haematologica
Journal of the Ferrata Storti Foundation

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

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

Received: July 24, 2025.
Accepted: October 27, 2025.

Citation: Fieke W. Hoff, Ying Huang, Rina Li Welkie, Ronan T. Swords, Elie Traer, Eytan M. Stein, Tara L. Lin, Maria R. Baer, Vu H. Duong, William G. Blum, Martha L. Arellano, Wendy Stock, Olatoyosi Odenike, Joshua F. Zeidner, Rebecca L. Olin, Catherine C. Smith, Gary J. Schiller, Emily K. Curran, Shivani V. Handa, Nyla A. Heerema, Timothy Chen, Molly Martycz, Mona Stefanos, Sonja G. Marcus, Leonard Rosenberg, Brian J. Druker, Ross L. Levine, Amy Burd, Ashley O. Yocum, Uma M. Borate, Alice S. Mims, John C. Byrd and Yazan F. Madanat. IDH2 mutation is associated with favorable outcome among older adults with newly diagnosed acute myeloid leukemia treated with hypomethylating agent-based therapy. Haematologica. 2025 Nov 6. doi: 10.3324/haematol.2025.288743 [Epub ahead of print]

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

*Current Address: National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD

Running head: *IDH* mutations older patients with AML

Corresponding author: Yazan F. Madanat, M.D., Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, 2201 Inwood Rd, NC8.106, Dallas, TX 75390-8565, Office: 214-648-5502, Fax: 214-648-4152, Email: yazan.madanat@utsouthwestern.edu

Data-sharing statement: data supporting the results of this study are available from the corresponding author upon reasonable request.

Funding

The study was sponsored by the Leukemia & Lymphoma Society. Funding for the trial was made possible by the Harry T. Mangurian Foundation, many other donors and the sites that enabled resources for rapid turnaround for cytogenetic analysis and other monitoring requirements for patients. Sub-studies in this trial were supported by pharmaceutical sponsors. We thank the pharmaceutical sponsors who paid the cost of performing the specific sub-studies with their investigational drugs.

Disclosures:

E.T. has participated in advisory boards and/or consulting for Abbvie, Astellas, Daiichi-Sankyo, Servier, and Rigel. He has received research funding from Prelude Therapeutics, Schrodinger, Incyte, and Astra-Zeneca. E.M.S. 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. He is an equity holder in Auron Therapeutics. T.L.L. has received research funding from Bio-path Holdings, Astellas Pharma, Celyad, Aptevo Therapeutics, Cleave Biosciences, Ciclomed, Jazz Pharmaceuticals and Kura Oncology and serves on the advisory board of Servier, Syndax, and Daiichi Sankyo. M.R.B. has institutional funding from AbbVie, Ascentage, Astellas, Curadev, Gilead, Kura, Takeda. W.G.B. has served on advisory boards of AbbVie and Syndax and has research funding from ImmuneOnc, Meryx, and Nkarta. O.O. has served on the advisory boards of Servier, Rigel, ABBVIE, Incyte, and data safety monitoring board for Threadwell therapeutics. J.F.Z. has received honoraria from advisory boards 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; 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. R.L.O. has received research

funds for Cellectis and consulted for Actinium, Astellas, Abbvie, Rigel, Servier. C.C.S. has received research funds from Abbvie, BMS, Erasca, Revolution Medicines and Zentalis and served on advisory boards for Abbvie, Genentech and Astellas. G.J.S. has commercial interests in BMS, Amgen, J&J. He has received fees from AbbVie, Agios, Amgen, Astellas, BMS, Incyte, Janssen, Jazz, Karyopharm, Kite, Pharmacyclics, Sanofi/Genzyme, Stemline. He has received research funds from AbbVie, Actinium, Actuate, Arog, Astellas, AltruBio, AVM Bio, BMS/ Celgene, Celator, Constellation, Daiichi-Sankyo, Deciphera, Delta-Fly, Forma, FujiFilm, Gamida, Genentech-Roche, Glycomimetics, Geron, Incyte, Karyopharm, Kiadis, Kite/Gilead, Kura, Marker, Mateon, Onconova, Pfizer, PrECOG, Regimmune, Samus, Sangamo, Sellas, Stemline, Syros, Takeda, Tolero, Trovagene, Agios, Amgen, Jazz, Orca, Ono-UK, Novartis. M.S. has been a consultant for Eilean Therapeutics. B.J.D. has the following disclosures. Cepheid, Labcorp, Nemucore Medical Innovations, Novartis, RUNX1 Research Program; SAB & Stock: Aptose Biosciences, Blueprint Medicines, Enliven Therapeutics, Iterion Therapeutics, GRAIL, Recludix Pharma; Board of Directors & Stock: Amgen, Vincerx Pharma; Board of Directors: Burroughs Wellcome Fund, CureOne (inactive); Joint Steering Committee: Beat AML LLS; Advisory Committee: Multicancer Early Detection Consortium; Founder: VB Therapeutics; Sponsored Research Agreement: Astra-Zeneca, DELiver Therapeutics, Immunoforge, Terns, Enliven Therapeutics (inactive), Recludix Pharma (inactive); Clinical Trial Funding: Novartis, Astra-Zeneca; Royalties from Patent 6958335 (Novartis exclusive license) and OHSU and Dana-Farber Cancer Institute (one Merck exclusive license, one CytoImage, Inc. exclusive license, one DELiver Therapeutics non-exclusive license, and one Sun Pharma Advanced Research Company non-exclusive license); US Patents 4326534, 6958335, 7416873, 7592142, 10473667, 10664967, 11049247. R.L.L. is on the supervisory board of Qiagen and is a scientific advisor to Imago, Mission Bio, Syndax. Zentalis, Ajax, Bakx, Auron, Prelude, C4 Therapeutics and Isoplexis for which he receives equity support. R.L.L. receives research support from Ajax and Abbvie and has consulted for Incyte, Janssen, Morphosys and Novartis. He has received honoraria from Astra Zeneca and Kura for invited lectures and from Gilead for grant reviews. U.M.B. has been a consultant for Genentech, Daiichi Sankyo, Takeda, Pfizer, AbbVie/Genentech and Novartis. A.S.M. has served on the advisory boards of AbbVie/Genentech, Novartis, Ryvu Therapeutics, Rigel Therapeutics, Treadwell Therapeutics, and Foghorn Therapeutics. J.C.B. is a current equity holder in Lomond Therapeutics Inc (a publicly traded company) and Eilean Therapeutics. J.C.B. holds membership on the Board of Directors or advisory committees of Lomond, Newave, Eilean, and Kartos, and Orange Grove. Y.F.M. has received honoraria/consulting fees from BMS, Kura Oncology, BluePrint Medicines, Geron, OncLive and MD Education, VJHemOnc and Medscape Live. Y.F.M. participated in advisory boards and received honoraria from Sierra Oncology, Stemline Therapeutics, Blueprint Medicines, Morphosys, Taiho Oncology, SOBI, Rigel Pharmaceuticals, Geron, Cogent Biosciences and Novartis. Y.F.M. received travel reimbursement from Blueprint Medicines, MD Education, and Morphosys. None of these relationships were related to this work.

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 patient care; all authors reviewed the manuscript and approved the final version.

Abstract

Mutations of isocitrate dehydrogenase (IDH) are recurrent in newly diagnosed (ND) acute myeloid leukemia (AML) and the 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 ND 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 the patients, including 9.7% *IDH1*^{mut}, 18.9% *IDH2*^{mut}, and 1.0% had a mutation in *IDH1* and *IDH2*. *IDH* frequently co-occurred with *DNMT3A* (38%), *NPM1* (35%), and *SRSF2* (34%). 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 of 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 (HR 0.60 [95% CI 0.41-0.89]). Outcome with a *TP53* or myelodysplasia-related gene mutation was also better with an *IDH* co-mutation (p=0.043, 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.

Introduction

Alterations in the 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 (α-KG) 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-KG to 2-hydroxyglutarate (2-HG). Accumulation of the oncometabolite 2-HG interferes with α-KG-dependent enzymes such as Tet Methylcytosine Dioxygenase 2 (TET2)-dependent DNA hydroxymethylation, histone demethylation and HIF-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 they 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-HG 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 (ND) AML age 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 ND 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 **Supplemental 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 0 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 (VAF).

Statistical analysis

Patient characteristics are summarized using median (range) for continuous variables and frequency (percentage) for categorial variables. Student's t-test or Wilcoxon Rank Sum test and Chi-square or Fisher's exact test were used to compare continuous or categorial variables, respectively. Significance was defined by a p-value < 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

Patient characteristics and *IDH* mutation prevalence

We identified a total of 1,023 patients with ND 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 point mutations at the 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 the inactive residues: A22V, D225N, E429K, I98T, V406L, Y179D. Six patients had a mutation in the active site 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* mutation was fairly stable among patients 60 years and older according to age groups (**Figure 1A**). A significantly greater proportion of the patients with *IDH*^{mut} were female, compared to patients with *IDH*^{wt} (48% vs 40%, p=0.045), and were classified as favorable risk by 2022 ELN (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 associated with *IDH* mutations.

IDH^{mut} was more frequently associated with 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 nonpathogenic mutation, *IDH2*-A22V.

IDH 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 (IC), 705 were treated with lower-intensity therapy (LIT) 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 **Supplemental Table S1**.

Among patients treated with IC, *IDH*^{mut} (n=50) compared to *IDH*^{wt} (n=137) had a similar median OS of 23.5 vs 22.4 months (p=0.76) with a hazard ratio (HR) of death of 1.09 (95% CI 0.64-1.83) (**Supplemental Figure S1A**, **Supplemental Table S2**). Analysis by type of *IDH* mutation did not show a difference between *IDH1*^{mut} vs *IDH2*^{mut} compared to *IDH*^{wt} (**Figure 2A, Supplemental 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 IC proceeded with allogeneic HSCT.

When comparing *IDH*^{mut} (n=195) to *IDH*^{wt} (n=510) in patients treated with any LIT 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 vs 10.2 months (p<0.001) for *IDH*^{mut} and *IDH*^{wt} respectively (**Supplemental 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]) (**Supplemental Table S3**). Given that most patients treated with LIT received a hypomethylating agent (HMA)-based regimen (n=666/705 (94.5%)), we then performed a similar analysis restricted to patients treated with an HMA-based therapy. Survival analysis showed a median OS of 16.7 vs 10.2 months (p<0.001) for *IDH*^{mut} (n=179) vs *IDH*^{wt} (n=487), respectively (**Supplemental Figure S1C**). Analysis by *IDH* subtypes showed that *IDH2*^{mut} was associated with a HR 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 vs 10.2 months for *IDH2*^{mut} vs *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 favorable

prognostic 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} (p=0.42), irrespective of *IDH1*^{mut} or *IDH2*^{mut}.

Survival in patients with *IDH* and karyotype

IDH mutations frequently co-occur with normal karyotype and less frequently with complex karyotype (19, 20). When we analyzed *IDH* mutations in patients with cytogenetically normal AML (n=203), *IDH*^{mut} was associated with a longer OS time (median OS 21.1 vs 15.8 months, p=0.035) compared to *IDH*^{wt} in patients receiving HMA-based therapy (*IDH1:* HR 0.78 [95% CI 0.43-1.40]; *IDH2*: HR of 0.65 [95% CI 0.42-1.00]). No significant prognostic impact of *IDH* was found in patients receiving IC (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 rearrangement AML.

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

With 35% of the 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] Therefore, we analyzed whether the favorable outcome associated with *IDH* in patient 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*^{mut} 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 vs 6.9 months for *IDH*^{mut} (n=20) and *IDH*^{wt} (n=167), respectively (p=0.043) (**Supplemental Figure S2A**). Among these 20 *TP53*-mutant AML patients with an *IDH* mutation, 9 were treated with an IDH inhibitor, with a trend towards longer OS time for patients treated with an IDH inhibitor (p=0.058) (**Supplemental 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 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) (**Supplemental Figure S2C**). The effect was mostly driven by *IDH2* (HR 0.64 [95% CI 0.47-0.88]). Half (n=58/116) of the patients were treated with an IDH inhibitor, which resulted in an improved median OS compared to patients who did not receive treatment with an IDH inhibitor (median OS 17.6 vs 14.1 months, p=0.029) (**Supplemental Figure S2D**).

Discussion

In this study we present a large, retrospective analysis of > 1,000 patients 60 years and older with ND 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 the patients overall and in 36% of the patients with normal karyotype, with *IDH2* occurring in 19% of the 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 the patients.[22-25] We observed a significantly favorable prognostic association between *IDH2* 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 in outcome in patients treated lower-intensity therapies has been studied much less.[30, 31] *IDH1* and *IDH2* mutation are associated with older age at presentation and patients are often ineligible for intensive therapy due poor performance status or co-morbidities. Instead, most older patients are offered epigenetic/lower-intensity treatments, making evaluation of the prognostic impact of *IDH* in this group relevant.

For patients with untreated ND *IDH*-mutated AML who are ineligible for intensive chemotherapy, the phase 3 randomized VIALE-A clinical trial performed a subgroup analysis showing superior OS with azacitidine+venetoclax vs azacitidine alone with a median OS of 19.9 months vs 6.2 months ($p<0.001$), and 35% of the responders who survived ≥ 2 years had an *IDH*

mutation.[23, 32] The phase 3 AGILE clinical trial evaluated ivosidenib in combination with azacitidine in a relatively similar patient cohort of patients with *IDH1*-mutated ND 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 2/1b Beat AML substudy applied a risk-adapted approach to assess the efficacy of enasidenib monotherapy for patients ≥ 60 years with ND 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 efficacy of enasidenib monotherapy in upfront treatment of *IDH2*-mutant 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 rate as compared to conventional care regimens in relapsed/refractory *IDH2*^{mut} AML, but did not improve OS with a median OS of 6.5 vs 6.2 months (p=0.23).[37]

In addition to the observation that *IDH2* was a favorable prognostic indicator in patients treated with HMA-based therapy overall, *IDH2* 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 *TP53*-mutant AML and AML with myelodysplasia-related gene mutations, which are both associated with extremely poor outcomes, *IDH*^{mut} were associated with prolonged OS, particularly in subsets of patients receiving a IDH inhibitor. It is unclear why, in our cohort, *IDH2* mutant 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*-mutated 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 with the combination of HMA-venetoclax combination being particularly effective in *IDH*-mutated AML, and ivosidenib may be preferred over venetoclax in *IDH1*-mutated AML.

The major limitations of our study are the 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 the Beat AML study had separate IDH^{mut} study arms.

In summary, our study demonstrates that *IDH2* mutation has a favorable prognosis in patients with ND 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 LIT regimens therapies for older patients with *IDH* mutated AML.

References

1. Figueroa ME, Lugthart S, Li Y, et al. DNA methylation signatures identify biologically distinct subtypes in acute myeloid leukemia. Cancer Cell. 2010;17(1):13-27.
2. Clark O, Yen K, Mellinghoff IK. Molecular Pathways: Isocitrate Dehydrogenase Mutations in Cancer. Clin Cancer Res. 2016;22(8):1837-1842.
3. Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. Cancer Cell. 2010;18(6):553-567.
4. Gross S, Cairns RA, Minden MD, et al. Cancer-associated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. J Exp Med. 2010;207(2):339-344.
5. Ward PS, Lu C, Cross JR, et al. The potential for isocitrate dehydrogenase mutations to produce 2-hydroxyglutarate depends on allele specificity and subcellular compartmentalization. J Biol Chem. 2013;288(6):3804-3815.
6. Lu C, Ward PS, Kapoor GS, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature. 2012;483(7390):474-478.
7. Wise DR, Ward PS, Shay JE, et al. Hypoxia promotes isocitrate dehydrogenase-dependent carboxylation of alpha-ketoglutarate to citrate to support cell growth and viability. Proc Natl Acad Sci U S A. 2011;108(49):19611-19616.
8. Xu W, Yang H, Liu Y, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer Cell. 2011;19(1):17-30.
9. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. N Engl J Med. 2009;361(11):1058-1066.
10. Im AP, Sehgal AR, Carroll MP, et al. DNMT3A and IDH mutations in acute myeloid leukemia and other myeloid malignancies: associations with prognosis and potential treatment strategies. Leukemia. 2014;28(9):1774-1783.
11. Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J Clin Oncol. 2010;28(22):3636-3643.
12. Thol F, Damm F, Wagner K, et al. Prognostic impact of IDH2 mutations in cytogenetically normal acute myeloid leukemia. Blood. 2010;116(4):614-616.
13. Green CL, Evans CM, Zhao L, et al. The prognostic significance of IDH2 mutations in AML depends on the location of the mutation. Blood. 2011;118(2):409-412.
14. Samra B, Konopleva M, Isidori A, Daver N, DiNardo C. Venetoclax-based combinations in acute myeloid leukemia: current evidence and future directions. Front Oncol. 2020;10:562558.
15. Wang F, Travins J, DeLaBarre B, et al. Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation. Science. 2013;340(6132):622-626.

16. Burd A, Levine RL, Ruppert AS, et al. Precision medicine treatment in acute myeloid leukemia using prospective genomic profiling: feasibility and preliminary efficacy of the Beat AML Master Trial. Nat Med. 2020;26(12):1852-1858.
17. Liehr T. International System for Human Cytogenetic or Cytogenomic Nomenclature (ISCN): some thoughts. Cytogenet Genome Res. 2021;161(5):223-224.
18. Milbury CA, Creeden J, Yip WK, et al. Clinical and analytical validation of FoundationOne(R)CDx, a comprehensive genomic profiling assay for solid tumors. PLoS One. 2022;17(3):e0264138.
19. DiNardo CD, Ravandi F, Agresta S, et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. Am J Hematol. 2015;90(8):732-736.
20. Abbas S, Lugthart S, Kavelaars FG, et al. Acquired mutations in the genes encoding IDH1 and IDH2 both are recurrent aberrations in acute myeloid leukemia: prevalence and prognostic value. Blood. 2010;116(12):2122-2126.
21. Shoukier M, Kadia T, Konopleva M, et al. Clinical characteristics and outcomes in patients with acute myeloid leukemia with concurrent FLT3-ITD and IDH mutations. Cancer. 2021;127(3):381-390.
22. Bataller A, DiNardo CD, Bazinet A, et al. Targetable genetic abnormalities in patients with acute myeloblastic leukemia across age groups. Am J Hematol. 2024;99(4):792-796.
23. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617-629.
24. Itzykson R, Fournier E, Berthon C, et al. Genetic identification of patients with AML older than 60 years achieving long-term survival with intensive chemotherapy. Blood. 2021;138(7):507-519.
25. Metzeler KH, Herold T, Rothenberg-Thurley M, et al. Spectrum and prognostic relevance of driver gene mutations in acute myeloid leukemia. Blood. 2016;128(5):686-698.
26. Chou WC, Lei WC, Ko BS, et al. The prognostic impact and stability of Isocitrate dehydrogenase 2 mutation in adult patients with acute myeloid leukemia. Leukemia. 2011;25(2):246-253.
27. Duchmann M, Micol JB, Duployez N, et al. Prognostic significance of concurrent gene mutations in intensively treated patients with IDH-mutated AML: an ALFA study. Blood. 2021;137(20):2827-2837.
28. Ma QL, Wang JH, Wang YG, et al. High IDH1 expression is associated with a poor prognosis in cytogenetically normal acute myeloid leukemia. Int J Cancer. 2015;137(5):1058-1065.
29. Qin Y, Shen K, Liu T, Ma H. Prognostic value of IDH2R140 and IDH2R172 mutations in patients with acute myeloid leukemia: a systematic review and meta-analysis. BMC Cancer. 2023;23(1):527.
30. Emadi A, Faramand R, Carter-Cooper B, et al. Presence of isocitrate dehydrogenase mutations may predict clinical response to hypomethylating agents in patients with acute myeloid leukemia. Am J Hematol. 2015;90(5):E77-E79.

31. DiNardo CD, Patel KP, Garcia-Manero et al. Lack of association of IDH1, IDH2 and DNMT3A mutations with outcome in older patients with acute myeloid leukemia treated with hypomethylating agents. Leuk Lymphoma. 2014;55(8):1925-1929.
32. Pratz KW, Jonas BA, Pullarkat V, et al. Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. Am J Hematol. 2024;99(4):615-624.
33. Montesinos P, Recher C, Vives S, et al. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. N Engl J Med. 2022;386(16):1519-1531.
34. Cai SF, Huang Y, Lance JR, et al. A study to assess the efficacy of enasidenib and risk-adapted addition of azacitidine in newly diagnosed IDH2-mutant AML. Blood Adv. 2024;8(2):429-440.
35. Cortes JE, Roboz GJ, Baer MR, et al. Olutasidenib in combination with azacitidine induces durable complete remissions in patients with relapsed or refractory mIDH1 acute myeloid leukemia: a multicohort open-label phase 1/2 trial. J Hematol Oncol. 2025;18(1):7.
36. Watts JM, Baer MR, Yang J, et al. Olutasidenib alone or with azacitidine in IDH1-mutated acute myeloid leukaemia and myelodysplastic syndrome: phase 1 results of a phase 1/2 trial. Lancet Haematol. 2023;10(1):e46-e58.
37. De Botton S, Montesinos P, Schuh AC, et al. Enasidenib vs conventional care in older patients with late-stage mutant-IDH2 relapsed/refractory AML: a randomized phase 3 trial. Blood. 2023;141(2):156-167.
38. Pollyea DA, DiNardo CD, Arellano ML, et al. Impact of venetoclax and azacitidine in treatment-naive patients with acute myeloid leukemia and IDH1/2 mutations. Clin Cancer Res. 2022;28(13):2753-2761.

Tables

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

Characteristic	**All (*N*=1,023)**	***IDH1*^{mut} (*n*=99)**	***IDH2*^{mut} (*n*=193)**	***IDH1/2*^{mut} *(n=282)***	***IDH*^{wt} (*n*=741)**	***P* value: *IDH*^{mut} vs *IDH*^{wt}**
Age, median (range), yr.	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	54 (6)	7 (7)	9 (5)	15 (5)	39 (5)	
abnormalities	35 (4)	0 (0)	2 (1)	2 (0.7)	33 (4)	
Core-binding factor	21 (2)	0 (0)	1 (0.1)	1 (0.3)	20 (3)	
KMT2A-rearrangement	203 (20)	20 (20)	48 (25)	64 (23)	139 (19)	
Other	97 (9)	11 (11)	22 (11)	32 (11)	65 (9)	
Unknown						
2022 ELN						<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 where not considered in *P* value calculations and are excluded from the results

[*]Mutations were considered present at any detectable variant allele frequency (VAF)

[‡]*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

Table 2. Univariate analysis for *IDH*-mutated patients treated with hypomethylating agent-based therapy

	n	**HR**	**95% CI**	***p***
Hypomethylating agent-based therapy (n=666) [†]				
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 mutationsw^{t}	116	0.70	0.53-0.91	0.009

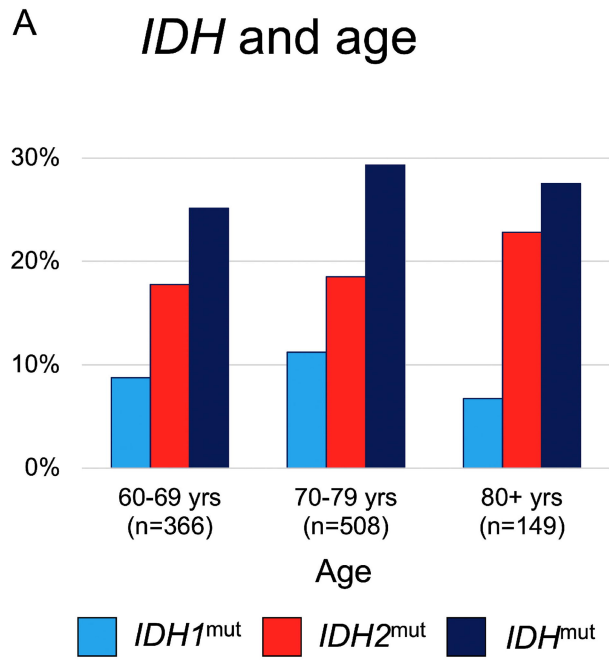
[†]Patients with an *IDH* mutation in the active domain of both *IDH1* and *IDH2* were excluded for *IDH1* and *IDH2* sub-analyses and only considered as having *IDH*^{mut}.

Figure legends

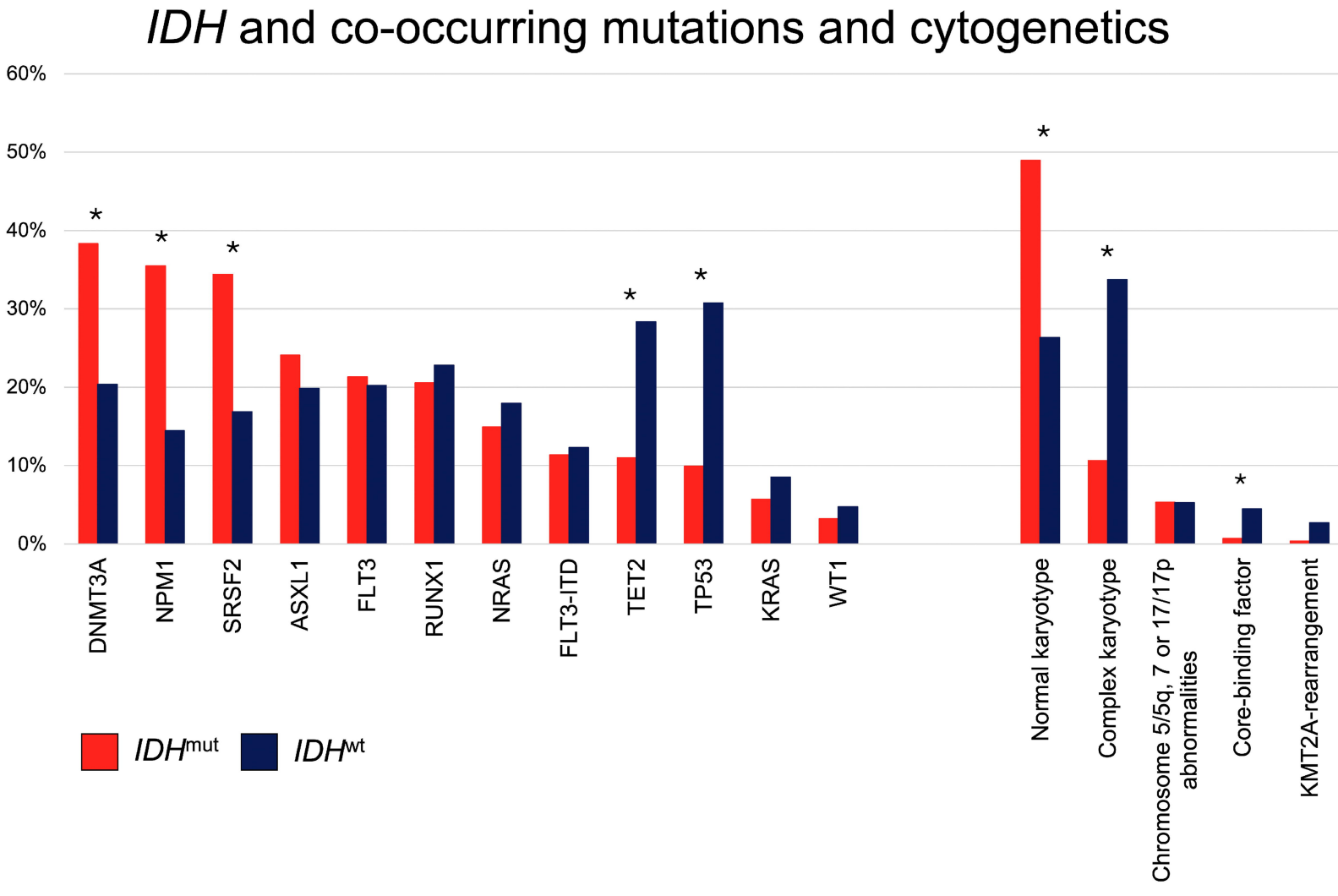
Figure 1. *IDH* mutations in older patients with AML. A. The prevalence of *IDH* mutation in AML according to age. **B**. Co-occurring mutations and karyotypes in IDH^{mut} (red) and IDH^{wt} (blue). Significant associations with a $p<0.05$ are denoted with an asterisk (*).

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

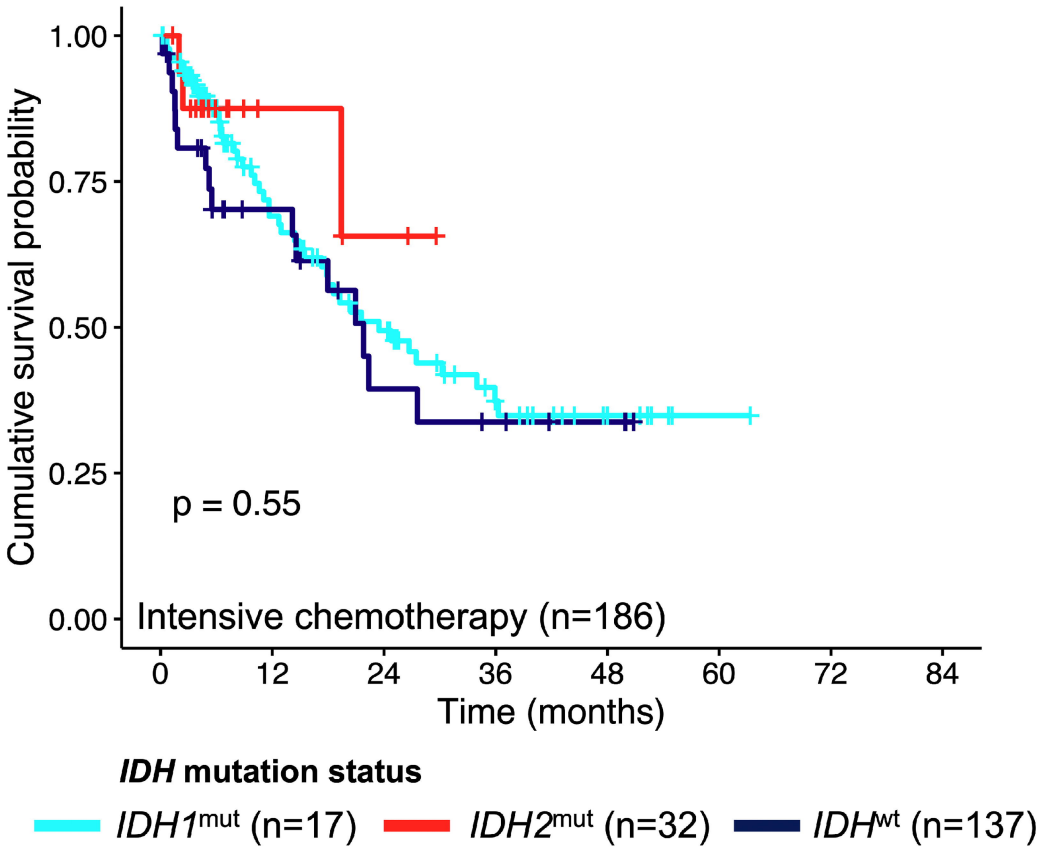
A


IDH and age
30%
20%
10%
0%
60-69 yrs (n=366)
70-79 yrs (n=508)
80+ yrs (n=149)
Age
IDH1mut
IDH2mut
IDHmut

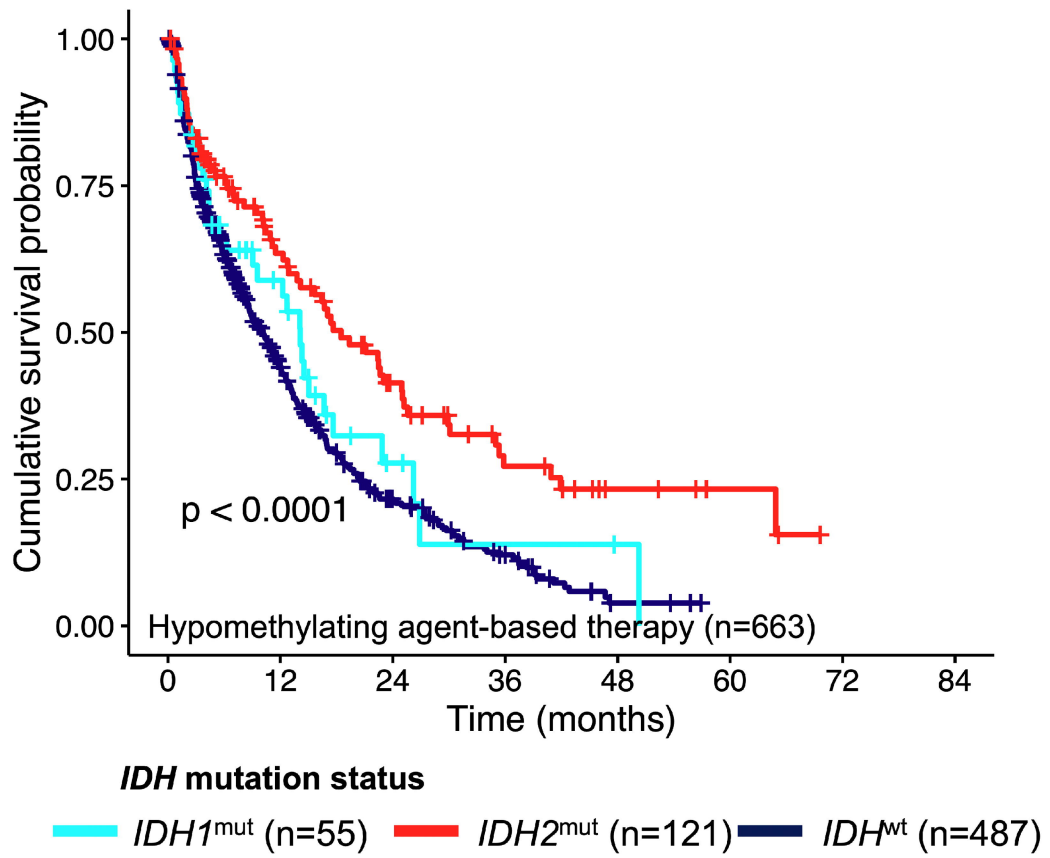
B


IDH and co-occurring mutations and cytogenetics
60%
50%
40%
30%
20%
10%
0%
DNMT3A
NPM1
SRSF2
ASXL1
FLT3
RUNX1
NRAS
FLT3-ITD
TET2
TP53
KRAS
WT1
Normal karyotype
Complex karyotype
Chromosome 5/5q, 7 or 17/17p abnormalities
Core-binding factor
KMT2A-rearrangement
IDHmut
IDHwt

A


1.00
0.75
0.50
0.25
0.00
Cumulative survival probability
p = 0.55
Intensive chemotherapy (n=186)
0
12
24
36
48
60
72
84
Time (months)
IDH mutation status
IDH1mut (n=17)
IDH2mut (n=32)
IDHwt (n=137)

B


1.00
0.75
0.50
0.25
0.00
Cumulative survival probability
p < 0.0001
Hypomethylating agent-based therapy (n=663)
0
12
24
36
48
60
72
84
Time (months)
IDH mutation status
IDH1mut (n=55)
IDH2mut (n=121)
IDHwt (n=487)

Supplemental Tables.

Supplemental Table S1. Beat AML treatment assignment.

Treatment regimen	**N (%)**
Total	1,023 (100)
HMA	59 (6)
HMA plus IDH inhibitor	84 (8)
HMA plus FLT3 inhibitor	23 (2)
HMA plus other	232 (23)
HMA plus venetoclax	244 (24)
HMA plus venetoclax plus IDH inhibitor	1 (0)
HMA plus venetoclax plus FLT3 inhibitor	20 (2)
HMA plus venetoclax plus other	10 (1)
Venetoclax	1 (0)
7+3	72 (7)
7+3 plus other	50 (5)
7+3 plus FLT3 inhibitor	18 (2)
7+3 plus IDH inhibitor	1 (0)
FLT3 inhibitor	3 (0)
IDH inhibitor	10 (1)
Other	15 (1)
Other + FLT3 inhibitor	1 (0)
Other + IDH inhibitor	1 (0)
Vyxeos	23 (2)
Vyxeos + IDH inhibitor	1 (0)
Supportive care	98 (10)
Unknown	55 (5)
Unknown + IDH inhibitor	1 (0)
Intensive	193 (19)
Non-intensive	712 (70)
Supportive care	98 (10)
Unknown	20 (2)

Abbreviations: HMA: hypomethylating agent, 7+3: to the physicians' discretion. Cytarabine x 7 days + anthracycline x 3 days (i.e., daunorubicin, idarubicin)

Supplemental Table S2. Univariate analysis for *IDH* mutated patients treated with intensive chemotherapy

	n	**HR**	**95% CI**	***p***
Intensive chemotherapy (n=187)[†]				
IDH^{wt}	137	1.00	-	-
IDH^{mut}	50	1.09	0.64-1.83	0.758
IDH1^{mut}	17	0.65	0.20-2.08	0.463
IDH2^{mut}	32	1.23	0.70-2.12	0.479

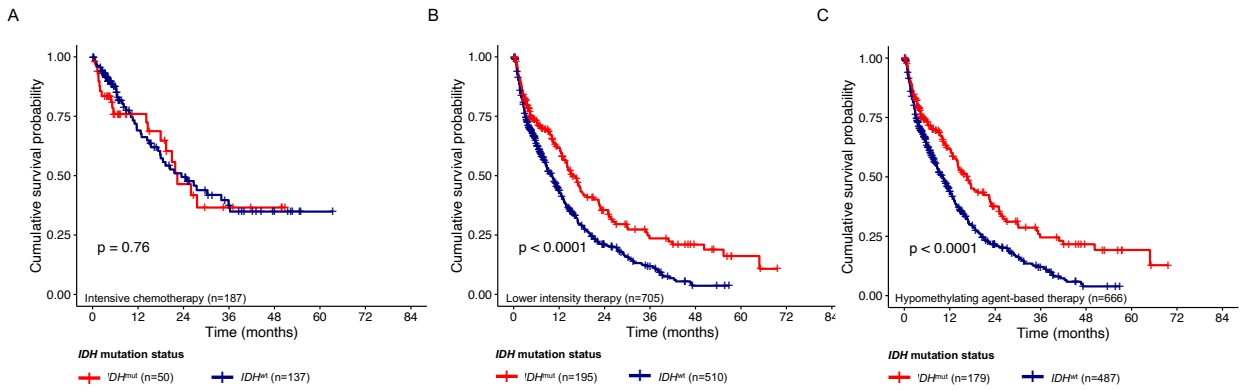
[†]Patients with an *IDH* mutation in the active domain of both *IDH1* and *IDH2* were excluded for *IDH1* and *IDH2* sub-analyses and only considered as having *IDH*^{mut}.

Supplemental Tables S3. Univariate analysis for *IDH* mutated patients treated with lower-intensity therapy.

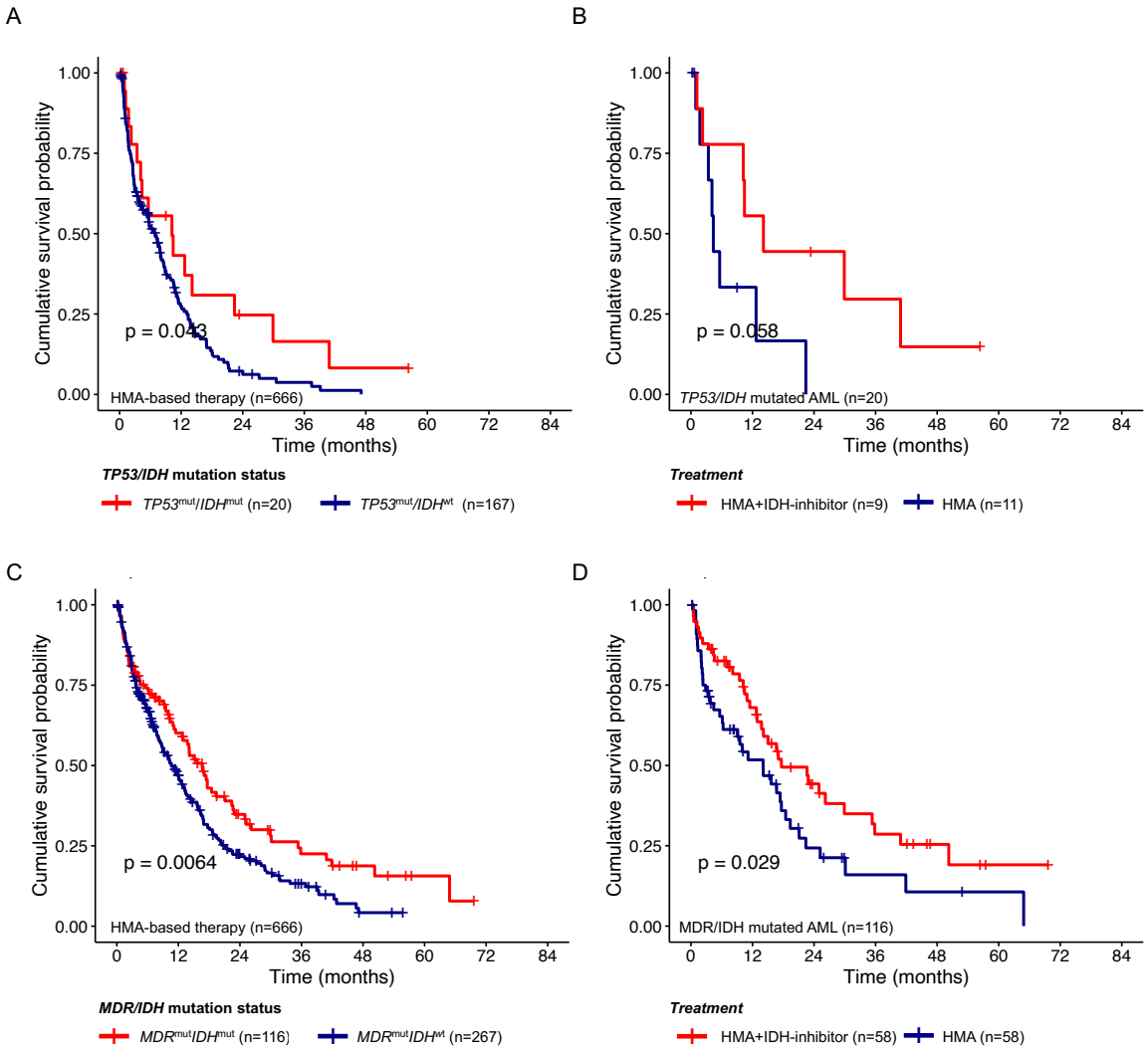
	n	**HR**	**95% CI**	***p***
Lower intensity treatment (n=705)[†]				
IDH^{wt}	510	-		
IDH^{mut}	195	0.63	0.51-0.78	<0.001
IDH1^{mut}	58	0.84	0.60-1.18	0.327
IDH2^{mut}	133	0.56	0.44-0.72	<0.001

[†]Patients with an *IDH* mutation in the active domain of both *IDH1* and *IDH2* were excluded for *IDH1* and *IDH2* sub-analyses and only considered as having *IDH*^{mut}.

Supplemental Figures



Supplemental Figure S1. Kaplan-Meier survival analysis for overall survival in **A**, patients treated with intensive chemotherapy stratified by *IDH1*^{mut} and *IDH*^{wt} and **B**, patients treated with any lower-intensity therapy regimen, and **C**, treated with hypomethylating agent-based therapy.



Supplemental Figure S2. Kaplan-Meier survival analysis for overall survival in **A**, *TP53* mutant patients with and without the *IDH* mutation, **B**, *TP53* mutant IDH mutant patients treated with HMA plus an IDH-inhibitor or without an IDH-inhibitor, **C**, myelodysplasia-related (MDR) gene mutant patients with and without the *IDH* mutation, **D**, MDR mutant patients with IDH co-mutation treated with HMA plus an IDH-inhibitor or without an IDH-inhibitor.