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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 (AML), 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 (CR) following induction chemotherapy. We currently lack prospective data to decide whether intensive chemotherapy (IC) versus 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 AML and deletion 7 (-7) and/or deletion 5 or 5q (-5/del5q) comparing outcomes between IC- versus HMA+ven-treated patients. 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 (MVA), treatment with IC vs HMA+ven did not significantly impact overall survival (OS) (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 OS 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, OS 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 MVA (HR 0.36, p<0.0001).

INTRODUCTION

Abnormalities in chromosome 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 history of an antecedent myelodysplastic syndrome.[8] -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 post-induction CR. However, the optimal upfront treatment strategy to achieve CR prior to allo-SCT remains unclear. Induction with IC consisting of cytarabine and daunorubicin (7+3) 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 have a superior OS when compared to standard 7+3.[11] More recently, HMA+ven has emerged as a successful therapeutic approach in older and frail patients given the favorable toxicity profile compared to 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 outcomes data in AML patients with either -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 and 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 (distribution of patients by center defined in **Supplemental Table 1**)**.** Patients were treated with upfront IC, either 7+3 or CPX-351, or HMA (decitabine or azacitidine) plus ven. Detection of -7 and/or -5/del5q was performed by conventional cytogenetic testing at the participating centers per 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 defined in **Supplemental Table 2**) were also collected. Molecular ontogeny of AML was defined as previously described.[22]. Complex karyotype was defined as ≥3 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. Monosomal karyotype was defined as 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 completed 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 HMA+ven-treated group.[23] Minimal residual disease (MRD) assessments were assessed by flow cytometry. OS was calculated from the time of induction therapy start 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 meeting the definition of *TP53* mutated AML per 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's 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 (CIs) 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 of <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 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 IC vs HMA+ven

A total 246 AML patients were found to have -7 and/or -5/del5q and received frontline treatment with either IC or HMA+ven. 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. Median age for the overall cohort was 69 years, and patients in the HMA+ven-treated group were significantly older with a median age of 73 years (range 22-92) compared to 62 years (range 33-79) in the IC-treated group ($p<0.001$). 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, respectively. Prior HMA exposure for an antecedent MDS was more common in IC-treated than HMA+ven-treated patients (19% vs 8%, $p=0.021$).

The molecular ontogeny of most patients 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 compared 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 vs. IC (10% vs 28%, p<0.001; 17% vs 32%, p<0.001; 17% vs 37%, p<0.001; 9% vs 25%, p=0.002).

Although the use of IC and HMA+ven are common in patients AML who are age <60 years >75 years, respectively, the optimal therapeutic approach in the age 60-75 population is unclear. Therefore, we also examined the demographic and clinical characteristics for 130 total patients age 60 to 75 with chromosome 5 and/or 7 abnormalities receiving IC and HMA+ven (**Supplemental Table 3**). In total, 60 (46%) of patients had -5/del5q, 44 (34%) had -7, and 26 (20%) had both -5 or del(5q) and -7. Of the 130 patients, 42 (32%) of 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 IC group (70 versus 66 years, p<0.001). In the age 60-75 cohort, 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 IC- and HMA+ven-treated groups in the 60-75 population, 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 IC vs HMA+ven

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 7+3 and 31 (36%) were treated with CPX-351. Of those treated with 7+3, 9 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+ven and 65

(40%) were treated with azacitidine+ven, with a median number of 2 treatment cycles amongst 120 patients with information on the cycle number available (range 1-19). There was no difference in rates of CR/CRi between IC- and HMA+ven-treated patients (43% vs 52%, p=0.20). Amongst those who had MRD assessed by flow cytometry, MRD negative rates were similar in HMA+ven-treated patients compared to 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 compared to HMA-ven-treated group (54% vs 19%, p<0.001). We also evaluated 30- and 60-day mortality after treatment initiation, with comparable rates amongst 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 year old with chromosome 5 and 7 abnormalities treated with IC and HMA+ven (**Supplemental Table 4**). Similarly, 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 compared to those treated with IC (56% vs 56%, p>0.99). The number of patients proceeding to allo-SCT in this 60-75 year old age group 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).

OS is not different in IC vs HMA+ven treated patients who are 60-75 years old

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

OS is improved with allo-SCT 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 those patients who did not (21 months (95% CI: 16-42) versus 3.8 months (95% CI: 3.2-6.1), p<0.0001) (**Figure 2A**).

We next assessed what the impact of allo-SCT was in patients treated with either IC or HMA+ven impacted OS outcomes amongst those patients who proceeded to transplant, again using 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 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**).

The presence of complex karyotype negatively impacts OS in patients treated with IC

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 variant allele frequency of at least 10%. Amongst those with complex karyotype, the rate of CR/CRi was 52% and 44% amongst those treated with HMA+ven and IC, respectively (p=0.037). Amongst those with non-complex karyotype, the rate of CR/CRi was 52% and 40% amongst 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, median OS was superior in patients without a complex karyotype compared to 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 significantly differ in the non-complex vs complex karyotype group (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 *TP53* mutation receiving either IC (**Figure 3C**) or HMA+ven (**Figure 3D**) were assessed. In patients treated with IC, 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). Amongst patients treated with HMA+ven, 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).

Response and survival outcomes in demographic and mutational subgroups

We evaluated response and survival outcomes in younger patients in the cohort. 59/246 patients were <60 years old at diagnosis, including 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 amongst 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 amongst 34 patients with *NRAS* and/or *KRAS* co-mutation was 31% overall and 31% in both 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). Amongst 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 (p>0.9). The median OS was 5.7 months (95% CI: 3.3-20) amongst those with splicing factor mutations and 6.3 months (95% CI: 5.2-7.6) amongst 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] Amongst this cohort, 7 patients had favorable, 36 had intermediate, and 118 had adverse risk disease. The rate of CR/CRi was 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 OS in AML patients with -7 and/or -5/del5q when adjusted for other patient and treatment characteristics

Finally, we performed univariable and multivariable analysis to determine which patient, disease, and treatment characteristics affected survival outcomes. In univariable analysis (**Supplemental Table 5**), 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 boundary significance (p=0.070; p=0.059). 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 and HMA+ven. Age at diagnosis, prior myeloid disease, monosomal karyotype, complex karyotype, treatment with HMA+ven vs IC, *KRAS* mutation, and time-varying transplant were covariates in the final model. Age at diagnosis (HR 1.02, 95% 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 vs 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 treatment response 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 -5/del5q and -7 as these are commonly seen in patients with AML, particularly those with therapy related AML or antecedent MDS, 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, independent of preceding treatment strategy. Importantly, in older adults (age 60-75) with AML and -5/del5q and/or -7, remission and survival outcomes were comparable between patients treated with IC and HMA+ven. Lastly, although OS was superior with IC compared to 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 vs HMA+ven did not significantly impact OS outcomes in AML patients with -5/del5q and -7.

Notably, 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 amongst patients age 60-75 (26% vs 7%). Patients with concomitant complex karyotype or mutations in *TP53* were more likely to be treated with HMA+ven than 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, amongst those with *RAS* pathway co-mutations, treatment with IC was more common than HMA+ven (37% vs 17%), presumably given 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- vs. HMA+ven-treated older patients 60-75 years old. Given these findings, we strongly advocate for randomized trials in this patient population between 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 after treatment initiation were low amongst 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, complex karyotype or *TP53* co-mutation did not have a significant effect on survival in those treated with HMA+ven. In contrast, patients with complex karyotype treated with IC had significantly shorter survival compared to those without 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 report include variation in chemotherapeutic approaches. Specifically, IC-treated patients received either 7+3 or CPX-351, with the latter being superior in OS and post-transplant survival outcomes in the secondary and therapy-related AML populations.[27] Comparative survival outcomes for the 7+3 versus CPX-351-treated IC patients 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 versus 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 is prospective randomized data emerging from China demonstrating noninferiority of decitabine + ven as compared to idarubicin + cytarabine in young, fit untreated AML patients.[28]

A phase 2 randomized study in the United States comparing azacitidine + ven 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 7+3 in comparison to CPX-351, 7+3+ven, aza/ven, and CPX-351+ven in higher-risk AML is ongoing and may provide further insights eventually (NCT05554406). However, until such larger clinical trials with sufficiently long follow up time read out and allow the comparison of the effectiveness of HMA+ven vs. IC in subgroups defined by specific mutations and cytogenetic abnormalities, retrospective studies such as ours will continue to be critical in guiding treatment decisions.

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Table 1: Baseline demographic and disease characteristics for patients with -7 and -5/del5q by overall group, IC treatment, and HMA+ven treatment.

	Overall N=246	IC N=85 (35%)	HMA+ven N=161 (65%)	P-value
Chromosome 5 and 7 abnormalities, N (%)				
-5/del5q	121 / 246 (49)	41 / 85 (48)	80 / 161 (50)	0.071
-7	74 / 246 (30)	32 / 85 (38)	42 / 161 (26)	
Both -5/del5q and -7	51 / 246 (21)	12 / 85 (14)	39 / 161 (24)	
Patient and treatment characteristics				
Median age (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
IDH 1 or 2	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)	**<0.001**
Secondary	55 / 246 (22)	27 / 85 (32)	28 / 161 (17)	
TP53 mutated	151 / 246 (61)	34 / 85 (40)	117 / 161 (73)	

Table 2: Treatment characteristics and rates of remission, MRD-negativity, and transplantation in patients with -7 and -5/del5q by overall group, IC treatment, and HMA+ven treatment.

	Overall N=246	**IC N=85 (35%)**	**HMA+ven N=161 (65%)**	**P-value**
Treatment characteristics, N (%)	-	7+3: 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

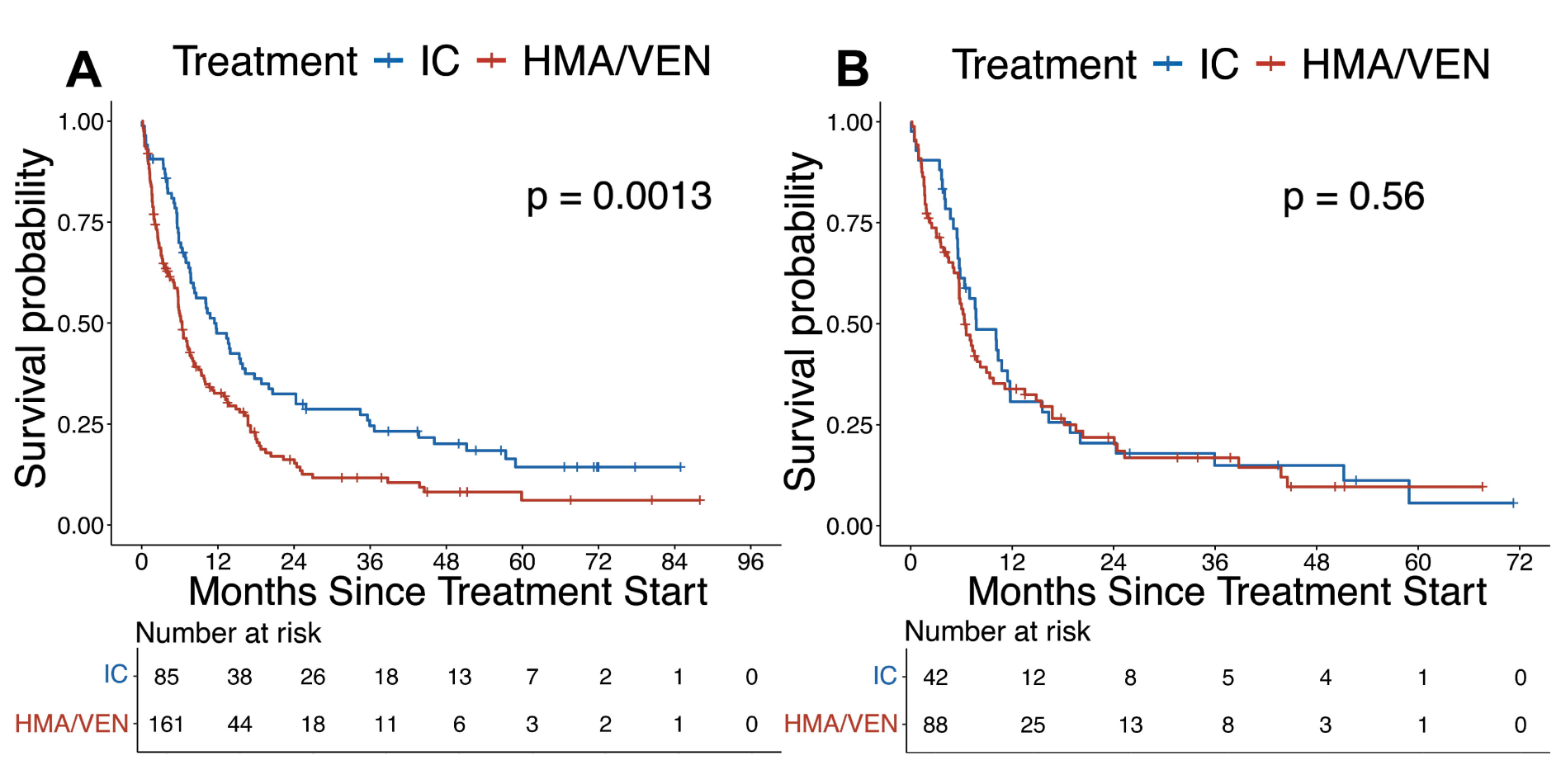
Figures:

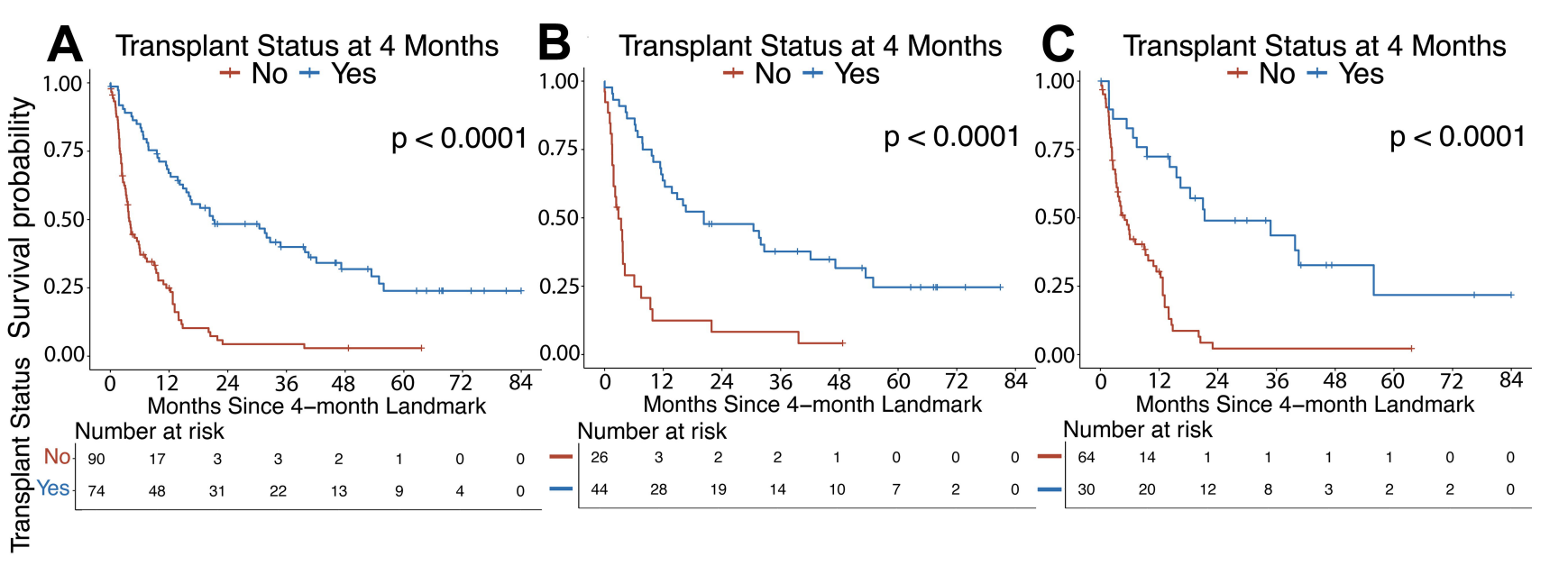
Figure 1: Survival outcomes in patients with -7 and -5/del5q stratified by therapy. (A) OS in all patients with -7 and -5/del5q treated with IC vs HMA+ven. (B) OS in patients aged 60-75 treated with IC vs HMA+ven.

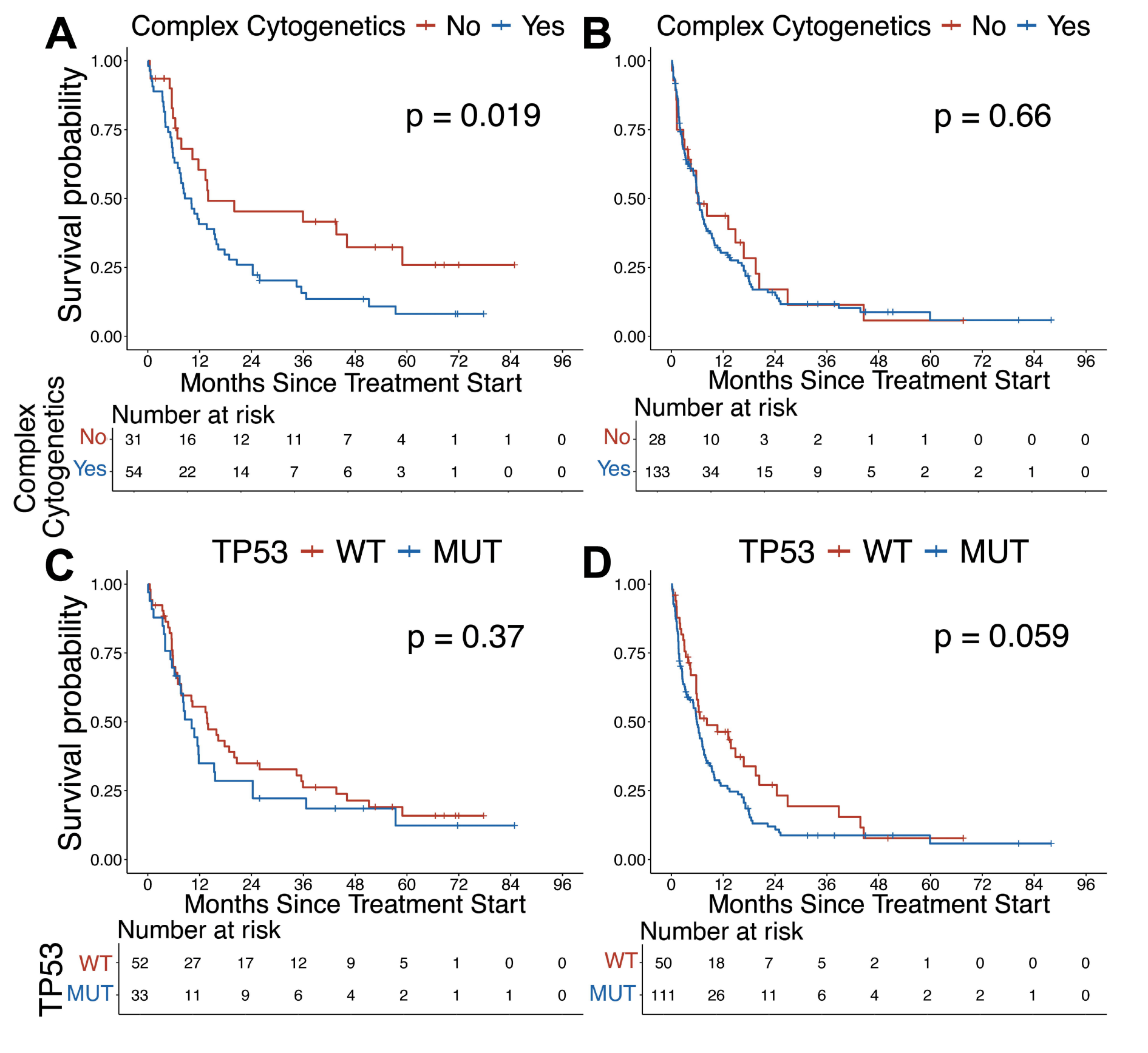
Figure 2: Landmark analysis in patients with -7 and -5/del5q who proceeded vs did not proceed to transplant using median transplant time of 4 months. (A) All patients with -7 and -5/del5q. (B) Patients with -7 and -5/del5q who received IC. (C) Patients with -7 and -5/del5q who received HMA+ven.

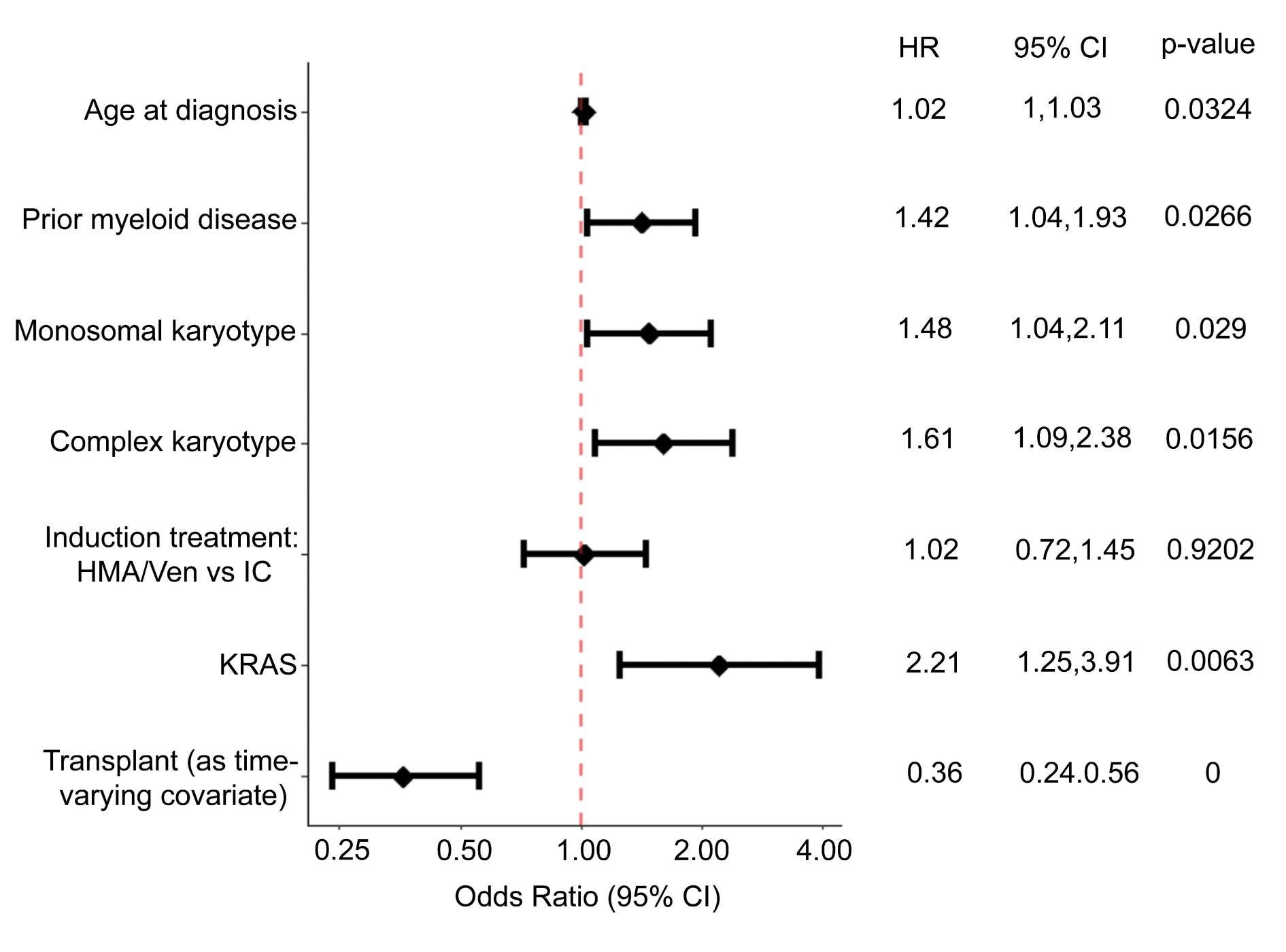
Figure 3: OS in patients with -7 and/or -5/del5q with concurrent complex karyotype or *TP53* co-mutation treated with IC and HMA+ven. (A) OS in all patients with vs without complex karyotype treated with IC. (B) OS in all patients with vs without complex karyotype treated with HMA+ven. (C) OS in all patients with vs without *TP53* co-mutation with allele frequency ≥10% treated with IC. (D) OS in all patients with vs without *TP53* co-mutation with allele frequency ≥10% treated with HMA+ven.

Figure 4: MVA of predictors of OS in patients with -7 and -5/del5q.


A
Treatment IC HMA/VEN
p = 0.0013
Survival probability
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72 84 96
Months Since Treatment Start
Number at risk
IC 85 38 26 18 13 7 2 1 0
HMA/VEN 161 44 18 11 6 3 2 1 0
B
Treatment IC HMA/VEN
p = 0.56
Survival probability
1.00
0.75
0.50
0.25
0.00
0 12 24 36 48 60 72
Months Since Treatment Start
Number at risk
IC 42 12 8 5 4 1 0
HMA/VEN 88 25 13 8 3 1 0


A
Transplant Status at 4 Months
No
Yes
p < 0.0001
Survival probability
1.00
0.75
0.50
0.25
0.00
0
12
24
36
48
60
72
84
Months Since 4−month Landmark
Number at risk
Transplant Status
No 90 17 3 3 2 1 0 0
Yes 74 48 31 22 13 9 4 0
B
Transplant Status at 4 Months
No
Yes
p < 0.0001
Months Since 4−month Landmark
Number at risk
No 26 3 2 2 1 0 0 0
Yes 44 28 19 14 10 7 2 0
C
Transplant Status at 4 Months
No
Yes
p < 0.0001
Months Since 4−month Landmark
Number at risk
No 64 14 1 1 1 1 0 0
Yes 30 20 12 8 3 2 2 0


A
Complex Cytogenetics No Yes
Survival probability
1.00
0.75
0.50
0.25
0.00
p = 0.019
0 12 24 36 48 60 72 84 96
Months Since Treatment Start
Number at risk
No 31 16 12 11 7 4 1 1 0
Yes 54 22 14 7 6 3 1 0 0
B
Complex Cytogenetics No Yes
p = 0.66
Months Since Treatment Start
Number at risk
No 28 10 3 2 1 1 0 0 0
Yes 133 34 15 9 5 2 2 1 0
Complex Cytogenetics
C
TP53 WT MUT
Survival probability
p = 0.37
Months Since Treatment Start
Number at risk
WT 52 27 17 12 9 5 1 0 0
MUT 33 11 9 6 4 2 1 1 0
D
TP53 WT MUT
p = 0.059
Months Since Treatment Start
Number at risk
WT 50 18 7 5 2 1 0 0 0
MUT 111 26 11 6 4 2 2 1 0
TP53


HR
95% CI
p-value
Age at diagnosis
1.02
1,1.03
0.0324
Prior myeloid disease
1.42
1.04,1.93
0.0266
Monosomal karyotype
1.48
1.04,2.11
0.029
Complex karyotype
1.61
1.09,2.38
0.0156
Induction treatment: HMA/Ven vs IC
1.02
0.72,1.45
0.9202
KRAS
2.21
1.25,3.91
0.0063
Transplant (as time-varying covariate)
0.36
0.24.0.56
0
0.25
0.50
1.00
2.00
4.00
Odds Ratio (95% CI)

Supplemental Table 1: Distribution of patients by center.

Center	N (%)
Memorial Sloan Kettering Cancer Center	66 / 246 (27)
Dana-Farber Cancer Institute	98 / 246 (40)
Yale Cancer Center	21 / 246 (8)
Institut Paoli-Calmettes	32 / 246 (13)
Vilnius University Hospital Santaros Klinikos	29 / 246 (12)

Supplemental Table 2: Mutational alterations evaluated.

ASXL1	FLT3	PHF6
ATM	GATA1	PPM1D
BCOR	GATA2	PRPF8
BCORL1	GNAS	PTPN11
BRAF	GNB1	RAD21
BRCC3	IDH1	RIT1
BTK	IDH2	RUNX1
CALR	IKZF1	SETBP1
CBL	JAK1	SETD2
CDKN2A	JAK2	SF3B1
CEBPA	KIT	SH2B3
CREBBP	KRAS	SMC1A
CSF3R	MPL	SMC3
CTCF	MYC	SRSF2
CUX1	NF1	STAG2
DDX41	NFE2	TET2
DNMT3A	NOTCH1	TP53
EP300	NPM1	U2AF1
ETNK1	NRAS	WT1
ETV6	NSD2	XPO1
EZH2	PDS5B	ZRSR2

Supplemental Table 3: Baseline demographic and disease characteristics for patients age 60-75 with -7 and -5/del5q by overall group, IC treatment, and HMA+ven treatment.

	Overall (60-75) N=130	IC (60-75) N=42 (32%)	HMA+ven (60-75) N=88 (68%)	P-value
Chromosome 5 and 7 abnormalities, N (%)				
-5/del5q	60 / 130 (46)	22 / 42 (52)	38 / 88 (43)	0.29
-7	44 / 130 (34)	15 / 42 (36)	29 / 88 (33)	
Both -5/del5q and -7	26 / 130 (20)	5 / 42 (12)	21 / 88 (24)	
Patient and treatment characteristics				
Median age (range)	69 (60, 75)	66 (60, 74)	70 (60, 75)	**<0.001**
Male sex, N (%)	79 / 130 (61)	28 / 42 (67)	51 / 88 (58)	0.44
Prior myeloid malignancy, N (%)	42 / 130 (32)	16 / 42 (38)	26 / 88 (30)	0.42
Therapy-related, N (%)	38 / 130 (29)	10 / 42 (24)	28 / 88 (32)	0.41
Prior hypomethylating agent, N (%)	17 / 130 (13)	11 / 42 (26)	6 / 88 (7)	**0.004**
Concomitant cytogenetic and molecular abnormalities, N (%)				
Complex karyotype	94 / 130 (72)	27 / 42 (64)	67 / 88 (76)	0.21
Monosomal karyotype	91 / 130 (70)	26 / 42 (62)	65 / 88 (74)	0.22
Deletion 17p	36 / 130 (28)	8 / 42 (19)	28 / 88 (32)	0.15
RAS pathway	26 / 127 (20)	10 / 39 (26)	16 / 88 (18)	0.35
ASXL1	13 / 130 (10)	3 / 42 (7)	10 / 88 (11)	0.55
DNMT3A	24 / 130 (18)	7 / 42 (17)	17 / 88 (19)	0.81
IDH 1 or 2	14 / 130 (11)	6 / 42 (14)	8 / 88 (9)	0.38
RUNX1	17 / 130 (13)	10 / 42 (24)	7 / 88 (8)	**0.023**
TET2	17 / 130 (13)	3 / 42 (7)	14 / 88 (16)	0.27
Splicing factor mutation	21 / 126 (17)	10 / 38 (26)	11 / 88 (13)	0.070
Ontogeny as defined by co-occurring mutations, N (%)				
De novo	23 / 130 (18)	11 / 42 (26)	12 / 88 (14)	0.061
Secondary	30 / 130 (23)	12 / 42 (29)	18 / 88 (20)	
TP53 mutated	77 / 130 (59)	19 / 42 (45)	58 / 88 (66)	

Supplemental Table 4: Treatment characteristics and rates of remission, MRD-negativity, and transplantation in patients age 60-75 with -7 and -5/del5q by overall group, IC treatment, and HMA+ven treatment.

	Overall (60-75) N=130	**IC (60-75) N=42 (32%)**	**HMA+ven (60-75) N=88 (68%)**	**P-value**
Treatment characteristics, N (%)	-	7+3: 23 / 42 (55) CPX-351: 19 / 42 (45)	Aza/Ven: 50 / 88 (57) Dec/Ven: 38 / 88 (43)	-
Clinical outcome, N (%)				
CR/CRi	50 / 106 (47)	17 / 39 (44)	33 / 67 (49)	0.69
MRD negativity	14 / 25 (56)	5 / 9 (56)	9 / 16 (56)	>0.99
Proceeded to transplant	43 / 130 (33)	20 / 42 (48)	23 / 88 (26)	**0.018**
30-day mortality	5 / 130 (4)	1 / 42 (2)	4 / 88 (5)	>0.99
60-day mortality	18 / 130 (14)	4 / 42 (10)	14 / 88 (16)	0.42

Supplemental Table 5: UVA of predictors of OS in patients with -7 and -5/del5q.

Characteristic	HR	95% CI	P-value
Both -5 or del(5q) and -7 vs. -5/del5q only	1.39	0.98, 1.97	0.068
-7 only vs. -5/del5q only	1.09	0.79, 1.52	0.6
Age at diagnosis	1.03	1.02, 1.05	<0.001
Prior myeloid malignancy	1.45	1.08, 1.94	0.014
Prior HMA	1.46	0.97, 2.19	0.070
Monosomal karyotype	1.68	1.21, 2.34	0.002
Complex karyotype	1.56	1.10, 2.20	0.012
Deletion 17p	0.89	0.65, 1.22	0.47
TP53 mutation	1.52	1.14, 2.03	0.023
BCOR mutation (available in 235/246 patients)	0.43	0.18, 1.06	0.066
KRAS mutation	1.69	0.98, 2.92	0.059
TET2 mutation	1.66	1.07, 2.58	0.023
Treatment with HMA+ven	1.63	1.21, 2.19	<0.001
Transplant (as a time-varying covariate)	0.31	0.21, 0.46	<0.001