mutation did not have a significant effect on survival in those treated with HMA+ven. In contrast, patients with a complex karyotype treated with IC had significantly shorter survival compared to those without a complex karyotype. Previous investigations have demonstrated that those with poor-risk cytogenetics who were *TP53* wild-type had comparable outcomes to those with intermediate-risk cytogenetics.[21] These data, together with our findings, suggest that adverse-risk cytogenetics may not be a major predictor of inferior response to HMA+ven compared to IC and that HMA+ven should be favored for patients with chromosome 5 and 7 abnormalities with concomitant complex karyotype. Notably, while both complex karyotype and *TP53* co-mutations were associated with significantly inferior survival in univariable analysis, only complex karyotype was associated with inferior survival by multivariable analysis, likely due to the significant

overlap between patients who had a complex karyotype and a *TP53* mutation.

Apart from the retrospective design of the study, lack of randomization, and heterogeneity of centers at which patients were treated, limitations of this study include variation in chemotherapeutic approaches. Specifically, IC-treated patients received either the 7+3 regimen or CPX-351, with the latter providing superior OS and post-transplant survival outcomes in the secondary and therapy-related AML populations.[27] Within the group treated with IC, comparative survival outcomes for those given the 7+3 regimen or CPX-351 could not be analyzed due to limitations in sample size. Over the decade-long span of patient accrual, evolution in clinical practice, including supportive care, transplant patterns, and availability of salvage options, may have influenced treatment decisions. A further limitation is the smaller number of young patients and resultant challenges in matching patients by age among those younger than 60 years old. Additionally, given that this study included large tertiary care centers, applications to community-based practices are limited. Details regarding allo-SCT conditioning (myeloablative *vs*. reduced intensity) and donor information which may have influenced outcomes were not collected as part of this retrospective study. Finally, unknown confounders cannot be adjusted for in multivariable analysis, and large phase III randomized clinical trials will be needed to adjust for both known and unknown confounders.

There are prospective randomized data emerging from China demonstrating non-inferiority of decitabine plus venetoclax as compared to idarubicin plus cytarabine in young, fit untreated AML patients.[28] A phase II randomized study in the USA comparing azacitidine plus venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with AML is ongoing as well (NCT04801797).[29] However, both studies include a relatively small number of patients and have limited survival follow-up, making it challenging to compare outcomes in small subgroups defined by specific cytogenetic abnormalities such as chromosome 5 and 7 alterations and underscoring the importance of our retrospective report. A larger phase II MyeloMATCH trial evaluating the 7+3 regimen in comparison to CPX-351, the 7+3 regimen plus venetoclax, azacitidine/venetoclax, and CPX-351 plus venetoclax in higher-risk AML is ongoing and may provide further insights eventually (NCT05554406). However, until such larger clinical trials with sufficiently long follow-up allowing the comparison of the effectiveness of HMA+ven *versus* IC in subgroups defined by specific mutations and cytogenetic abnormalities, retrospective studies such as ours will continue to be critical in guiding treatment decisions.

Disclosures

ECC has provided consultancy services for GLG, Dedham Group, Guidepoint, Merck, AbbVie and Rigel. RPB has served on a steering committee for Servier. RS has provided consultancy services for Gilead Sciences, Servier, Rigel and Kura Oncology and has served on a steering committee for Servier. AZ has provided consultancy services for AbbVie, Astellas, Pfizer, Novartis and Johnson & Johnson and has received travel support from AbbVie, Novartis, Johnson & Johnson and Takeda. SG has provided consultancy services for BMS, Servier, AbbVie and Sanofi. DJD has provided consultancy services for Amgen, Autolus, Blueprint, Gilead, Incyte, Jazz, Novartis, Pfizer, Servier and Takeda; has received research funding from AbbVie, Blueprint, GlycoMimetics and Novartis; and has served on a Data and Safety Monitoring Board for Daiichi-Sankyo, Fibrogen and the Mount Sinai MPN Consortium. RMS has provided consultancy services for GSK, Hemavant, Takeda, Amgen, Aptevo, AvenCell, BerGenBio, Cellularity, CTI Pharma, Epizyme, Jazz, Kura, Rigel and Syntrix. MRL has received research funding from Novartis and AbbVie and honoraria from Novartis, Jazz, Kite and Pfizer. JSG has provided consultancy services for AbbVie, Genentech and Servier; has served on an advisory board for Genentech; and has received research funding from AbbVie, Genentech, Taiho and Newave. AMZ has provided consultancy services for and received honoraria from AbbVie, Agios, Akeso Pharma, ALX Oncology, Amgen, Astellas, BeiGene, BioCryst, BMS/Celgene, Boehringer-Ingelheim, Chiesi, Daiichi Sankyo, Epizyme, Novartis, Otsuka, Regeneron, Schroedinger, Zentalis, Syndax, Taiho, Treadwell, Faron, Genentech, Geron, Gilead, GlycoMimetics, Hikma, Janssen, Karyopharm, Keros, Kura Kyowa Kirin, Lava Therapeutics, Medus, Notable, Orum, Pfizer, Rigel, Servier, Sumitomo, Syros, Takeda and Vinerx and has received research funding from AbbVie, Amgen, BMS/Celgene, Novartis, Otsuka, Geron, Kura, Syros, Takeda, Astex and Shattuck Labs. ADG has provided consultancy services and/or served on advisory boards for AbbVie, Astellas, BMS, Daiichi Sankyo, Genentech, Molecular Partners, Remedy Plan and Syndax Pharmaceuticals; has received research funding from AbbVie, Aprea, Aptose, AROG, Cellularity, Kura Oncology and Pfizer; and has received honoraria from DAVA Oncology and Kura Oncology. EMS has provided consultancy services for Servier, Jazz, Agios, Astellas, Celgene, AstraZeneca, Boehringer Ingelheim, Genentech, Gilead, AbbVie and Daiichi Sankyo. MS has served on advisory boards for Novartis, Kymera, Sierra Oncology, GSK, Rigel, BMS, Sobi, Syndax and Kura; has provided consultancy services for Boston Consulting, GLG and the Dedham group; has participated in CME activities for Novartis, Curis Oncology, Haymarket Media and Clinical Care Options; and is a member of the Medical Safety Monitoring Board for Keros Pharmaceuticals. LB, JPB, YL, LEA, ESW, MW, KL and SS have no conflicts of interest to disclose.

Contributions

LB and MS conceptualized the study. LB, JPB, RMS, LEA, RPB, AZ, SG, GB and ADG collected data and performed the

chart reviews. YL, SS, LB and MS analyzed and interpreted data. LB, RMS, AZ, SG, DJD, RMS, MRL, JSG, ESW, ECC, AZ, EMS, SS and MS wrote the manuscript, which was reviewed and approved by all authors.

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Data-sharing statement

The data that support the findings of this study are available upon request from the corresponding author.

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