IDH2 mutation is associated with favorable outcome among older adults with newly diagnosed acute myeloid leukemia treated with hypomethylating agent-based therapy

Fieke W. Hoff,[1°] Ying Huang,[2] Rina Li Welkie,[2] Ronan T. Swords,[3] Elie Traer,[3] Eytan M. Stein,[4] Tara L. Lin,[5] Maria R. Baer,[6] Vu H. Duong,[6] William G. Blum,[7] Martha L. Arellano,[7] Wendy Stock,[8] Olatoyosi Odenike,[8] Joshua F. Zeidner,[9] Rebecca L. Olin,[10] Catherine C. Smith,[10] Gary J. Schiller,[11] Emily K. Curran,[12] Shivani V. Handa,[2] Nyla A. Heerema,[2] Timothy Chen,[2] Molly Martycz,[2] Mona Stefanos,[2] Sonja G. Marcus,[13] Leonard Rosenberg,[13] Brian J. Druker,[3] Ross L. Levine,[4] Amy Burd,[13] Ashley O. Yocum,[13] Uma M. Borate,[2] Alice S. Mims,[2] John C. Byrd[12] and Yazan F. Madanat[1]

[1]University of Texas Southwestern Medical Center, Dallas, TX; [2]The Ohio State University, Columbus, OH; [3]Knight Cancer Institute, Oregon Health & Science University, Portland, OR; [4]Memorial Sloan Kettering Cancer Center, New York, NY; [5]University of Kansas Medical Center, Kansas City, KS; [6]University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD; [7]Winship Cancer Institute of Emory University, Atlanta, GA; [8]University of Chicago, Chicago, IL; [9]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; [10]University of California San Francisco, San Francisco, CA; [11]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA; [12]University of Cincinnati, Cincinnati, OH and [13]Blood Cancer United, Washington, DC, USA

°Current address: National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA

Correspondence: Y.F. Madanat
yazan.madanat@utsouthwestern.edu

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Abstract

Mutations of isocitrate dehydrogenase (IDH) are recurrent in newly diagnosed acute myeloid leukemia (AML) and their prevalence increases with age. The prognostic impact of *IDH* mutations in AML remains controversial. IDH inhibitors generally have a favorable side-effect profile, making them an attractive option for older patients. This retrospective analysis aimed to describe the prevalence and prognostic impact of *IDH* mutations in a large cohort of newly diagnosed AML patients aged ≥60 years enrolled in the Beat AML clinical trial. A total of 1,023 patients were included. *IDH* mutations were detected in 28% of patients, including 9.7% with *IDH1*^{mut}, 18.9% with *IDH2*^{mut}, and 1.0% with mutations in both *IDH1* and *IDH2*. *IDH* mutations frequently co-occurred with *DNMT3A* (38%), *NPM1* (35%), and *SRSF2* (34%) mutations. In patients treated with intensive chemotherapy, *IDH* mutations were not prognostic for overall survival (OS) (*P*=0.76), while OS was longer for patients with *IDH2*^{mut} compared to *IDH*^{wt} in patients treated with hypomethylating agent (HMA)-based therapy (median OS, 18.5 *vs*. 10.2 months, *P*<0.001). *IDH1* was not significant for outcome. *IDH2* remained prognostic for OS after exclusion of patients receiving an IDH inhibitor (hazard ratio=0.60, 95% confidence interval: 0.41-0.89). Outcomes with *TP53* or myelodysplasia-related gene mutations were also better with an *IDH* co-mutation (*P*=0.043, and *P*=0.006, respectively). In patients treated with HMA plus venetoclax (N=243), *IDH*^{mut} was not prognostic (*P*=0.42). The high prevalence of *IDH*^{mut} and favorable impact in patients treated with HMA-based therapy supports studies investigating the addition of targeted therapies to HMA-based regimens for older patients with *IDH*-mutant AML; mut: mutated; wt: wild-type.

Introduction

Alterations in cellular metabolism and epigenetic regulation are implicated in the pathogenesis of acute myeloid leukemia (AML).[1] Isocitrate dehydrogenase (IDH) is involved in cellular metabolism, histone demethylation, and DNA modification.[2,3] IDH1 and IDH2 are homodimeric nicotinamide adenine dinucleotide phosphate (NADP)-dependent enzymes that catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate in the cytoplasm and mitochondria,

respectively.[4] The vast majority of *IDH1* mutations in AML occur at arginine 132 (R132), while IDH2 mutations typically occur at arginine 140 (R140) or arginine 172 (R172).[5] These mutations occur within the conserved, active site of the enzyme, resulting in a partially reversed reaction that reduces α-ketoglutarate to 2-hydroxyglutarate. Accumulation of the oncometabolite 2-hydroxyglutarate interferes with α-ketoglutarate-dependent enzymes such as Tet methylcytosine dioxygenase 2 (TET2)-dependent DNA hydroxymethylation, histone demethylation and hypoxia-inducible factor-1α activation leading to impaired hematopoietic differentiation and enhanced proliferation.[3,6-8]

IDH mutations were first identified in AML in 2008 and have since been found to be among the most common recurrently mutated genes in AML.[9] The prognostic impact of *IDH1* and *IDH2* mutations remains controversial, and may be influenced by cytogenetic context (i.e., normal karyotype) and the presence of other molecular abnormalities (i.e., *NPM1, FLT3*-ITD) in patients treated with intensive chemotherapy.[10-13] In patients receiving lower-intensity treatment, recent studies have reported particularly favorable outcomes with incorporation of venetoclax-based therapies for patients with *IDH1* and *IDH2* mutations.[14]

IDH inhibitors are small molecules that bind within the IDH enzymatic active site blocking aberrant 2-hydroxyglutarate production and inducing myeloid differentiation and enhanced proliferation.[15] Although they can lead to differentiation syndrome, they generally have a favorable side-effect profile, making them an attractive option, particularly for older patients. While *IDH* mutations are known to occur more frequently in older AML patients, only a few studies have reported on the prevalence of *IDH* mutations in patients 60 years or older. We aimed to describe the incidence and prognostic impact of *IDH* mutations in patients with newly diagnosed AML aged 60 years or older in a large cohort of AML patients treated on the Beat AML clinical trial.

Methods

Study cohort

Eligible patients were adults aged 60 years or older with newly diagnosed AML who met the screening criteria for enrollment in the Beat AML trial (NCT03013998) and provided consent before 10 May, 2023.[16] Informed consent was obtained in accordance with the Declaration of Helsinki. The study was approved by institutional review boards. Details of treatments received are provided in *Online Supplementary Table S1*.

Details of genomic analysis have been reported previously.[16] Cytogenetic analysis from diagnostic assessment was centrally reviewed and reported in accordance with the International System for Human Cytogenomic Nomenclature.[17] Complex karyotype was defined by the presence of ≥3 unrelated chromosome abnormalities. Normal karyotype was defined by the detection of no chromosome abnormalities in a minimum of at least 20 metaphases analyzed. Cytogenetics were centrally reviewed (NH). *IDH* molecular testing was performed by next-generation sequencing using FoundationOne Heme (Foundation Medicine).[18] A mutation was considered present at any detectable variant allele frequency.

Statistical analysis

The patients' characteristics are summarized using the median (range) for continuous variables and frequency (percentage) for categorial variables. The Student *t* test or Wilcoxon rank sum test and χ^2 or Fisher exact test were used to compare continuous or categorial variables, respectively. Statistical significance was defined by a $P<0.05$. Patients with an *IDH* mutation outside the active site (N=11) were excluded from the outcome analysis. Patients with active site mutations in both *IDH1* and *IDH2* (N=6) were included in analyses that evaluated the impact of IDH^{mut} on outcome but were excluded from sub-analyses for *IDH1* or *IDH2*. Patients with a mutation in both an active site of one and an inactive site in the other were assigned based on their mutation in the active site. As an example, a patient with mutated *IDH1*-R132C and *IDH2*-V406L was assigned to *IDH1*. Overall survival (OS) was estimated using the Kaplan-Meier method from the date of trial inclusion until death. OS was censored for date of allogeneic hematopoietic stem cell transplantation (HSCT) or last follow-up. Group differences were calculated using the log-rank test. Cox proportional hazard models were used to describe the relative risk of each variable on death over time from the date of trial inclusion. Statistical analyses were conducted in RStudio, version 4.2.3.

Results

Patients' characteristics and prevalence of *IDH* mutations

We identified a total of 1,023 patients with newly diagnosed AML who were 60 years or older at the date of trial inclusion. Patients had a median age of 72 (range, 60-92) years. The majority were non-Hispanic White (82%), and 42% were female (Table 1). There were 282 (28%) patients identified with an *IDH* mutation. Ninety-nine (9.7%) patients had *IDH1*-mutated ($IDH1^{mut}$) AML, with nearly all *IDH1* mutations at the active site, *IDH1*-R132 (N=90/99, 91%), including R132C (N=46), R132H (N=33), R132G (N=6), and R132S (N=5). The remaining nine mutations were outside the active sites at A353D (N=1), D38N (N=1), D220G (N=1), F32V (N=2), F355S (N=1), M318T (N=1), and V294M (N=2). There were 193 (19%) *IDH2* mutations identified with nearly all being point mutations at active sites, including *IDH2*-R140 (N=144 [75%]: R140W [N=6], R140Q [N=136], R140L [N=2]) or *IDH2*-R172 (N=43 [22%]: R172K [N=43]).

The remaining six *IDH2* mutations were at inactive residues: A22V, D225N, E429K, I98T, V406L, Y179D. Six patients had mutations in the active sites of both *IDH1* and *IDH2*, and four patients had a mutation in the active site of *IDH1* (N=2) or *IDH2* (N=2) as well as a mutation in the inactive site of the other.

The prevalence of *IDH* mutations was fairly stable among patients 60 years and older according to age groups (Figure 1A). A significantly greater proportion of patients with *IDH*^{mut} were female, compared to patients with wildtype *IDH* (*IDH*^{wt}) (48% *vs*. 40%, *P*=0.045), and were classified as favorable risk by 2022 European LeukemiaNet criteria (24% *vs*. 12%, *P*<0.001) (Table 1).

IDH associated with mutations and cytogenetics

The most commonly co-occurring mutations with *IDH*^{mut} compared to *IDH*^{wt} were *DNMT3A* (38% *vs*. 20%, *P*<0.001), *NPM1* (35% *vs*. 14%, *P*<0.001), and *SRSF2* (34% *vs*. 17%, *P*<0.001) (Figure 1B). Genes that were observed in *IDH*^{wt} compared to *IDH*^{mut} included *TP53* (31% *vs*. 10%, respectively, *P*<0.001) and *TET2* (28% *vs*. 11%, respectively, *P*<0.001). *ASXL1, KRAS, NRAS, WT1, RUNX1* and *FLT3* were all not statistically

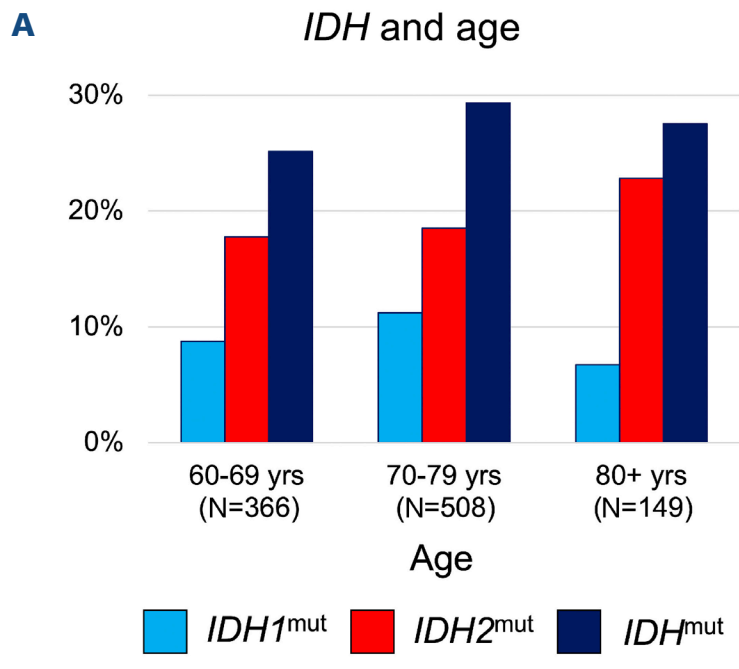
Table 1. Baseline characteristics of the study patients (N=1,023).

Characteristic	All patients N=1,023	*IDH1*^{mut} N=99	*IDH2*^{mut} N=193	*IDH1/2*^{mut} N=282	*IDH*^{wt} N=741	*P* *IDH*^{mut} *vs. IDH*^{wt}
Age, years, median (range)	72 (60-92)	72.4 (61-87)	73.2 (60-91)	72.9 (60-91)	72.2 (60-92)	0.141
Female sex, N (%)	433 (42)	46 (46)	91 (47)	134 (48)	299 (40)	0.045
Ethnicity, N (%)†						0.323
Hispanic	23 (2)	2 (2)	8 (4)	9 (3)	14 (2)	
Non-Hispanic	951 (93)	94 (95)	177 (92)	262 (93)	689 (93)	
Unknown	49 (5)	3 (3)	8 (4)	11 (4)	38 (4)	
Race, N (%)†						0.743
White	801 (75)	80 (81)	149 (77)	222 (78)	579 (78)	
African American	47 (5)	3 (3)	8 (4)	11 (4)	36 (5)	
Asian	30 (3)	3 (3)	7 (4)	10 (4)	20 (3)	
Multiple or other	78 (80)	9 (9)	17 (9)	24 (9)	54 (7)	
Unknown	67 (7)	4 (4)	12 (6)	15 (5)	52 (7)	
Cytogenetics, N (%)†						<0.001
Normal karyotype	333 (36)	51 (52)	90 (47)	138 (41)	195 (26)	
Complex karyotype	280 (30)	10 (10)	21 (11)	30 (11)	250 (34)	
Chromosome 5/5q, 7 or 17/17p abnormalities	54 (6)	7 (7)	9 (5)	15 (5)	39 (5)	
Core-binding factor	35 (4)	0 (0)	2 (1)	2 (0.7)	33 (4)	
KMT2A rearrangement	21 (2)	0 (0)	1 (0.1)	1 (0.3)	20 (3)	
Other	203 (20)	20 (20)	48 (25)	64 (23)	139 (19)	
Unknown	97 (9)	11 (11)	22 (11)	32 (11)	65 (9)	
2022 ELN category						<0.001
Favorable	159 (16)	26 (26)	43 (22)	67 (24)	92 (12)	
Intermediate	102 (10)	14 (14)	25 (13)	38 (13)	64 (9)	
Adverse	674 (66)	48 (48)	103 (53)	145 (51)	529 (71)	
Unknown	88 (9)	11 (11)	22 (11)	32 (11)	56 (8)	
Mutation, N (%)*						
DNMT3A	259 (25)	42 (42)	69 (36)	108 (38)	151 (20)	<0.001
TP53	256 (25)	10 (10)	18 (9)	28 (10)	228 (31)	<0.001
TET2	241 (24)	21 (21)	13 (7)	31 (11)	210 (28)	<0.001
RUNX1	227 (22)	18 (18)	43 (22)	58 (21)	169 (23)	0.493
SRSF2	222 (22)	29 (29)	74 (38)	97 (34)	125 (17)	<0.001
ASXL1	215 (21)	28 (28)	44 (23)	68 (24)	147 (20)	0.157
FLT3‡	210 (21)	25 (25)	38 (20)	60 (21)	150 (20)	0.780
NPM1	207 (20)	44 (44)	60 (31)	100 (35)	107 (14)	<0.001
NRAS	175 (17)	19 (19)	26 (13)	42 (15)	133 (18)	0.286

†Unknown values were not considered in *P* value calculations and are excluded from the results. *Mutations were considered present at any detectable variant allele frequency. ‡*FLT3* was mutated in 210 patients; 109 patients had *FLT3*-ITD, 65 patients had a *FLT3*-TKD mutation, 14 patients had both *FLT3*-ITD and *FLT3*-TKD. ELN: European LeukemiaNet; ITD: internal tandem duplication; TKD: tyrosine kinase domain.

associated with *IDH* mutations.

IDH^{mut} was more frequently associated with a normal karyotype compared to *IDH*^{wt} (41% *vs*. 26%, *P*<0.001), while complex karyotype (34% in *IDH*^{wt} *vs*. 11% in *IDH*^{mut}, *P*<0.001) and core-binding factor (CBF) (4% *IDH*^{wt} *vs*. 0.7% in *IDH*^{mut}, *P*=0.035) cytogenetic abnormalities were significantly more commonly detected in patients with *IDH*^{wt} (Figure 1B). Only one patient with CBF-AML had an active site *IDH2* mutation, a second patient had a non-pathogenic mutation, *IDH2*-A22V.



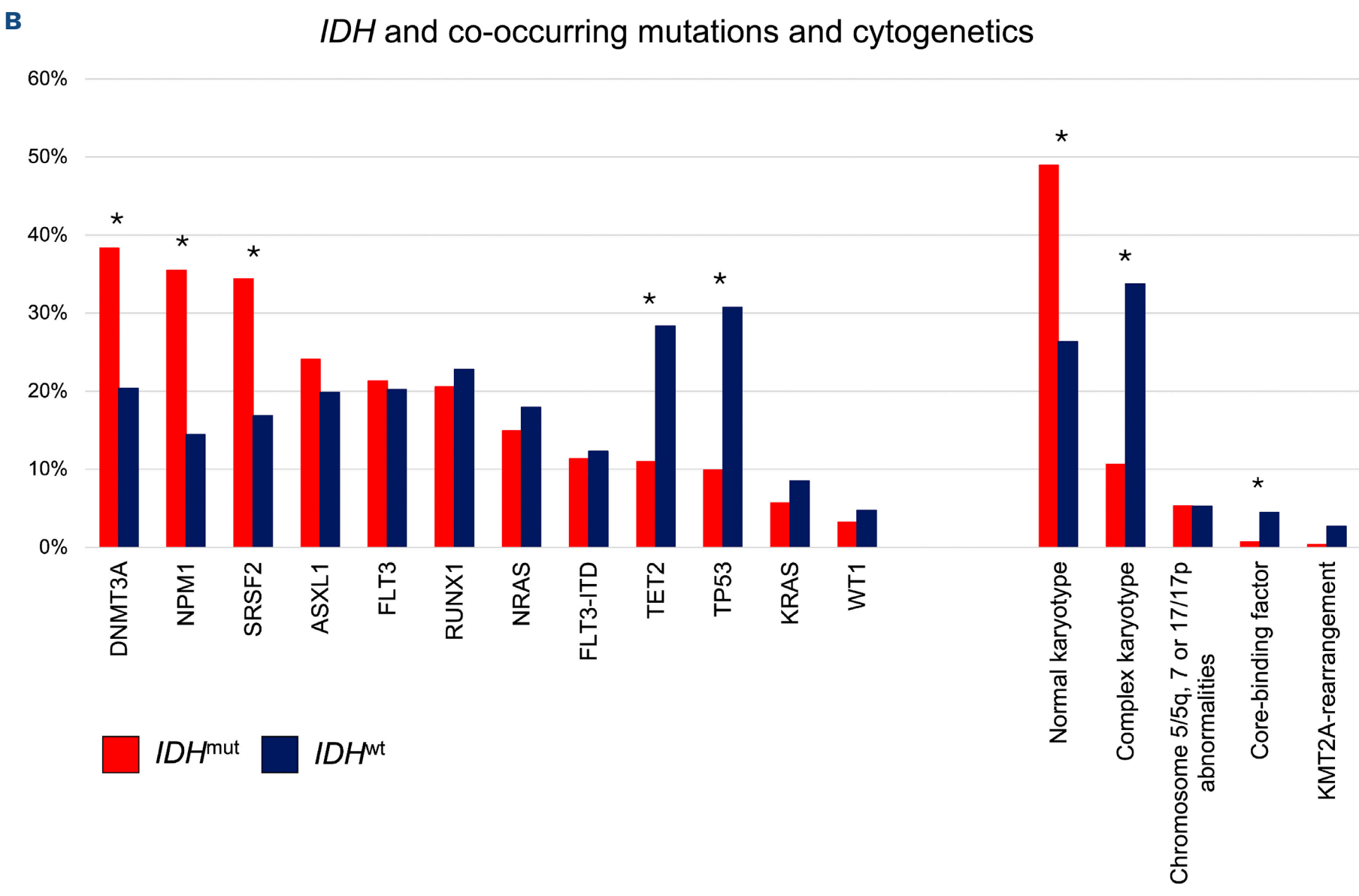


Figure 1. *IDH* mutations in older patients with acute myeloid leukemia. (A) The prevalence of *IDH* mutations in acute myeloid leukemia according to age. (B) Co-occurring mutations and karyotypes in patients with mutated *IDH* (*IDH*^{mut}) (red) and wild-type *IDH* (*IDH*^{wt}) (blue). Significant associations with *P*<0.05 are denoted with an asterisk (*).

IDH mutations and clinical outcome

A total of 1,002/1,023 (98.0%) patients were eligible for outcome analysis; ineligibility was due to lack of follow-up data (N=10) or an *IDH* mutation outside the active site (N=11). Of the 1,002 patients, 187 were treated with intensive chemotherapy, 705 were treated with lower-intensity therapy and 96 patients received supportive care or therapy regimen was unknown (N=14). Ninety-eight patients were treated with an IDH inhibitor (ivosidenib [N=24] or enasidenib [N=74]). One hundred forty-six (14.6%) patients proceeded with allogeneic HSCT. A summary of the various treatment regimens is shown in *Online Supplementary Table S1*.

Among patients treated with intensive chemotherapy, *IDH*^{mut} patients (N=50) and *IDH*^{wt} patients (N=137) had a similar median OS of 23.5 and 22.4 months, respectively (P=0.76) with a hazard ratio (HR) of death of 1.09 (95% confidence interval 95% CI:]: 0.64-1.83) (*Online Supplementary Figure S1A, Online Supplementary Table S2*). Analysis by type of *IDH* mutation did not show a difference between *IDH1*^{mut} *versus IDH2*^{mut} compared to *IDH*^{wt} (Figure 2A, *Online Supplementary Table S2*). One patient was excluded from the analysis due to the presence of active site mutations in both *IDH1* and *IDH2*. Seventy (37%) patients treated with intensive chemotherapy proceeded with allogeneic HSCT. When comparing *IDH*^{mut} patients (N=195) to *IDH*^{wt} patients (N=510) among those treated with any lower-intensity therapy regimen (N=705), *IDH*^{mut} was statistically associated with a higher survival probability compared to *IDH*^{wt} (HR=0.63, 95% CI: 0.51-0.78), with a median OS of 15.6 *versus* 10.2 months (P<0.001) for *IDH*^{mut} and *IDH*^{wt}, respectively (*Online Supplementary Figure S1B*). The prognostic impact was mainly driven by *IDH2* (N=133) compared to *IDH*^{wt} (HR=0.56, 95% CI: 0.44-0.72), whereas *IDH1*^{mut} (N=58) was not significantly prognostic (HR=0.84, 95% CI: 0.60-1.18) (*Online Supplementary Table S3*). Given that most patients treated with lower-intensity therapy received a hypomethylating agent (HMA)-based regimen (N=666/705, 94.5%), we then performed a similar analysis restricted to patients treated with HMA-based therapy. Survival analysis showed a median OS of 16.7 *versus* 10.2 months (P<0.001) for *IDH*^{mut} (N=179) *versus IDH*^{wt} (N=487), respectively (*Online Supplementary Figure S1C*). Analysis by *IDH* subtypes showed that *IDH2*^{mut} was associated with a hazard ratio of 0.55 (95% CI: 0.43-0.72) for death compared to *IDH*^{wt}, irrespective of *IDH2* mutation subtype (Table 2), with a median OS of 18.5 *versus* 10.2 months for *IDH2*^{mut} *versus IDH*^{wt}, respectively (Figure 2B). *IDH1*^{mut} was not significant for survival outcome. Seventy patients (10.5%) treated with HMA-based therapy received allogeneic HSCT; *IDH1*^{mut} (N=9), *IDH2*^{mut} (N=17), *IDH*^{wt} (N=44). *IDH*^{mut} was a favorable prognostic factor among the patients receiving a HSCT (P=0.043); numbers were too small to evaluate the impact of *IDH1*^{mut} or *IDH2*^{mut}.

After exclusion of patients also receiving a IDH inhibitor as part of their treatment regimen (N=84), *IDH2* (N=57) remained favorably associated with outcome (HR=0.60, 95% CI: 0.41-0.89) compared to *IDH*^{wt}. In patients treated with HMA in combination with venetoclax (N=243), OS was similar for *IDH*^{mut} and *IDH*^{wt} patients (P=0.42), irrespective of whether the mutation was in *IDH1* or *IDH2*.

Survival in patients with *IDH* mutations and karyotype abnormalities

IDH mutations frequently co-occur with normal karyotype and less frequently with a complex karyotype.[19,20] When we analyzed *IDH* mutations in patients with cytogenetically normal AML (N=203), *IDH*^{mut} was associated with a longer

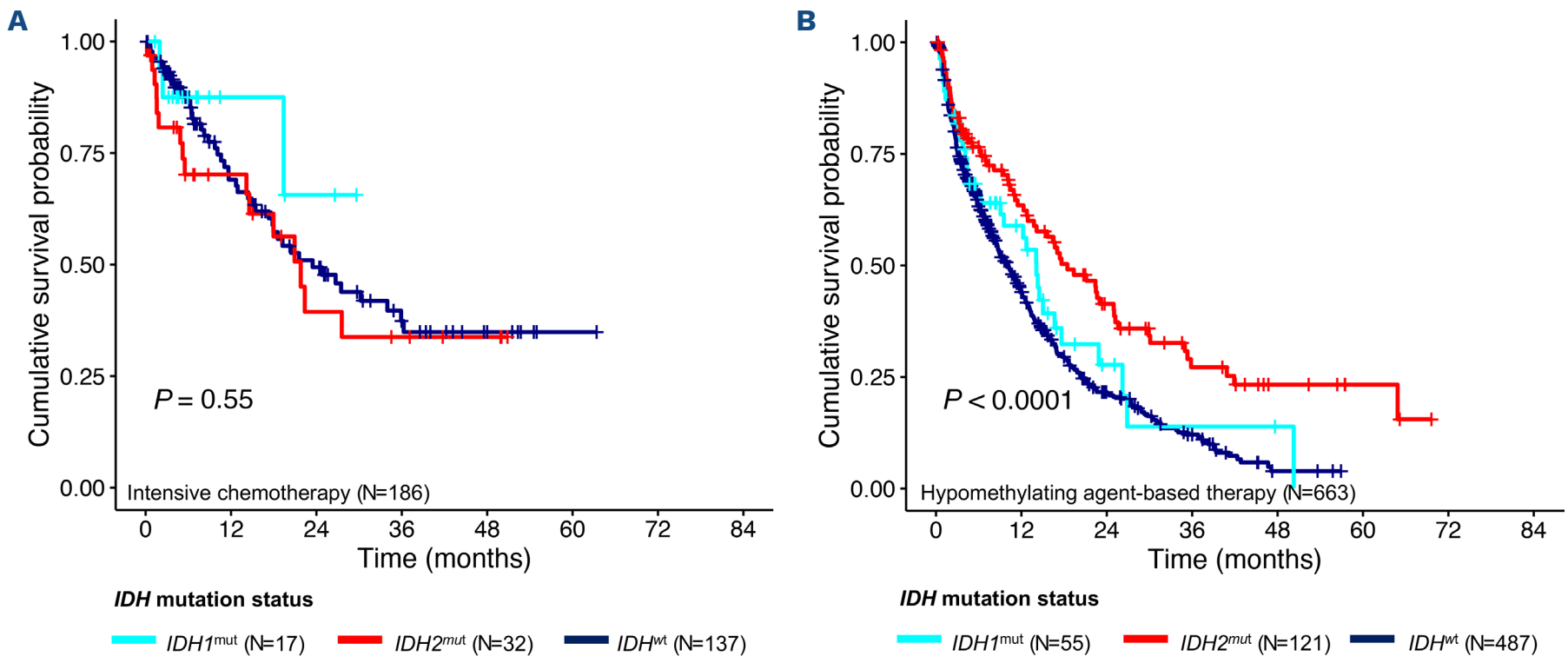


Figure 2. Kaplan-Meier survival analysis for overall survival stratified by *IDH* mutation. (A, B) Overall survival analysis in patients treated with intensive chemotherapy (A) and hypomethylating agent-based therapy (B). Patients with a mutation in both *IDH1* and *IDH2* were excluded from the analysis. mut: mutated; wt: wild-type.

OS (median OS 21.1 *vs*. 15.8 months, *P*=0.035) compared to *IDH*^{wt} among those receiving HMA-based therapy (*IDH1*: HR=0.78, 95% CI: 0.43-1.40; *IDH2*: HR=0.65, 95% CI: 0.42-1.00). No significant prognostic impact of *IDH* was found in patients receiving intensive chemotherapy (N=90). In patients with complex cytogenetics (N=209), *IDH*^{mut} (N=23) was associated with a superior OS compared to *IDH*^{wt} (N=186) (median OS 10.9 *vs*. 6.9 months, *P*=0.05). Numbers were too small to investigate the effect of *IDH* in CBF-AML or *KMT2A*-rearranged AML.

Clinical impact of *IDH* in combination with *NPM1, TP53* or myelodysplasia-related gene mutations

With 35% of patients having a co-occurring *NPM1* mutation, previous studies have shown that *IDH* mutations with *NPM1*-mutant and *FLT3*-ITD-negative molecular status have been associated with particularly favorable outcomes, while others showed worse outcomes in subsets of patients with *NPM1*- and *IDH*-mutated AML.[11,21] We, therefore, analyzed whether the favorable outcome associated with *IDH* in patients receiving HMA-based therapy further improved in the presence of a *NPM1* mutation in *FLT3*-ITD-negative AML. *IDH*^{mut} (N=47) did not prolong OS compared to *IDH*^{mut} (N=27) in patients with *NPM1*-mutant and *FLT3*-ITD-negative AML (HR=0.82, 95% CI: 0.44-1.56) (Table 2).

OS for patients with *TP53*-mutant AML treated with HMA-based therapy improved when co-mutated with *IDH*, with a median OS of 10.2 *versus* 6.9 months for *IDH*^{mut} (N=20) and *IDH*^{wt} (N=167) patients, respectively (*P*=0.043) (*Online Supplementary Figure S2A*). Among these 20 *TP53*-mutant AML patients with an *IDH* mutation, nine were treated with an IDH inhibitor, with a trend towards longer OS time for patients treated with an IDH inhibitor (*P*=0.058) (*Online Supplementary Figure S2B*).

Like *TP53* mutations, myelodysplasia-related mutations, including *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, and *ZRSR2*, are common in older patients with AML and are associated with dismal outcomes. When co-mutated with *IDH* (N=116), the median OS improved compared to that of patients with myelodysplasia related-gene mutations and wild-type *IDH* (N=267) from 10.6 months to 16.7 months in patients treated with HMA-based therapy (*P*=0.006) (*Online Supplementary Figure S2C*). The effect was mostly driven by *IDH2* (HR=0.64, 95% CI: 0.47-0.88). Half of the patients (N=58/116) were treated with an IDH inhibitor, which resulted in an improved median OS compared to that of patients who did not receive treatment with an IDH inhibitor (median OS 17.6 *vs*. 14.1 months, *P*=0.029) (*Online Supplementary Figure S2D*).

Discussion

In this study we present a large, retrospective analysis of more than 1,000 patients 60 years and older with newly diagnosed AML enrolled in the Beat AML clinical trial (NCT03013998) describing the incidence and prognostic impact of *IDH* mutations. *IDH* mutations were found in 28% of patients overall and in 36% of patients with a normal karyotype, with *IDH2* mutations occurring in 19% of patients and accounting for approximately two-thirds of the *IDH* mutations. This is concordant with other cohorts focused on older patients with AML reporting *IDH* mutations in 21% to 28% of patients.[22-25] We observed a significantly favorable prognostic association between *IDH2* mutations and survival in patients treated with HMA-based therapy.

The impact of *IDH* mutations on outcome has been studied extensively in the setting of intensive treatment and remains controversial.[12,13,26-29] In contrast, the importance of *IDH* mutations for outcome in patients treated with lower-intensity therapies has been studied much less.[30,31] *IDH1* and *IDH2* mutations are associated with older age at presentation

Table 2. Univariate analysis for *IDH*-mutated patients treated with hypomethylating agent-based therapy (N=666).[†]

Mutation status	N	HR	95% CI	*P*
IDH^{wt}	487	1.00	-	-
IDH^{mut}	179	0.62	0.49-0.77	<0.001
IDH1^{mut}	55	0.83	0.58-1.18	0.292
IDH2^{mut}	121	0.55	0.43-0.72	<0.001
IDH2-R140^{mut}	94	0.63	0.47-0.84	0.002
IDH2-R172^{mut}	27	0.39	0.23-0.66	<0.001
IDH^{wt}*NPM1*^{mut}/*FLT3*-ITD^{neg}	27	1.00	-	-
IDH^{mut}/*NPM1*^{mut}/*FLT3*-ITD^{neg}	47	0.82	0.44-0.1.56	0.548
IDH^{wt}/*TP53*^{mut}	167	1.00	-	-
IDH^{mut}/*TP53*^{mut}	20	0.58	0.34-0.99	0.046
IDH^{wt}/myelodysplasia-related gene mutations^{mut}	267	1.00	-	-
IDH^{mut}/myelodysplasia-related gene mutations^{wt}	116	0.70	0.53-0.91	0.009

[†]Patients with an *IDH* mutation in the active domain of both *IDH1* and *IDH2* were excluded from *IDH1* and *IDH2* sub-analyses and only considered as having *IDH*^{mut}. HR: hazard ratio; 95% CI: 95% confidence interval; mut: mutated; wt: wild-type.

and patients are often ineligible for intensive therapy due to poor performance status or co-morbidities. Instead, most older patients are offered epigenetic/lower-intensity treatments, making evaluation of the prognostic impact of *IDH* mutations in this group relevant.

For patients with untreated newly diagnosed IDH-mutated AML who are ineligible for intensive chemotherapy, the phase III randomized VIALE-A clinical trial performed a subgroup analysis showing superior OS with azacitidine+venetoclax *versus* azacitidine alone with a median OS of 19.9 months *versus* 6.2 months (P<0.001), and 35% of the responders who survived ≥2 years had an *IDH* mutation.[23,32] The phase III AGILE clinical trial evaluated ivosidenib in combination with azacitidine in a relatively similar cohort of patients with *IDH1*-mutated newly diagnosed AML who were ineligible for intensive chemotherapy, showing significant clinical benefit of the addition of ivosidenib as compared with azacitidine alone.[33] After a median follow-up of 15.1 months, the median OS was 24.0 months compared to 7.9 months. Both trials showed most benefit for patients 75 years and older. The phase II/Ib Beat AML substudy applied a risk-adapted approach to assess the efficacy of enasidenib monotherapy for patients 60 years of age or older with newly diagnosed AML in whom genomic profiling demonstrated that mutant *IDH2* was the dominant leukemia clone.[34] The study showed an overall response rate of 46%, demonstrating the efficacy of enasidenib monotherapy in upfront treatment of *IDH2*^{mut} AML. For patients with relapsed/refractory *IDH1*^{mut} AML, olutasidenib has shown efficacy in combination with azacitidine with overall response rates exceeding 50%,[35,36] and enasidenib showed meaningful improved event-free survival and overall response rates as compared to conventional care regimens in relapsed/refractory *IDH2*^{mut} AML, but did not improve OS with a median OS of 6.5 *versus* 6.2 months (P=0.23).[37]

In addition to the observation that an *IDH2* mutation was a favorable prognostic indicator in patients treated with HMA-based therapy overall, *IDH2*^{mut} remained prognostic in normal karyotype AML, and *IDH*^{mut} did not abrogate the favorable prognostic impact of patients with *NPM1*-mutant *FLT3*-ITD wild-type AML. Among patients with *TP53*-mutant AML and AML with myelodysplasia-related gene mutations, which are both associated with extremely poor outcomes, *IDH*^{mut} was associated with prolonged OS, particularly in subsets of patients receiving an IDH inhibitor. It is unclear why, in our cohort, *IDH2*^{mut} AML did not show favorable survival in patients treated with venetoclax, as *IDH* mutations generally show high sensitivity to venetoclax therapy.[38] We did not find a high frequency of co-occurring mutations in *TP53* or kinase pathway genes, which have been linked to inferior responses to venetoclax.

The discovery of targetable mutations has expanded the therapeutic landscape of AML, particularly of *IDH*^{mut} AML. While IDH inhibitors can lead to differentiation syndrome, they generally have a favorable side-effect profile, making them an attractive option for older patients either alone or in combination with HMA-based therapy. Combinations of HMA and IDH inhibitors have shown encouraging results in frontline older AML patients with the combination an HMA and venetoclax being particularly effective in *IDH*^{mut} AML, and ivosidenib may be preferred over venetoclax in *IDH1*^{mut} AML. The major limitations of our study are its retrospective design, the relatively small number of patients treated with HMA with venetoclax as a significant proportion of the patients were consented prior to the approval of venetoclax in November 2018, and a potential selection bias as Beat AML study had separate *IDH*^{mut} study arms.

In summary, our study demonstrates that *IDH2* mutations have a favorable prognosis in patients with newly diagnosed AML who are 60 years or older and are treated with HMA-based therapy. The data support studies investigating the addition of targeted therapies to lower-intensity therapy regimens for older patients with *IDH*-mutated AML.

Disclosures

ET has participated in advisory boards and/or consulting for Abbvie, Astellas, Daiichi-Sankyo, Servier and Rigel and has received research funding from Prelude Therapeutics, Schrodinger, Incyte and AstraZeneca. EMS has served on the advisory boards of Astellas Pharma, AbbVie, Genentech, Daiichi Sankyo, Novartis, Amgen, Seattle Genetics, Syros Pharmaceuticals, Syndax Pharmaceuticals, Agios Pharmaceuticals and Celgene and is an equity holder in Auron Therapeutics. TLL has received research funding from Biopath Holdings, Astellas Pharma, Celyad, Aptevo Therapeutics, Cleave Biosciences, Ciclomed, Jazz Pharmaceuticals and Kura Oncology and serves on the advisory boards of Servier, Syndax and Daiichi Sankyo. MRB has received institutional funding from AbbVie, Ascentage, Astellas, Curadev, Gilead, Kura and Takeda. WGB has served on advisory boards of AbbVie and Syndax and has received research funding from ImmuneOnc, Meryx and Nkarta. OO has served on the advisory boards of Servier, Rigel, AbbVie and Incyte and on a data safety monitoring board for Threadwell Therapeutics. JFZ has received honoraria for advisory board participations and/or consultancy from AbbVie, Astellas, AstraZeneca, Crossbow Therapeutics, Daiichi Sankyo, Foghorn, Genmab, Ipsen, Jazz, Johnson & Johnson, Neogenomics, Novartis, Relmada, Rigel, Sellas, Servier, Shattuck Labs, Sumitomo Pharma and Syndax and has received research funding from AbbVie, Arog, Ascentage, AstraZeneca, Auron Therapeutics, Daiichi Sankyo, Faron, Jazz, Loxo, Newave, Novartis, Sellas, Servier, Shattuck Labs, Stemline, Sumitomo Pharma and Zentalis. RLO has received research funds from Cellectis and consulted for Actinium, Astellas, AbbVie, Rigel and Servier. CCS has received research funds from AbbVie, BMS, Erasca, Revolution Medicines and Zentalis and served on advisory boards for AbbVie, Genentech and Astellas. GJS has commercial interests in BMS, Amgen and J&J; he has received fees from AbbVie, Agios, Amgen, Astellas, BMS, Incyte, Janssen, Jazz, Karyopharm, Kite, Pharmacyclics, Sanofi/Genzyme

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Contributions

FWH and YFM performed the research and wrote the manuscript. YH, RLW, RTS, ET, EMS, TLL, MRB, VHD, WGB, MLA, WS, OO, JFZ, RLO, CCS, GJS, EKC, SVH, NAH, TC, MM, MS, SGM, LR, BJD, RLL, AB, AOY, UMB, ASM, JCB and YFM collected and assembled data, and were involved in the care of patients. All authors reviewed the manuscript and approved the final version.

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Data-sharing statement

Data supporting the results of this study are available from the corresponding author upon reasonable request.

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