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TITLE: Prognostic significance of concurrent gene mutations in intensively treated patients with *IDH*-mutated AML, an ALFA study

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KEY POINTS

- Presence of *NPM1* mutation is the main prognostic factor for OS in *IDH1* and *IDH2R140* mutated AML treated by intensive chemotherapy.
- In non-favorable ELN-2010 *IDH*-mutated AML, patients achieving transplantation in first complete remission had longer OS and DFS.

ABSTRACT

IDH inhibitors are effective in AML, and trials evaluating frontline combinations with intensive chemotherapy (IC) are ongoing. Data on the prognostic significance of co-occurring genetic alterations and allogeneic hematopoietic stem cell transplantation (HSCT) are conflicting in each *IDH*-mutated subgroup treated by IC, while this information is important for trial design and results interpretation. We retrospectively analyzed 127 *IDH1*, 135 *IDH2R140* and 57 *IDH2R172* newly diagnosed AML patients treated with IC in three Acute Leukemia French Association (ALFA) prospective trials. We addressed in each *IDH* subgroup the prognostic impact of clinical and genetic covariates, and the role of HSCT in eligible patients. In *IDH1* patients, presence of *NPM1* mutations was the only variable predicting improved OS in multivariate analysis ($p < 0.0001$). In *IDH2R140*, normal karyotype ($p = 0.008$) and *NPM1* mutations ($p = 0.01$) predicted better OS. *NPM1* mutations were associated with better DFS ($p = 0.0009$) whereas presence of *DNMT3A* mutations was associated with shorter DFS ($p = 0.0006$). In *IDH2R172*, platelet count was the only variable retained in the multivariate model for OS ($p = 0.002$). Among non-favorable ELN-2010 eligible patients, 71 (36%) achieved an HSCT in first complete remission (CR1) and had longer OS ($p = 0.03$) and DFS ($p = 0.02$) than not-transplanted patients. Future clinical trial testing frontline IDH inhibitors combined with IC may consider stratification on *NPM1* mutational status, the main prognostic factor in *IDH1* and *IDH2R140* mutated AML. HSCT improve OS of non-favorable *IDH1/2*-mutated AML and should be fully integrated in the treatment strategy.

MAIN TEXT

INTRODUCTION

Point mutations in isocitrate dehydrogenase *IDH1* and *IDH2* genes are found in 7-14% and 8-19% of adult patients with acute myeloid leukemia (AML), respectively.¹ *IDH1/2*-mutant enzymes gain neomorphic enzymatic activity, producing D-2-hydroxyglutarate (D-2HG) in excess,²⁻⁴ leading to histone and DNA hypermethylation and cell differentiation blockade.⁵⁻⁹ Despite a shared oncogenic mechanism, *IDH* mutation subtypes (*IDH1*, *IDH2R140* and *IDH2R172*) have distinct patterns of co-occurring genetic alterations and may correspond to distinct entities.¹⁰⁻¹³ However, risk stratification within each *IDH* mutation subtypes remains conflicting in AML patients treated with intensive chemotherapy (IC).^{11,14-22} One large comprehensive series investigated the mutational landscape of *IDH* subtypes AML patients but did not investigate the prognostic impact of co-occurring mutations in each group.¹² Furthermore, some studies addressed the role of allogeneic hematopoietic stem cell transplantation (HSCT) in limited cohorts of *IDH*-mutated AML, but none analyzed its impact in specific *IDH* subgroups.^{23,24} Oral targeted inhibitors of mutant *IDH1* and *IDH2* enzymes (ivosidenib²⁵ and enasidenib²⁶, respectively) were recently approved by the FDA for the treatment of relapse/refractory AML as single agents and in newly diagnosed AML for ivosidenib²⁷⁻²⁹. In the context of clinical trials evaluating the combination of *IDH* inhibitors with IC (NCT02632708³⁰, NCT03839771) it seems important to identify the main prognostic factors for each *IDH* mutation subtype, to guide study design (i.e patients stratification) and results interpretation. Here, we report an *IDH* subgroup analysis of the prognostic impact of clinical and genetic covariates and the outcome after HSCT in a large cohort of 319 newly diagnosed *IDH*-mutated AML patients

treated with IC in three prospective Acute Leukemia French Association (ALFA) clinical trials.

PATIENTS AND METHODS

Patients

We analyzed 319 newly diagnosed AML patients with an *IDH1/2* mutation treated with IC in three Acute Leukemia French Association (ALFA) prospective clinical trials (**Supplementary Figure 1**). Patients provided written consent, the study was conducted according to the Declaration of Helsinki and approved by institutional review boards. Eight patients with dual *IDH1* and *IDH2* mutations were excluded. Fifty-eight older patients (50-70 years) were treated between 2008 and 2010 in ALFA-0701³¹ (EudraCT 2007-002933-36), 132 younger patients (18-60 years) were treated between 2009 and 2013 in ALFA-0702³² (NCT00932412) and 129 older patients (> 60 years) were treated between 2012 and 2016 in ALFA-1200³³ (NCT01966497) trials. All patients received an induction course including an anthracycline and cytarabine. Patients in ALFA-0701 who were randomized to receive gemtuzumab ozogamycin were excluded from survival analyses in order to obtain a homogenous patient cohort treated with IC. Both ALFA-0701 and ALFA-0702 trials included a salvage course based on high-dose cytarabine. Patients in ALFA-1200 received a second intermediate-dose course of cytarabine (IDAC) regardless of response. Consolidation included daunorubicine + cytarabine in ALFA-0701, high-dose cytarabine or clofarabine + IDAC in ALFA-0702 and IDAC in ALFA-1200. Patients with non-favorable European LeukemiaNet (ELN) 2010³⁴ risk were eligible for HSCT if they had a sibling or a fully 10/10 HLA-matched unrelated donor.

Cytogenetic and Molecular Analyses

Conventional karyotype and fluorescence *in situ* hybridization were centrally reviewed. Molecular analyses were performed centrally by high-throughput

sequencing (HTS) on diagnostic peripheral blood or bone marrow samples, as previously published for the ALFA-0701,³⁵ ALFA-0702,³⁶ and ALFA-1200³³ studies. Analyses focused on the 37 genes overlapping in the three studies, namely *IDH1*, *IDH2*, *ASXL1*, *BCOR*, *BCORL1*, *CALR*, *CBL*, *CEBPA*, *CSF3R*, *DNMT4A*, *ETV6*, *EZH2*, *FLT3*, *GATA2*, *JAK2*, *KIT*, *KRAS*, *MPL*, *NIPBL*, *NPM1*, *NRAS*, *PHF6*, *PTPN11*, *RAD21*, *RIT1*, *RUNX1*, *SETBP1*, *SF3B1*, *SMC1A*, *SMC3*, *SRSF3*, *STAG2*, *TET3*, *TP53*, *U2AF1*, *WT1* and *ZRSR2*, **Supplementary Table 1**. Screening for *NPM1* mutations and *FLT3* internal tandem duplications (*FLT3-ITD*) was also performed by fragment analysis and screening for mutations in *CEBPA* was performed by Sanger sequencing.

Statistical analyses

Continuous variables are reported as medians and interquartile ranges (IQR) and categorical and ordinal variables are reported as numbers and proportions. Difference of quantitative variable between groups was assessed by Kruskal-Wallis, followed by pairwise Mann-Whitney test if significant. Correlation between genotype and frequent covariates (present in >5% of the whole *IDH* cohort) was made using point biserial correlation for continuous variables and evaluated with the Phi coefficient and tested with Fisher test for dichotomic variables. P-values were corrected for multiple testing using the Benjamini-Hochberg procedure³⁷ (q-values). Standard National Cancer Institute (NCI) criteria were used to define CR and CRp³⁸ after the first-course and salvage therapy in ALFA-0701 and ALFA-0702 and after the first and second courses in ALFA-1200. Patients alive after induction or induction and salvage, but not reaching CR/CRp criteria, were considered as patients with refractory disease. Relapse was defined as reappearance of circulating leukemic

blasts, recurrence of more than 5% marrow blasts and/or appearance of extramedullary leukemia. Bi-variate analyses for response were done by logistic regression stratified on the trial. Follow-up duration was calculated with the inverse method. Overall survival (OS) analyses were considered from date of diagnosis to date of death or last follow up. Disease-free survival (DFS) analyses were restricted to patients achieving CR/CRp after 2 courses and were considered from date of response to date of death, relapse or last follow-up. OS and DFS were obtained according to the Kaplan Meier method and censored at HSCT. For survival analysis, frequent variables (present in > 10% of each *IDH* subgroup) were selected using a LASSO penalized regression with the R package glmnet, using the regularization parameter lambda-min determined on 100 cross-validations. Selected variables were included in multivariate Cox models, followed by backward regression. The proportional hazard assumption was tested on the basis of Schoenfeld residuals. To determine the role of HSCT in first CR, HSCT was considered as a time dependent covariate, survival curves for OS and DFS were obtained with the Simon-Makuch method and were compared using a time-dependent bi-variate Cox-model. All tests were two-sided, statistical significance was defined as a p-value or q-value < 0.05 and all analyses for response and survival were stratified on the clinical trial. All analyses were performed with R version 3.5.2.

Data sharing: Data are available under accession number ALFA0701 (EudraCT 2007-002933-36, Castaigne et al. Lancet 2012) - ALFA0702 (NCT00932412, Thomas et al. JCO 2017) - ALFA1200 (NCT01966497, Gardin et al. Blood Adv 2020).

RESULTS

Characteristics of patients

Three hundred and nineteen *IDH1/2*-mutated patients from ALFA-0701 (n = 58), ALFA-0702 (n = 132) and ALFA-1200 (n = 129) prospective clinical trials were analyzed in the study, including 127 *IDH1* (40%), 135 *IDH2R140* (42%) and 57 *IDH2R172* (18%) mutated AML patients (**Supplementary Figure 1**). Characteristics of patients at diagnosis are listed in **Table 1**. Overall, 164 were men (52%) with a median age of 61 years [IQR: 52-67]. Most patients had a normal karyotype (67%), and ELN-2010 risk was favorable, intermediate-1, intermediate-2 and high in 29%, 38%, 25% and 8% of evaluable patients, respectively. Among *IDH1* patients, 60 had a p.R132C (47%), 44 a p.R132H (35%), 11 a p.R132G (9%), 10 a p.R132S (8%) and 2 a p.R132L (2%). Among *IDH2R140* patients, 127 had a p.R140Q (94%), 7 a p.R140W (5%) and 1 a p.R140L (1%). The *IDH2R172* variants were p.R172K (n=56) and p.R172S (n=1). The majority of *IDH* patients (> 95%) had at least one co-mutation, mostly in *DNMT3A* (42%), *NPM1* (40%), *SRSF2* (20%), *FLT3-ITD* (15%) and *NRAS* (14%), **Figure 1A-B, Supplementary Figure 2**. *IDH2R172* patients had significantly fewer co-mutations than other patients (median 2 [IQR: 1-3] versus 3 [IQR: 2-4] for *IDH1* and 3 [IQR:2-4] for *IDH2R140*, q = 0.004 and q=0.01 respectively, **Figure 1B**). *IDH2R172* patients also had a significantly smaller allele burden (median variant-allele frequency (VAF) of *IDH2R172* variant of 27% [IQR: 18-38] versus 38% [IQR:15-43] for *IDH1* and 42% for *IDH2R140* [IQR: 24-47], q = 0.04 and q < 0.001, respectively **Figure 1C**).

After exclusion of the 26 patients who received gemtuzumab ozogamycin, 224 patients (76%) and 244 patients (83%) achieved a CR/CRp after one and two

courses of IC, respectively. On bivariate analyses stratified on the trial, *IDH2R140* mutations predicted higher response rates after one course (86% versus 74% in *IDH1* and 59% in *IDH2R172*, $q = 0.03$ and $q < 0.001$, respectively) and after two courses (91% versus 79% in *IDH1* and 74% in *IDH2R172*, $q = 0.02$ and $q = 0.02$ respectively, **Figure 1D**). Of note, concomitant *NPM1* mutations were associated with significantly higher CR/CRp rates in *IDH1* (94% (50/53) vs 66% (41/62) in *NPM1* wild-type, $p = 0.0002$) and *IDH2R140* patients (100% (62/62) vs 82% (51/62) in *NPM1* wild-type, $p = 0.0003$).

Median follow-up was 46.0 months [IQR: 38.0-58.4]. Median OS censored at HSCT (OS-HSCT) was 39.7 months [IQR: 14.7-Not Reached (NR)] and in bivariate analyses stratified on clinical trial, *IDH2R140* patients had better OS-HSCT than *IDH1* (3-year OS of 61% vs 46% for *IDH1*, HR = 0.60 [95CI; 0.40-0.93], $p = 0.02$) but not than *IDH2R172* (3-year OS of 61% vs 39% for *IDH2R172*, HR = 0.65 [95CI; 0.38-1.09], $p = 0.10$), **Figure 1E**. Median DFS censored at HSCT was 22.3 months [IQR: 10.8-NR] and there was no significant difference according to *IDH* subtype, **Figure 1F**. Of note, both ELN-2010 and ELN-2017 risk stratification poorly discriminate intermediate and adverse risk *IDH*-mutated AML patients (**Supplementary Figure 3**).

***IDH1R132* cohort**

Only frequent co-variables (> 5% of the whole *IDH* cohort, listed in **Supplementary Table 2**) were included in the correlation analyses. The only covariate associated with *IDH1* mutations was *NRAS* mutation (24% vs 8% in *IDH1^{wt}*, $q = 0.003$). We investigated the association with the 2 most frequent *IDH1* variants, namely p.R132H and p.R132C, within the *IDH1* cohort. *IDH1* p.R132H variants were present in

younger patients (median age of 56 years vs 63 years in other *IDH1*, $q = 0.02$) and were associated with higher rates of *NPM1* mutations (64% vs 34%, $q = 0.01$), *FLT3-ITD* (27% vs 6%, $q = 0.01$) and higher WBC ($17.9 \times 10^9/L$ vs $2.4 \times 10^9/L$, $q = 0.0006$). *IDH1* p.R132C variants were significantly associated with higher rates of trisomy 8 (23% vs 5%, $q = 0.01$), *PHF6* mutations (13% vs 0%, $q = 0.01$), *BCOR* mutations (15% vs 1%, $q = 0.03$) and *BCORL1* mutations (13% vs 1%, $q = 0.048$), **Figure 2A**. Despite these 2 distinct mutational patterns, there was no difference in survival between p.R132C and p.R132H variants, **Figure 2B**.

To identify the prognostic impact of covariates in *IDH1*-mutated AML, we included all covariates present in at least 10% of *IDH1* patients (list in **Supplementary Table 3**) in a LASSO penalized regression for OS and DFS censored at HSCT. The final multivariate Cox models stratified on the trial are summarized in **Table 2**. *NPM1* mutational status was the only variable predicting prolonged OS (3-year OS of 65% in *NPM1^{mut}* vs 28% in *NPM1^{wt}*, HR = 0.29 [95CI: 0.16-0.54], $p < 0.0001$, **Figure 2C**). No variable was retained in the multivariate analysis for DFS.

***IDH2R140* cohort**

Compared to other *IDH* mutations, *IDH2R140* variants were associated with higher rates of *NPM1* mutations (53% vs 30%, $q = 0.0005$), *FLT3-ITD* (22% vs 10%, $q = 0.01$), *SRSF2* mutations (28% vs 14%, $q = 0.01$), normal karyotypes (77% vs 59%, $q = 0.01$) and higher WBC (median $8.80 \times 10^9/L$ vs $2.60 \times 10^9/L$, $q = 0.0005$), **Figure 3A**. Results of the multivariate analyses for OS and DFS censored at HSCT are summarized in **Table 2**. Normal karyotype (3-year OS of 67% vs 28%, HR = 0.38 [95CI: 0.19-0.78], $p = 0.008$) and *NPM1* mutations (3-year OS of 77% vs 40%, HR = 0.41, [95CI: 0.21-0.81], $p = 0.01$) predicted prolonged OS, **Figure 3B**. Considering

DFS, *NPM1* mutations predicted prolonged DFS (3-year DFS of 63% vs 23%, HR = 0.33 [95CI: 0.17-0.63], $p = 0.0009$), whereas *DNMT3A* mutations were detrimental (3-year DFS of 22% vs 67%, HR = 3.05, [95CI: 1.61-5.78], $p = 0.0006$), **Figure 3C**.

***IDH2R172* cohort**

IDH2R172 variants were associated with higher rates of *BCOR* mutations (30% vs 8%, $q < 0.001$), no *NPM1* mutations (0% vs 49%, $q < 0.001$), fewer *SRSF2* mutations (2% vs 24%, $q < 0.001$) and *FLT3-ITD* (2% vs 18%, $q < 0.001$) and lower WBC (median $1.80 \times 10^9/L$ vs $6.25 \times 10^9/L$, $q < 0.001$), **Figure 4A**.

Results of the multivariate analyses for OS and DFS censored at HSCT are summarized in **Table 2**. Log-transformed platelet count was the only variable retained in the multivariate model for OS (HR = 0.19 [95CI: 0.07-0.53], $p = 0.002$). Using an arbitrary cut-off at $100 \times 10^9/L$, 3-year OS was 17% for patients with thrombocytopenia versus 52% for others, **Figure 4B**. *IDH2R172* patients with low platelet counts ($< 100 \times 10^9/L$) suffered more early deaths (3/20 versus 0/34 with high platelet counts) and had significantly higher rates of induction failure after one (CR/CRp rates of 25% versus 79%, $p = 0.001$) and two courses (CR/CRp rates of 45% versus 91%, $p = 0.001$). No variable was retained as an independent prognostic factor for DFS. Of note, the 16 *IDH2R172* patients without other classifying abnormalities as defined by Papaemmanuil et al.¹¹ did not have distinct co-mutations, neither prolonged outcome (**Supplementary Figure 4**).

Impact of HSCT in *IDH*-mutated patients

Finally, we investigated the role of HSCT in CR1 for the 197 eligible patients, namely patients with non-favorable AML according to ELN-2010 risk and who did not receive

gemtuzumab ozogamycin. Overall, 71 (36%) eventually received an HSCT after a median time from diagnosis of 5.3 months [IQR: 4.5-6.1], including 23 (33%), 28 (36%) and 20 (39%) in *IDH1R132*, *IDH2R140* and *IDH2R172* patients respectively, **Table 1**. Main characteristics between the transplant and no-transplant cohorts were similar, however most transplanted patients came from the ALFA-0702 trial, resulting in a younger age in this group, **Supplementary Table 4**. When we considered HSCT as a time-dependent covariate in bivariate analyses stratified on the clinical trial, transplantation in CR1 was associated with a prolonged OS (HR = 0.60 [95CI: 0.37-0.96], $p = 0.03$, **Figure 5A**) and a prolonged DFS (HR = 0.55 [95CI: 0.34-0.89], $p = 0.02$, **Figure 5B**). Analyses in *IDH* subtypes revealed a benefit in OS only for *IDH1R132* patients (HR = 0.48 [95CI: 0.23-0.99], $p = 0.048$), and a trend to better DFS for *IDH2R172* patients (HR = 0.41 [95CI: 0.14-1.20], $p = 0.10$, **Supplementary Figure 5**).

DISCUSSION

In recent years, there was a renewed interest in *IDH1/2* mutations in AML with the advent of specific inhibitors. However, the prognostic impact of *IDH1/2* mutations and their co-mutations remained unclear because in most studies *IDH1*, *IDH2R140* and *IDH2R172* mutations were analyzed together^{12,20,21} and in cohorts treated with different intensity regimens.^{21,39} The present study represents one of the largest series of *IDH1/2* mutated AML patients prospectively enrolled in three clinical trials with sequencing data on 37 genes, in which we assessed for each *IDH* mutation subtype the prognostic impact of clinical and genetic covariates, as well as the impact of HSCT in CR1.

Our cohort included 127 *IDH1* (40%), 135 *IDH2R140* (42%) and 57 (18%) *IDH2R172* patients, proportions in line with previous reports.^{12,17,40} Clinical and genetic covariates differed between *IDH* mutations subtypes. Among *IDH1*-mutated patients, we could highlight that p.R132H variants were more frequently associated with *NPM1* and *FLT3-ITD* mutations than other *IDH1*, as previously reported.¹³ In line with previous reports,^{11,12} *IDH2R140* patients had significantly higher WBC, more frequent normal karyotype and *NPM1*, *FLT3-ITD*, *SRSF2* mutations, whereas *IDH2R172* mutations had lower WBC, more frequent *BCOR* mutations and were mutually exclusive with *NPM1* alterations. These differences in clinical and genetic covariates suggest that *IDH* mutation subtypes are distinct entities that should be considered separately, which is supported by biological differences.^{41,42}

After intensive treatment CR/CRp rates were significantly higher in *IDH2R140* patients (86%) than in *IDH1* (74%) and *IDH2R172* patients (59%), as previously reported.⁴⁰ *NPM1* mutations were associated with remarkably high CR/CRp rates in *IDH1R132* (94%) and *IDH2R140* (100%). Considering long term outcome, *IDH2R140* patients had a significantly prolonged OS compared to *IDH1* patients ($p=0.02$), and a trend to prolonged OS compared to *IDH2R172* patients ($p=0.1$). Higher rates of *NPM1* mutations and normal karyotype may account for the better outcome of *IDH2R140* mutated patients. In keeping with studies on patients accrued to ALFA,¹⁶ MRC,⁴⁰ and CALGB¹⁰ clinical trials, *IDH2R172* did not have a prolonged survival compared to other *IDH* patients in our cohort, even in the 16 *IDH2R172* patients without other classifying abnormalities as defined by Papaemmanuil et al.¹¹ (**Supplementary Figure 4**). These results are conflicting with two other studies,^{11,12} perhaps owing to greater treatment heterogeneity in them.

Most importantly, our study identified in each *IDH* mutation subtype the main prognostic factors for long term outcome. *NPM1* was the only mutation predicting OS in multivariate analysis for *IDH1* and *IDH2R140* patients. Surprisingly, other stratifying mutations such as *FLT3* mutations^{11,43,44} (**Supplementary Figure 6**) had no significant prognostic impact in our cohort, but we acknowledge that the number of patients with high allelic ratio of *FLT3-ITD* was low (n = 11). We report for the first time the negative impact of cytogenetic abnormalities in *IDH2R140* on OS, like in *NPM1*-mutated AML.⁴⁵ We also found that platelet count was the only variable retained in the multivariate model for OS in *IDH2R172*. *IDH2R172* patients with low platelet counts (< 100 x 10⁹/L) had a more advanced and resistant disease with higher rates of induction failure. Interestingly, no variable was retained as an independent prognostic factor for DFS in *IDH1* or *IDH2R172*. In *IDH2R140*, *NPM1* mutations were associated with prolonged DFS only in patients wild-type for *DNMT3A*. These results are in line with previous results in *NPM1*-mutated AML.⁴⁶ In patients with both *IDH* and *DNMT3A* mutations (n=135), cancer cells fraction (CCF) of *IDH* and *DNMT3A* mutations were similar across all 3 *IDH* subgroups (**Supplementary Table 5**). However, in *IDH1* and *IDH2R140* patients, *NPM1* mutations had a lower allelic burden (p < 0.001), suggesting they are later events. The poorer prognosis of the association of *IDH2R140* and *DNMT3A* mutations has already been reported.¹¹ Both mutations are early events and are associated with clonal dominance in single-cell genotyping studies,⁴⁷ a feature associated with poorer prognosis in AML.⁴⁸ Mouse models suggest an epigenetic cooperation between the two alterations, leading to activation of a stem-cell like gene signature.⁴⁹ Following previous reports in Refractory/Relapsing *IDH*-mutated AML,^{50,51} it will be interesting to further study the genetic landscape and molecular predictors in relapsed *IDH* AML patients, to compare trials conducted in this population.

In the three prospective trials, HSCT in CR1 was only recommended for patients with intermediate or adverse-risk AML according to the ELN 2010 classification when a fully 10/10 HLA matched donor could be identified. ELN 2010 is a valid stratification for allogeneic HSCT, and the more recent ELN 2017 only reclassifies < 5% of patients considered as favorable.⁵² Seventy-one (36%) of the eligible patients aged 70 years or less underwent transplantation in CR1 and we were able to compare transplant and no-transplant cohorts with similar main characteristics. As expected, HSCT in CR1 was associated with improved OS and DFS. However, analyses in *IDH* subtypes were impaired by a limited power and only revealed a benefit in OS for *IDH1R132* patients. Combining IDH inhibitors with intensive induction and consolidation chemotherapy could be synergistic as primary resistance to IDH inhibitors is related to the number of co-occurring mutations^{28,50} but also to the expansion of a clone harboring mutations in receptor tyrosine kinase (RTK) pathway genes (i.e *NRAS*, *KRAS*, *PTPN11*, *KIT*, and *FLT3*) which are associated with significantly lower CR/CRh rates.^{28,50} In the present cohorts, mutations in signaling pathway genes, including *FLT3* mutations, had no impact on the outcome after IC (**Supplementary Figure 6**). Thus, the combination of IC + IDH inhibitors might prevent primary resistance and relapses conveyed by signaling mutations. This is supported by a recent report of a Phase 1 evaluating the association of IDH inhibitor and IC in newly diagnosed AML,³⁰ in which *FLT3* and *RAS* mutations were cleared after induction chemotherapy. Whether combination therapies might also prevent secondary resistance to IDH inhibitors related to second site mutations hampering the binding of the drugs or a mutational switch has yet to be proven.^{50,53,54}

Future clinical trials testing frontline IDH inhibitors with intensive chemotherapy should thus consider stratification on *NPM1* mutational status. HSCT should be fully

integrated in the treatment strategy, with important implications for trials design (guidelines for HSCT indications, censoring at HSCT in survival outcomes analyses, post-HSCT maintenance). Future studies should also evaluate alternative strategies (i.e. HSCT indications based on MRD levels, maintenance therapy with IDH inhibitors).

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AUTORSHIP CONTRIBUTIONS

MD and SDB designed the study, analyzed the data and drafted the paper. RI, HD and SDB supervised the study. MD performed the statistical analyses. ND and CPr performed the genotyping. CT performed the cytogenetic analyses. JBM, ER, XT, JPM, TB, LA, SC, EL, CB, JVM, CPa, JL, NB, KCL, DC, PT, NV, AP, CR, CG, RI, HD and SDB provided clinical data. All authors revised the paper and accepted its final version.

DISCLOSURE OF CONFLICTS OF INTEREST

LA reports receiving research support from Celgene and Agios, and advisory board fees from Celgene. The remaining authors declare no competing financial interests.

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TABLES

Table 1. Characteristics of patients (median [IQR], or number (%)).

	All	IDH1 ^{R132}	IDH2 ^{R140}	IDH2 ^{R172}
Patients	319	127 (40%)	135 (42%)	57 (18%)
Age, years	61 [52-67]	61 [52-67]	61 [50-67]	62 [56-68]
Sex, male	164 (52%)	68 (54%)	74 (55%)	22 (39%)
sAML	16 (5%)	10 (8%)	4 (3%)	2 (4%)
WBC, x 10⁹/L	3.7 [1.6-23.8]	4.5 [1.6-20.7]	8.8 [2.3-31.6]	1.8 [1.2-2.7]
Cytogenetics				
Normal	198 (67%)	72 (63%)	98 (77%)	28 (52%)
Complex	11 (4%)	9 (8%)	2 (2%)	0
Trisomy 8/8q	31 (10%)	16 (14%)	10 (8%)	5 (9%)
Monosomy 7	12 (3%)	10 (9%)	2 (2%)	0
Trisomy 11/11q	13 (4%)	3 (3%)	2 (2%)	8 (15%)
Not available	22	12	7	3
ELN-2010 risk groups				
Favorable	86 (29%)	38 (33%)	48 (37%)	0 (0%)
Intermediate-1	112 (38%)	34 (29%)	50 (39%)	28 (52%)
Intermediate-2	75 (25%)	25 (22%)	24 (19%)	26 (48%)
Adverse	24 (8%)	18 (16%)	6 (5%)	0 (0%)
Not available	22	12	7	2
Trials				
ALFA-0701	58 (18%)	26 (20%)	21 (16%)	11 (19%)
ALFA-0702	132 (41%)	54 (43%)	57 (42%)	21 (37%)
ALFA-1200	129 (41%)	47 (37%)	57 (42%)	25 (44%)
HSCT in CR1				
Eligible patients*	197 (62%)	69 (54%)	77 (57%)	51 (89%)
HSCT in CR1	71 (36%)	23 (33%)	28 (36%)	20 (39%)

sAML: Secondary AML, WBC: white blood cells, ELN-2010: risk group according to ref, HSCT: allogeneic stem cell transplant

*patients with non-favorable AML, and not receiving GO in ALFA-0701

Table 2. Multivariate analyses for Survival.

	Overall survival censored at HSCT, stratified on the trial			Disease-free survival censored at HSCT, stratified on the trial		
	<i>IDH1</i>	<i>IDH2R140</i>	<i>IDH2R172</i>	<i>IDH1</i>	<i>IDH2R140</i>	<i>IDH2R172</i>
<i>NPM1</i> , mut	0.29 [0.16-0.54] p < 0.0001	0.41 [0.21-0.81] p= 0.01	-	-	0.33 [0.17-0.63] p = 0.0009	-
<i>DNMT3A</i> , mut	-	-	-	-	3.05 [1.61-5.78] p = 0.0006	-
Karyotype, normal	-	0.38 [0.19-0.78] p = 0.008	-	-	-	-
Log ₁₀ (Platelets)	-	-	0.19 [0.07-0.53] p =0.002	-	-	-

FIGURES LEGEND

Figure 1. Characteristics of the *IDH1/2* AML cohort. **A:** Molecular and Cytogenetic characteristics of the *IDH*-mutated AML cohort according to *IDH* subgroup. **B:** Boxplot showing the number of co-occurring mutations in each *IDH* subgroup. **C:** Violin-plot showing the VAF of the *IDH* variant in each *IDH* subgroup. **D:** Barplot showing the CR/CRp rates after 1 and 2 courses in each *IDH* subgroup. The error-bars represent the upper limit of the 95% confidence interval. **E:** Overall Survival censored at HSCT according to *IDH* subgroup. **F:** Disease-free Survival censored at HSCT according to *IDH* subgroup.

Figure 2. Characteristics of the *IDH1*-mutated AML patients. **A:** Volcano plot representing the association between *IDH1*, *IDH1R132C* and *IDH1R132H* variants and covariates (estimate of the point-biserial correlation (continuous variables) or Phi (dichotomous variables) on the x-axis) and the significance of the difference (p-value from Mann-Whitney (continuous variables) or Fisher's exact (dichotomous) tests, expressed on an inverted logarithmic scale on the y-axis). The size of the circle corresponds to the frequency of the variable in the cohort. Only covariates with a q-value < 0.05 are highlighted. **B:** Overall Survival censored at HSCT according to the type of *IDH1* variant. **C:** Overall Survival censored at HSCT according to the mutational status of *NPM1*.

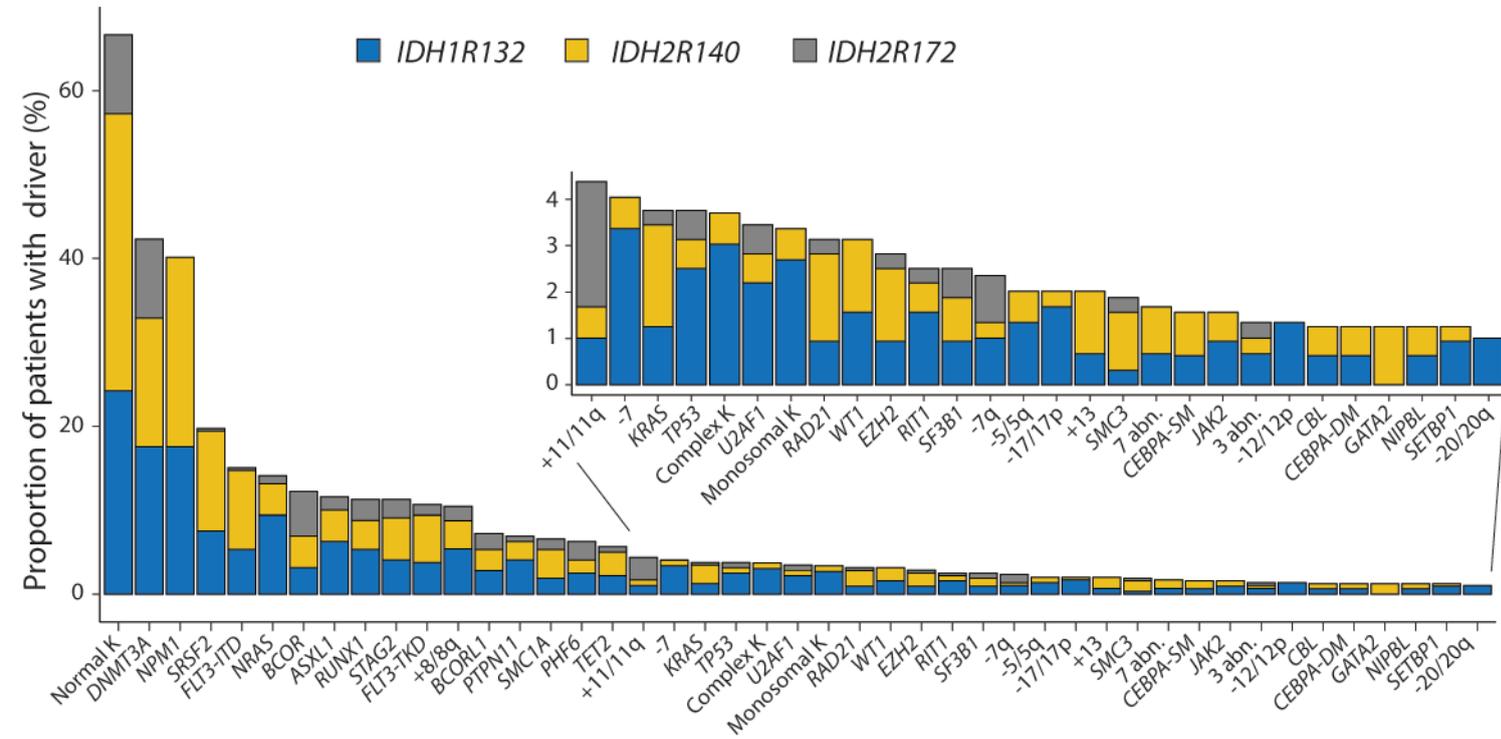
Figure 3. Characteristics of the *IDH2R140*-mutated AML patients : **A:** Volcano plot representing the association between *IDH2R140* variants and covariates (estimate of the point-biserial correlation (continuous variables) or Phi (dichotomous variables) on the x-axis) and the significance of the difference (p-value from Mann-

Whitney (continuous variables) or Fisher's exact (dichotomous) tests, expressed on an inverted logarithmic scale on the y-axis). The size of the circle corresponds to the frequency of the variable in the cohort. Only covariates with a q-value < 0.05 are highlighted. **B:** Overall Survival censored at HSCT in *IDH2R140* patients according to the karyotype and *NPM1* mutational status. **C:** Disease-Free Survival censored at HSCT according to the mutational statuses of *NPM1* and *DNMT3A*.

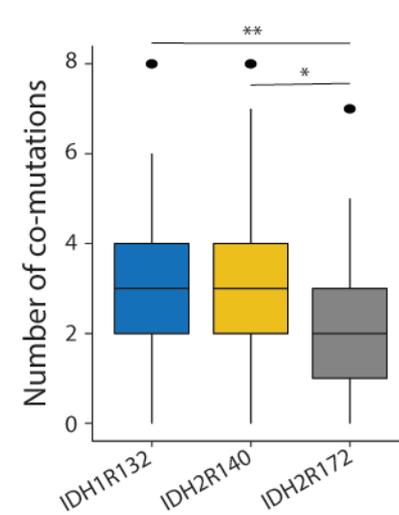
Figure 4. Characteristics of the *IDH2R172*-mutated AML patients. A: Volcano plot representing the association between *IDH2R172* variants and covariates (estimate of the point-biserial correlation (continuous variables) or Phi (dichotomous variables) on the x-axis) and the significance of the difference (p-value from Mann-Whitney (continuous variables) or Fisher's exact (dichotomous) tests, expressed on an inverted logarithmic scale on the y-axis). The size of the circle corresponds to the frequency of the variable in the cohort. Only covariates with a q-value < 0.05 are highlighted. **B:** Overall Survival censored at HSCT in *IDH2R172* patients, according to the platelet counts at diagnosis (arbitrary cut-off at $100 \times 10^9/L$).

Figure 5. Impact of HSCT in first CR/CRp in *IDH*-mutated AML patients. A: Simon-Makuch plot of Overall Survival according to achievement of HSCT. HSCT was considered as a time-dependent variable. **B.** Simon-Makuch plot of Disease-free Survival according to achievement of HSCT. HSCT was considered as a time-dependent variable.

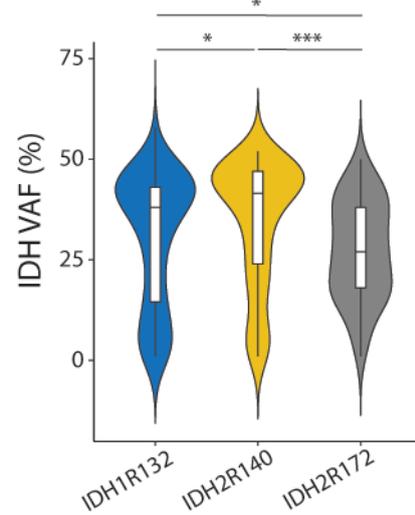
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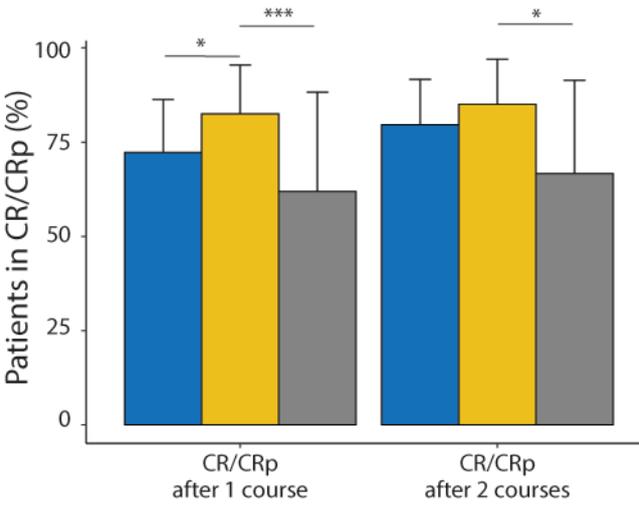
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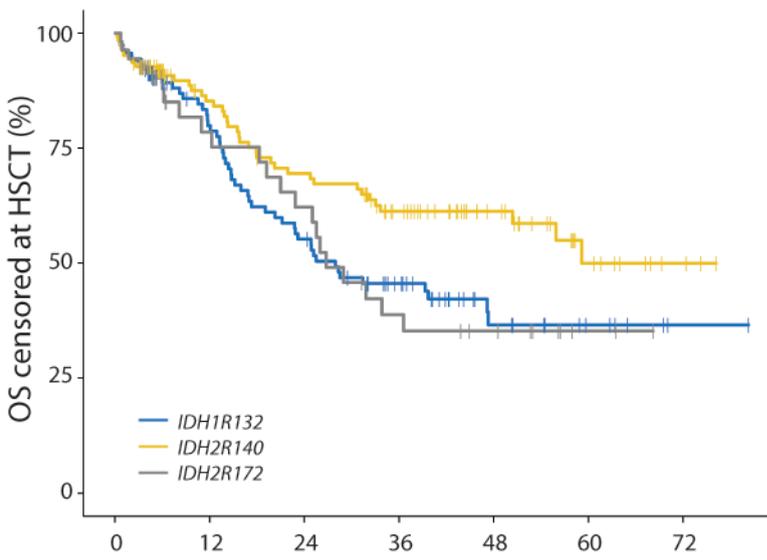
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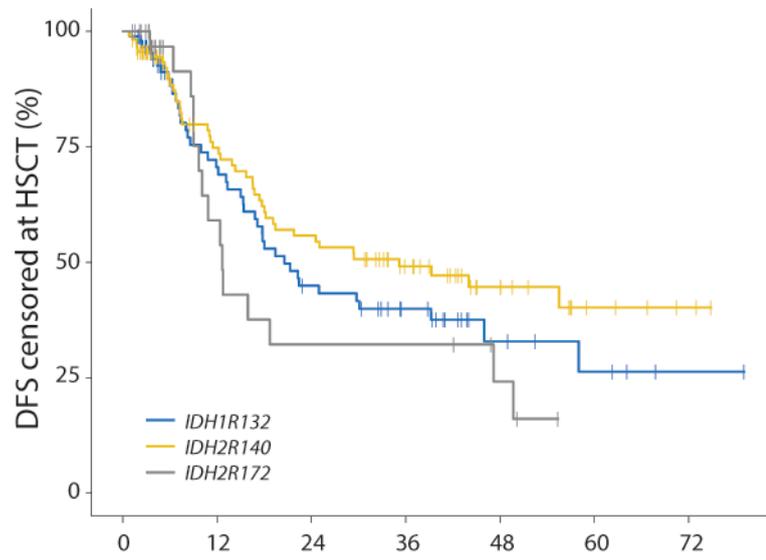


E.



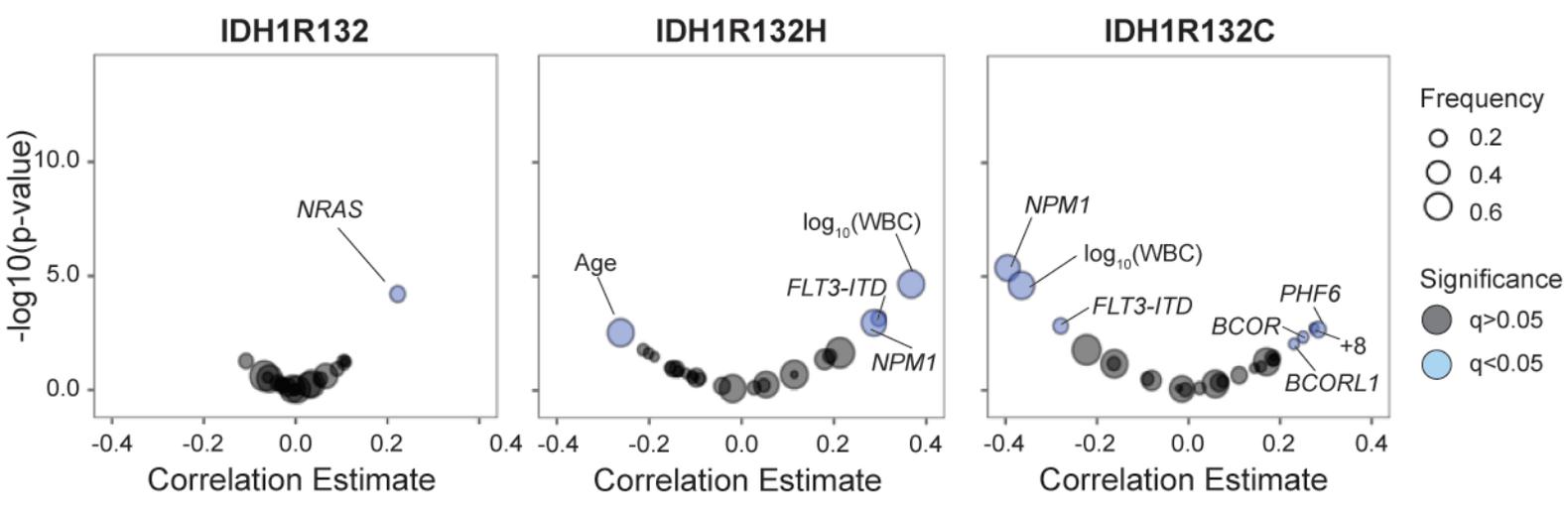
N° at risk	0	12	24	36	48	60	72
IDH1R132	115	68	47	31	13	6	1
IDH2R140	124	76	61	45	25	10	3
IDH2R172	54	24	19	11	8	2	0

F.

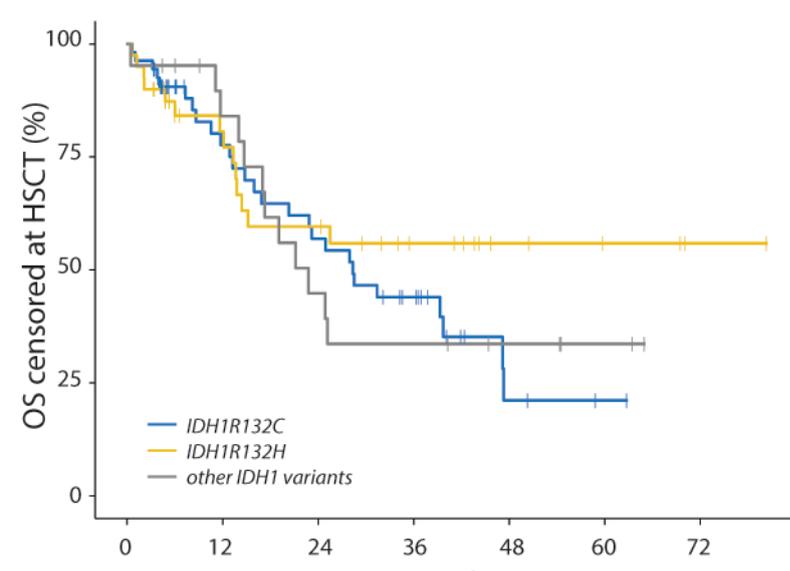


N° at risk	0	12	24	36	48	60	72
IDH1R132	91	44	27	18	7	4	1
IDH2R140	113	59	44	29	14	5	2
IDH2R172	40	11	6	6	3	0	0

A.

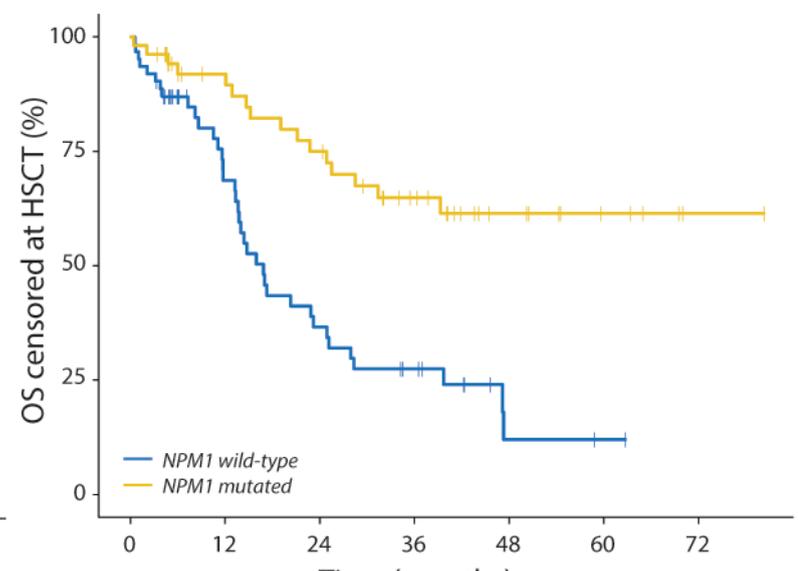


B.



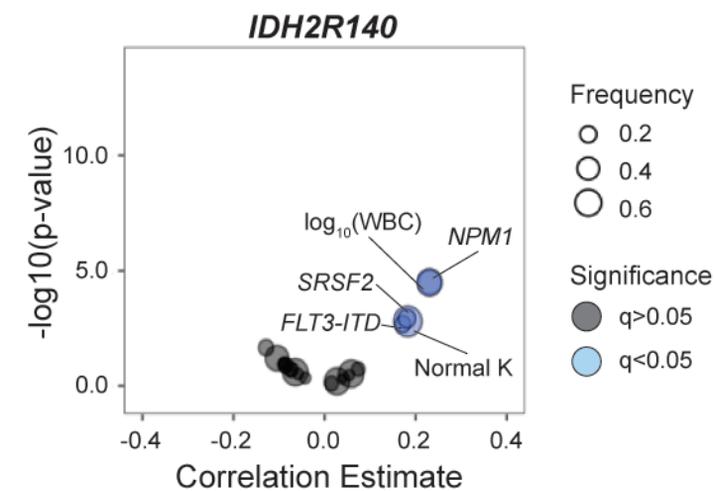
N° at risk		Time (months)						
		0	12	24	36	48	60	72
R132C	54	30	22	14	3	1	0	
R132H	40	23	17	11	6	3	1	
Other	21	15	8	6	4	2	0	

C.

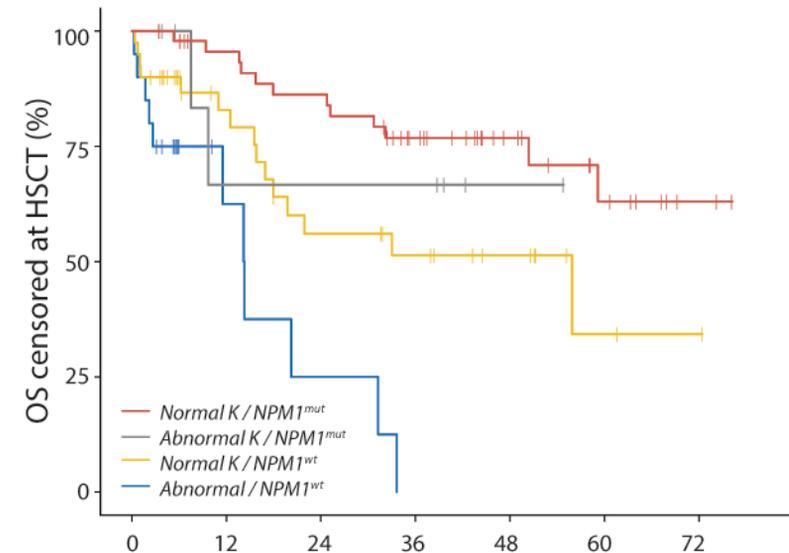


N° at risk		Time (months)						
		0	12	24	36	48	60	72
NPM1-Wt	62	30	16	10	2	1	0	
NPM1-Mut	53	38	31	21	11	5	1	

A.

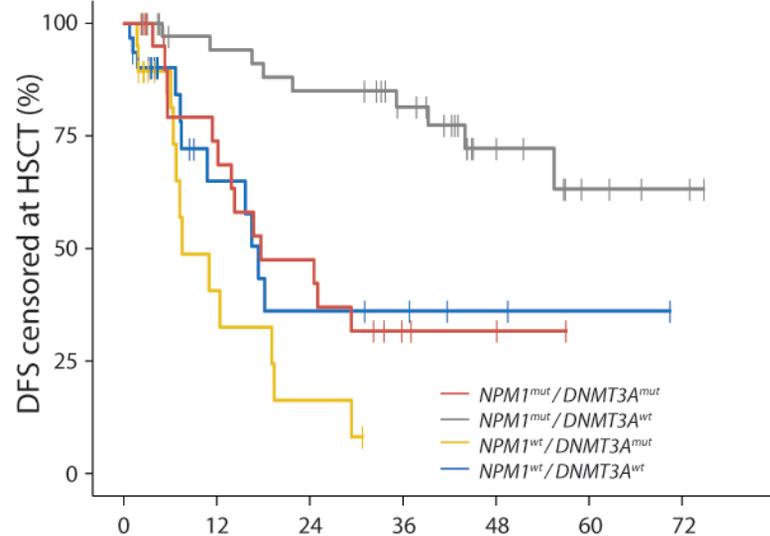


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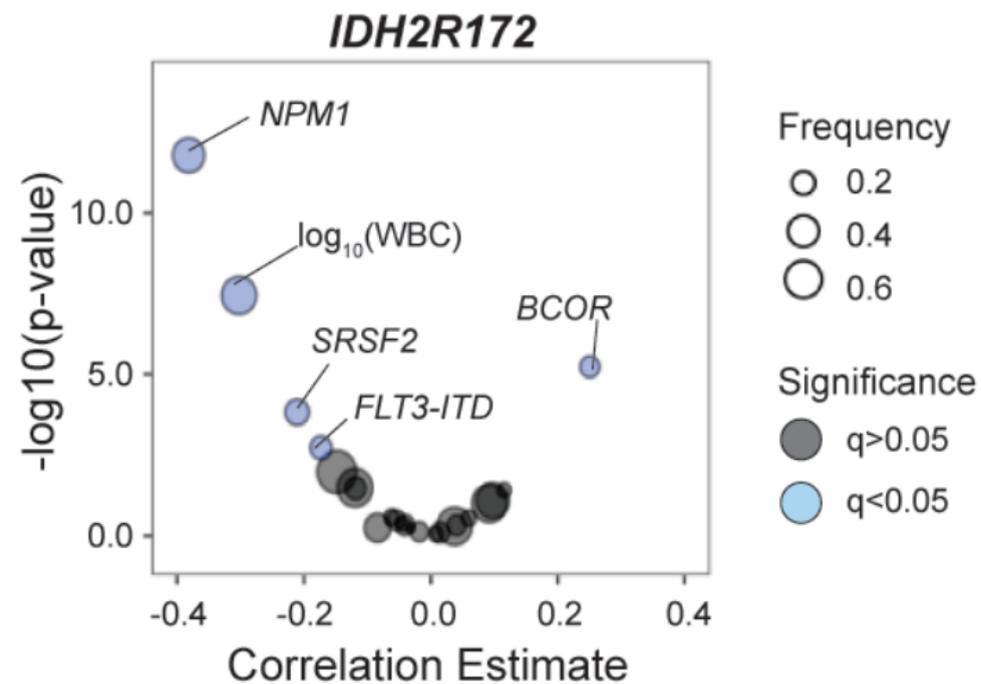
	N° at risk							
Normal K / <i>NPM1</i> ^{mut}	49	41	37	27	15	8	2	
Abnormal K / <i>NPM1</i> ^{mut}	8	4	4	4	1	0	0	
Normal K / <i>NPM1</i> ^{wt}	40	22	14	11	7	2	1	
Abnormal / <i>NPM1</i> ^{wt}	20	5	2	0	0	0	0	

C.

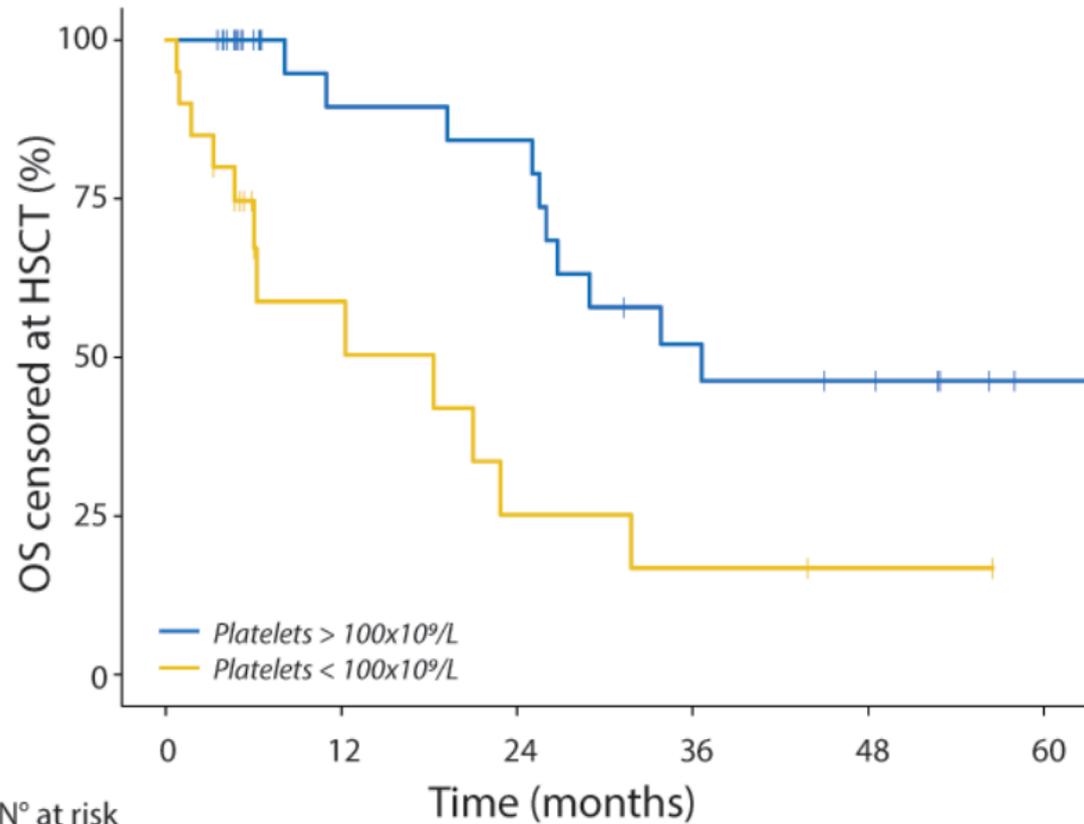


	N° at risk							
Both	23	15	9	3	2	0	0	
<i>NPM1</i>	39	31	28	22	10	4	2	
<i>DNMT3A</i>	20	5	2	0	0	0	0	
wild-type	31	9	5	4	2	1	0	

A.

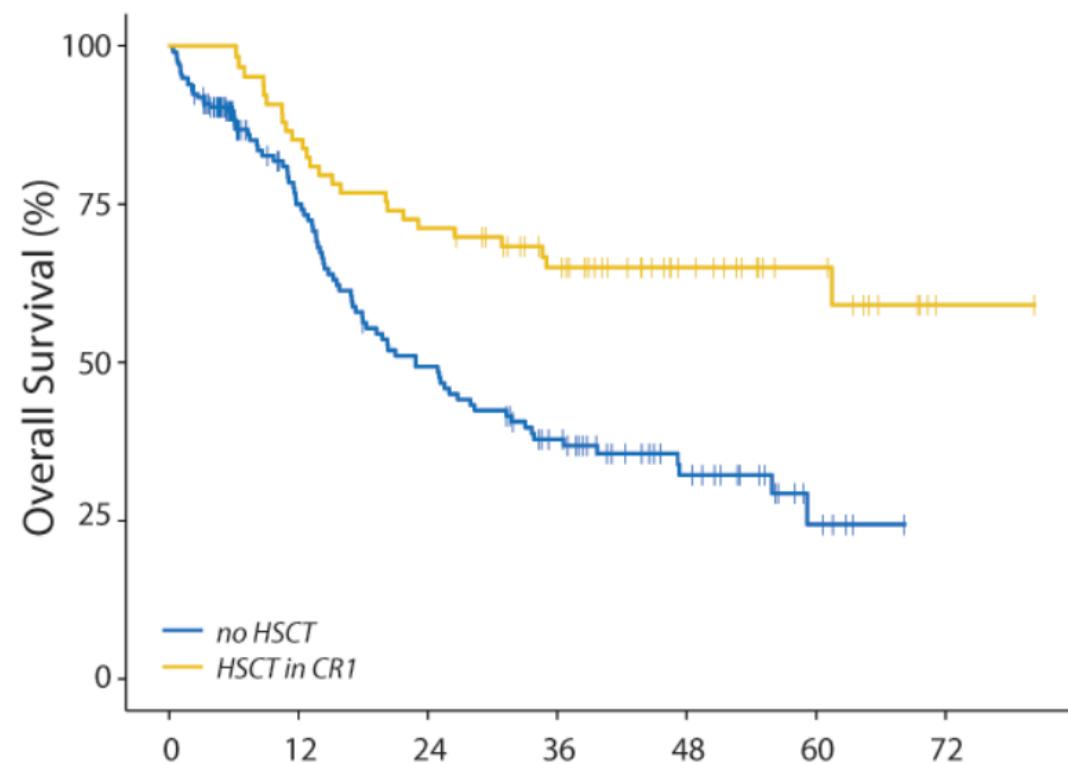


B.



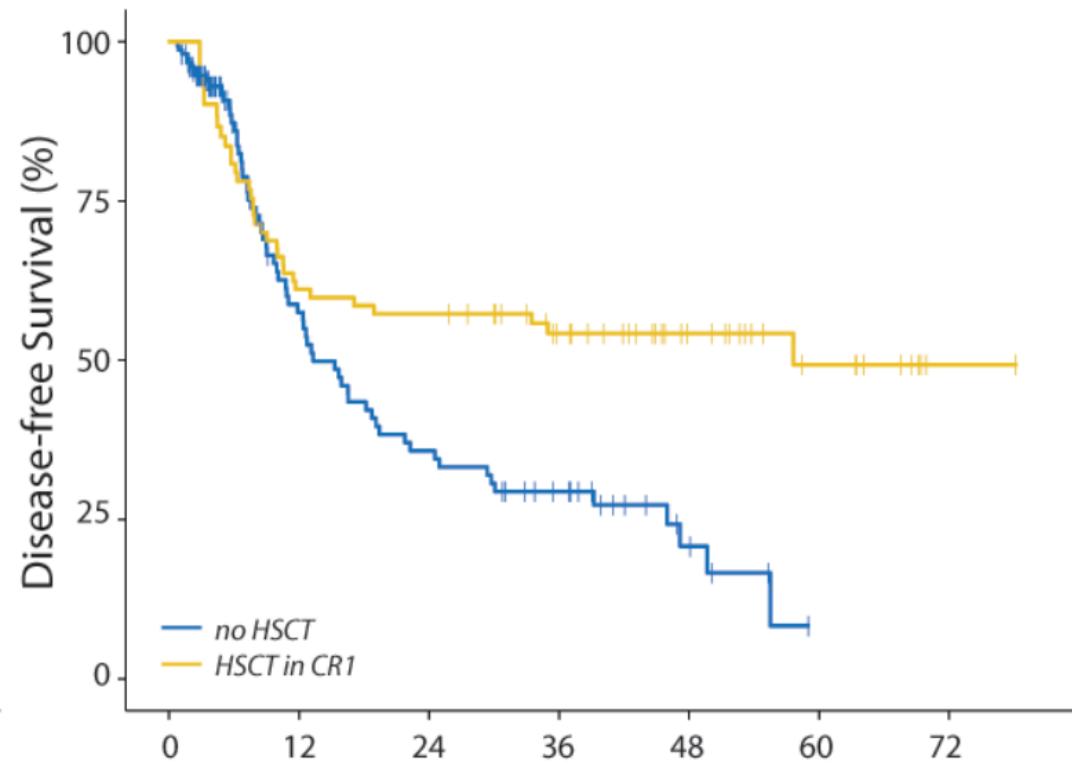
	0	12	24	36	48	60
N° at risk						
Platelets > 100	34	17	16	9	7	2
Platelets < 100	20	7	3	2	1	0

A.



N° at risk	0	12	24	36	48	60	72
HSCT in CR1	0	61	51	39	21	12	1
no HSCT	197	88	57	38	19	5	0

B.



N° at risk	0	12	24	36	48	60	72
HSCT in CR1	0	48	45	32	18	9	1
no HSCT	155	45	28	18	6	0	0