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Research paper

Somatic gene mutation patterns and burden influence outcomes with enasidenib in relapsed/refractory *IDH2*-mutated AML

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ABSTRACT

Limited treatment options are available for patients with relapsed/refractory acute myeloid leukemia (R/R AML). We recently reported results from the phase 3 IDHENTIFY trial (NCT02577406) showing improved response rates and event-free survival with enasidenib monotherapy compared with conventional care regimens (CCR) in heavily pretreated, older patients with late-stage R/R AML bearing *IDH2* mutations. Here we investigated the prognostic impact of mutational burden and different co-mutation patterns at study entry within the predominant *IDH2* variant subclasses, *IDH2*-R140 and *IDH2*-R172. The prognostic relevance of these variants is well documented in newly diagnosed AML, but data are lacking in R/R AML. In this large R/R AML patient cohort, targeted next-generation sequencing at baseline (screening) revealed distinct co-mutation patterns and mutational burden between subgroups bearing different *IDH2* variants: variant *IDH2*-R140 was associated with greater mutational burden and was enriched predominantly with poor-risk mutations, including *FLT3*, *RUNX1*, and *NRAS*, while variant *IDH2*-R172 was associated with lower mutational burden and was preferentially co-mutated with *DNMT3A*. In multivariable analyses, RAS and RTK pathway mutations were significantly associated with decreased overall survival, after adjusting for treatment arm, *IDH2* variant, and mutational burden. Importantly, enasidenib-mediated survival benefit was more pronounced in patients with *IDH2*-R172 variants.

1. Introduction

Acute myeloid leukemia (AML) is a clinically and molecularly heterogeneous, aggressive disease that predominantly affects older people [1,2]. Although intensive chemotherapy induces remission, most patients relapse, and subsequent lines of therapy yield poor results. Median overall survival (OS) for older patients with relapsed/refractory (R/R) AML who are unfit for reinduction is only a few months [3,4]. Mutations in the *IDH2* gene, typically at sites R140 and R172, occur in 8–19% of patients with AML [5,6] with very few specific treatment options for these patients, particularly those with R/R *IDH2*-mutated AML [7]. Mutated IDH2 enzymes acquire neomorphic activity that produces the oncometabolite D-2-hydroxyglutarate (2-HG), which competitively inhibits α-ketoglutarate-dependent enzymes, such as ten-eleven-translocation (TET) family enzymes and histone demethylases. This leads to aberrant hypermethylation of DNA and histones and blocking of hematopoietic cell differentiation [8,9].

Enasidenib is an oral, small-molecule inhibitor of mutant-IDH2 enzymes that suppresses production of 2-HG and has been shown to reverse the leukemogenic blockade of cell differentiation [10,11].

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Enasidenib is approved in the United States and conditionally approved in Canada for the treatment of adults with R/R AML with an *IDH2* mutation [12,13]. In the randomized, phase 3 IDHENTIFY trial, which investigated enasidenib monotherapy versus conventional care regimens (CCR) in older patients with heavily pretreated, *IDH2*-mutated R/R AML, enasidenib treatment meaningfully improved morphologic and hematologic response rates and prolonged event-free survival (EFS) [14]. Additionally, in a phase 1/2 trial, enasidenib treatment led to an overall response rate of 30.8% in a subset of patients with *IDH2*-mutated newly diagnosed AML [15].

In the current post hoc analyses, we investigated the molecular characteristics and prognostic impact of co-occurring gene mutations in patients who participated in the IDHENTIFY trial [14]. We describe novel molecular characteristics associated with clinical response during enasidenib monotherapy. Furthermore, we provide new insights into the prognostic impact of concomitant somatic gene mutations and the opportunity for potential combination therapy in older patients with AML.

2. Methods

The study design, patient characteristics, and CONSORT diagram of the IDHENTIFY trial (AG-221-AML-004, NCT02577406) have been previously reported [14]. Treatment in the experimental arm comprised enasidenib 100 mg daily. Therapies received by patients in the CCR arm included subcutaneous azacitidine, intermediate- or low-dose cytarabine-based regimens, or best supportive care.

DNA extraction from 20 of 269 samples did not meet the DNA concentration requirement, leaving 249 patients profiled for mutational data. Gene mutation analyses and variants reported were based on the sequence coverages of the 37-gene AML panel. Co-occurring gene mutations were identified by targeted next-generation sequencing (NGS) using the 37-gene Archer VariantPlex Core Myeloid panel (ArcherDx; Boulder, CO, USA) at a $\geq$ 1% variant allele frequency (VAF) positivity threshold. The filtering strategy was performed as per ArcherDx recommendations; however, a more stringent approach was used for low allele frequencies at $>$ 0.01 (except for *IDH2*). All samples passed a quality control filter for $>$ 10 average unique start sites per gene-specific primers 2 (GSP2).

IDH2 VAF was quantified in DNA from bone marrow mononuclear cells (BMMC) by digital polymerase chain reaction (dPCR; Sysmex; Baltimore, MD, USA). Total 2-HG concentration in peripheral blood was assessed by liquid chromatography-tandem mass spectrometry (Covance; Princeton, NJ, USA).

Statistical analyses and visualization were performed using Prism Software (v. 8.0.0; GraphPad Software, San Diego, CA, USA) and the R survival (v. 3.2.11), survminer (v. 049), and ggplot2 (v. 3.3.5) packages.

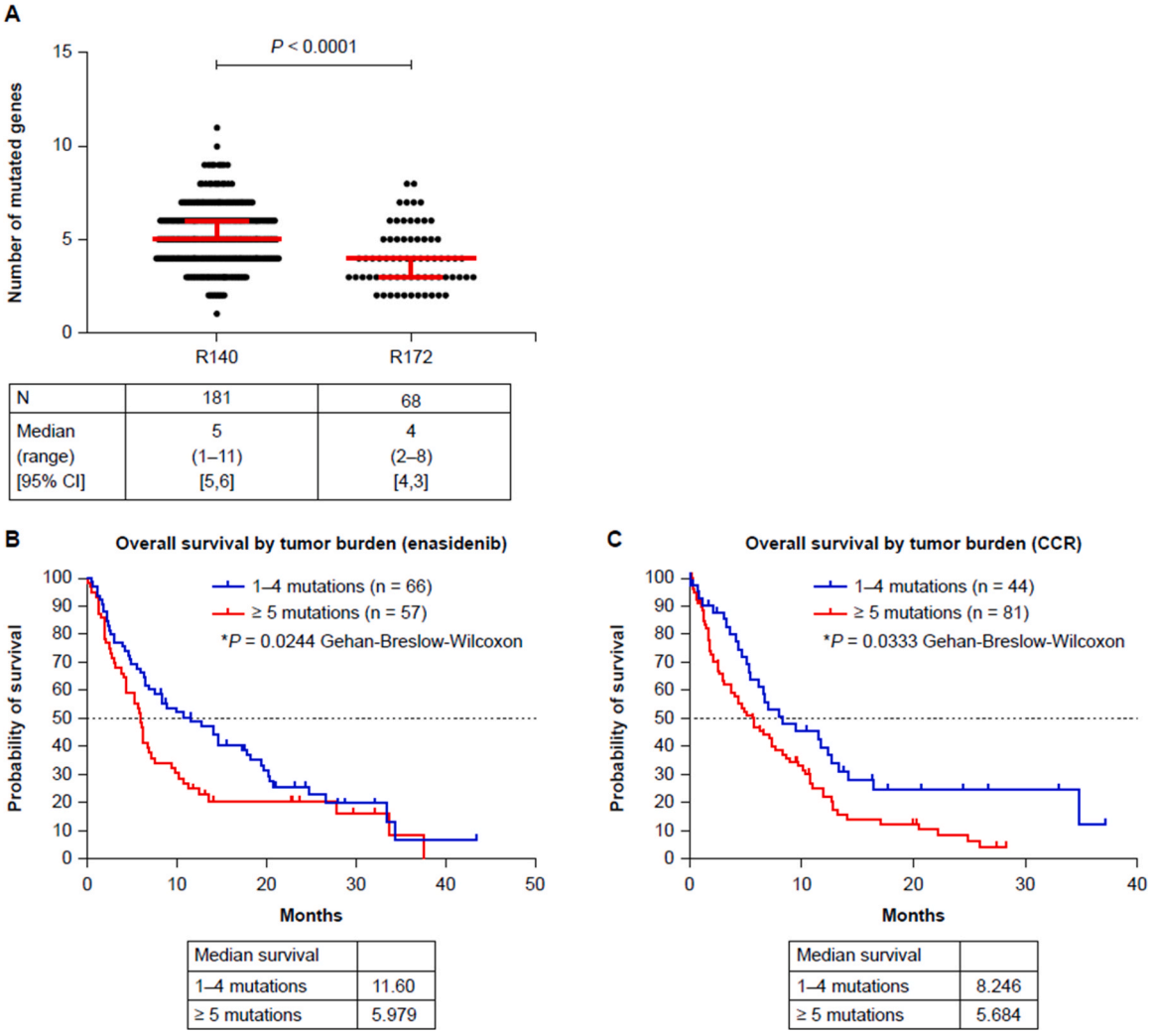

Fig. 1. Baseline mutational burden and prognostic impact. (A) Number of co-occurring gene mutations in patients with *IDH2* variants R140 or R172 (*P* value calculated using Mann-Whitney test). (B) OS in patients treated with enasidenib according to the number of baseline co-mutations (1–4 mutations vs. $\geq$ 5 mutations). (C) OS in patients treated with CCR according to the number of baseline co-mutations (1–4 vs. $\geq$ 5). Dotted lines represent 50% survival, used to calculate median survival times. CCR, conventional care regimens; CI, confidence interval; OS, overall survival; * significant *P* value ($<$ 0.05).

Differences between groups were assessed by Mann-Whitney test for baseline (at screening) mutational burden, 2-HG, and *IDH2* VAF; Fisher's exact test for baseline co-mutation frequency; Gehan-Breslow-Wilcoxon test for OS and EFS; and Cox regression for multivariable analyses of prognostic factors.

CONSORT reporting guidelines were followed when preparing this article [16].

3. Results

Targeted NGS was performed using available samples from 249 patients, including 181 patients with the *IDH2*-R140 variant and 68 patients with the *IDH2*-R172 variant. The subgroup with the *IDH2*-R140 variant had a significantly greater number of mutations at baseline compared with the *IDH2*-R172 variant subgroup (median 5 and 4 mutations, respectively; $P < 0.0001$; Fig. 1**A**). In the overall population, patients with a high mutational burden (≥ 5 mutations) at baseline had shorter median OS within each treatment arm when compared with those with a baseline mutational burden of 4 mutations or fewer (Figs. 1**B** and 1**C**).

IDH2-variant VAF analysis was performed on BMMC samples from 265 patients. There was a high correlation in VAF between NGS and dPCR (r = 0.92), although *IDH2*-R140 variant VAFs appear inflated in NGS (Figure S1). There were no significant differences between *IDH2* variant subgroups in baseline *IDH2* VAF or 2-HG level (Fig. 2).

The most commonly observed co-mutations were in *SRSF2* and *RUNX1* in the *IDH2*-R140 cohort (each in 59% of patients), and in *DNMT3A* in 57% of the *IDH2*-R172 cohort (Table 1). The *IDH2*-R172 variant was preferentially co-mutated with *DNMT3A* (57%), with less frequent co-mutations in *FLT3*-ITD (1.5%), *NPM1* (1.5%), and *NRAS* (7%) (Table 1). Statistically significant differences in co-mutational patterns were found between the *IDH2*-mutated subgroups for *SRSF2, FLT3*-ITD, *NPM1, DNMT3A, FLT3*-TKD, *RUNX1*, and *JAK2* (Table 1). When comparing the genes that are significantly different between *IDH2* variants, there was a trend suggesting that *IDH2*-R140 was predominantly enriched (vs. *IDH2*-R172) with poor-risk co-mutations, including *FLT3*-ITD, *FLT3*-TKD, *RUNX1*, and *NRAS*. *DNMT3A* and *TP53* were preferentially co-mutated with *IDH2*-R172 (vs. *IDH2*-R140) (Table 1).

While *TP53* is poor risk, the number of patients with an *IDH2*+*TP53* double mutation was insufficient to conclude any meaningful association (3 responders: 2 patients with *IDH2*-R140 and 1 patient with *IDH2*-R172; 9 non-responders: 6 patients with *IDH2*-R140 and 3 patients with *IDH2*-R172). Indeed, analysis of EFS focusing on the contribution of individual gene mutations indicated that only the *DNMT3A* mutation was significantly associated with longer EFS ($P = 0.021$) during enasidenib monotherapy (Fig. 3**A**).

Table 1
Proportions of patients with *IDH2* variants R140 or R172 and co-mutations in selected genes.

Gene mutation	R140 n = 181 n (%)	R172 n = 68 n (%)	Preference; unadjusted *P* value
SRSF2	107 (59)	5 (7)	R140; < 0.0001
***FLT3*-ITD**	30 (17)	1 (1)	R140; 0.0005
NPM1	25 (14)	1 (1)	R140; 0.0024
DNMT3A	69 (38)	39 (57)	R172; 0.0095
***FLT3*-TKD**	30 (17)	3 (4)	R140; 0.0111
RUNX1	106 (59)	29 (43)	R140; 0.0320
JAK2	11 (6)	0	R140; 0.0384
TP53	19 (11)	14 (21)	R172; 0.0569
NRAS	30 (17)	5 (7)	R140; 0.0676

Unadjusted *P* values calculated using Fisher's exact test.

Next, a multivariable analysis was performed for each treatment arm to investigate whether gene mutations related to different pathways were associated with distinct clinical outcomes. Patients with mutations in the RAS pathway genes (NRAS, PTPN11, KRAS, CBL, BRAF) and RTK pathway genes (KIT, CSF3R, FLT3 & JAK2) had significantly shorter OS when adjusting for treatment arm (enasidenib vs. CCR), *IDH2* variant (*IDH2*-R140 vs. *IDH2*-R172), and the number of mutated genes (Fig. 3**B**). A multivariable analysis was performed for each treatment arm to explore possible associations with clinical outcome when adjusting for *DNMT3A* mutation status (mutant vs. wild type), *IDH2* variant (*IDH2*-R140 vs. *IDH2*-R172), and the number of mutated genes (continuous variable). The results showed that the *IDH2*-R172 variant was significantly associated with increased OS in patients treated with enasidenib (compared with *IDH2*-R140), while a greater number of mutated genes was significantly associated with decreased OS in patients treated with CCR (Fig. 3**C**).

4. Discussion

In the current analyses, the molecular characteristics and prognostic impact of co-occurring gene mutations in patients who participated in the IDHENTIFY trial [14] were investigated. To our knowledge, the

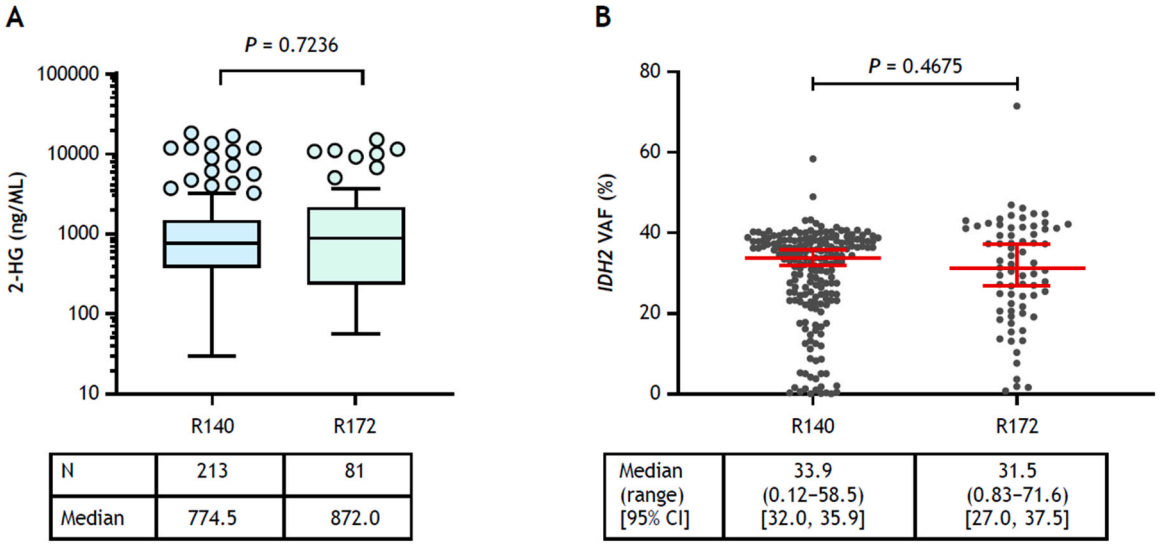

Fig. 2. Baseline 2-HG concentrations (A) and *IDH2* VAF (B) according to *IDH2* variant. *P* values calculated using Mann-Whitney test. 2-HG, D-2-hydroxyglutarate; CI, confidence interval; VAF, variant allele frequency.

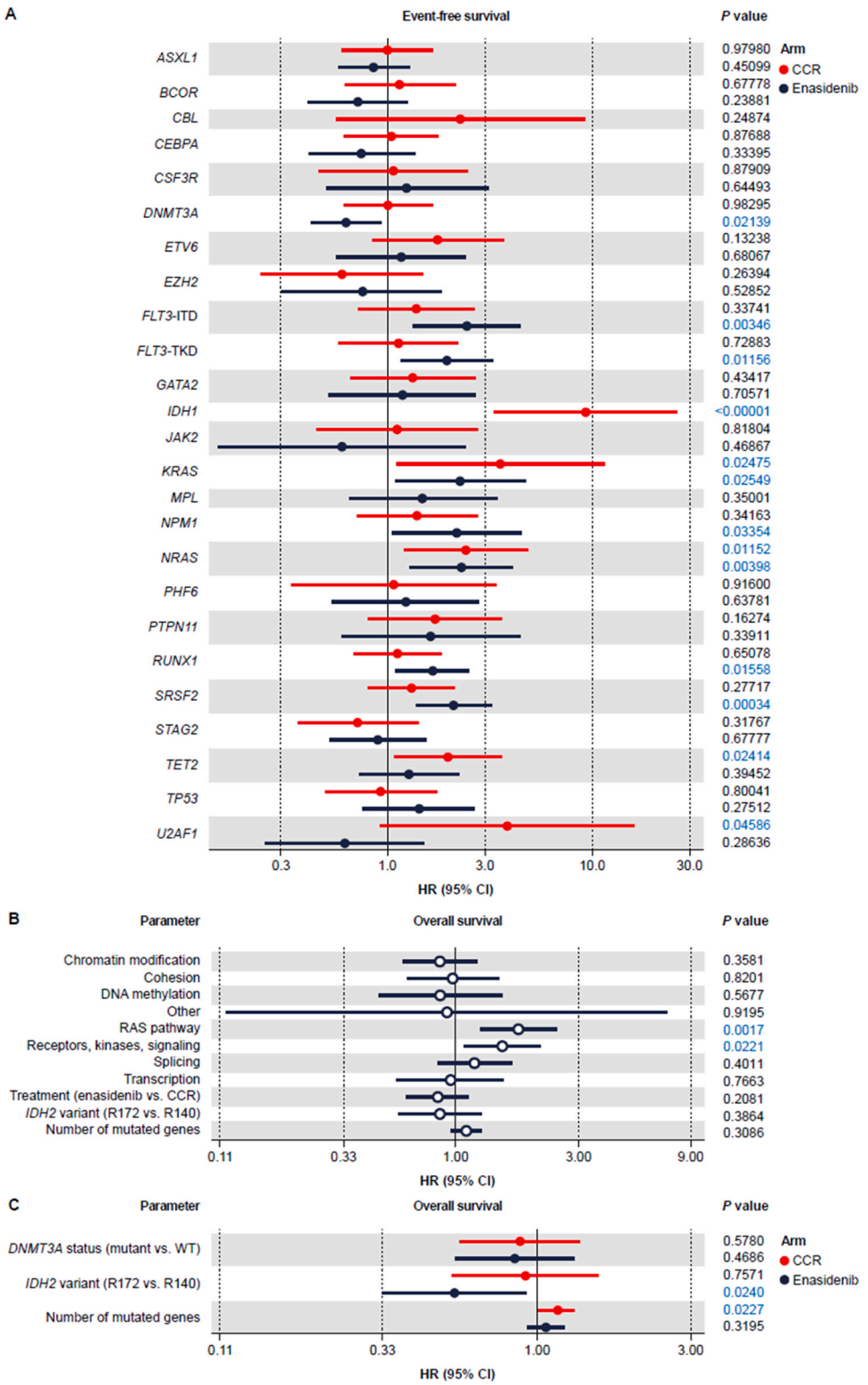

Fig. 3. Survival outcomes according to mutation status. (A) Forest plot of EFS in patients with individual gene mutations. *P* values calculated by log-rank test. (B and C) Multivariable analyses of OS adjusted for gene pathways, *IDH2* variant, treatment group, and mutational burden (B) or *DNMT3A* mutation status, *IDH2* variant, and mutational burden within each treatment group (C). *P* values calculated by Cox regression analysis. *P* values ≤ 0.05 are indicated in blue. CCR, conventional care regimen; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival; RAS, RAS pathway genes (NRAS, PTPN11, KRAS, CBL, BRAF); WT, wild-type.

targeted NGS molecular profiling data presented here represent the largest dataset reported to date for *IDH2* variants in patients with R/R AML.

In the overall population, patients with a high baseline mutational burden within each treatment arm had reduced survival compared with those with lower mutational burden. Interestingly, in patients with AML with *IDH2*-R172 or *IDH2*-R140 mutations receiving chemotherapy treatment, significantly better relapse-free survival, and OS was found in patients with the *IDH2*-R172 mutation compared to wild-type *IDH2*. In contrast, there was no significant difference in patients with the *IDH2*-R140 mutation [17].

There were no significant differences between *IDH2* variant subgroups at baseline *IDH2* VAF, which is in line with previous studies [17]. In the primary analysis of the IDHENTIFY study, *IDH2* VAFs were relatively unchanged from baseline after enasidenib and chemotherapy, though change from baseline in VAFs was correlated with clinical response, and the median maximal VAF reduction from baseline was significantly greater in patients who achieved complete response than those who achieved incomplete response or no response [14]. There were also no significant differences between *IDH2* variant subgroups in baseline 2-HG levels in our analysis, although in previous studies, *IDH2*-R172 was shown to induce higher levels of 2-HG compared with *IDH2*-R140 [17,18].

The co-mutation profiles for IDH2 mutation subtypes are heterogenous and the distinct mutational profiles could contribute to the distinct disease pathophysiology and treatment outcomes between *IDH2* variants in R/R AML. The multivariable analysis revealed that patients with mutations in the RAS and RTK pathways had significantly shorter OS. Earlier studies identified the *IDH2*-R172 variant as a distinct genomic subclass in younger patients (aged < 60 years) with newly diagnosed AML and found that particular co-mutational phenotypes could influence treatment outcome [17,19]. In our cohort, the *IDH2*-R172 variant was preferentially co-mutated with *DNMT3A* (57%), with less frequent co-mutations in *FLT3*-ITD (1.5%), *NPM1* (1.5%), and *NRAS* (7%) (Table 1). In line with our findings, *IDH2*-R172 and *NPM1* mutations have been reported as mutually exclusive by previous studies [19,20].

When adjusting for *DNMT3A* mutation status, *IDH2* variant type, and the number of mutated genes, a greater number of mutated genes were significantly associated with decreased OS in patients treated with CCR compared with enasidenib. Additionally, the *IDH2*-R172 variant was associated with increased OS in patients treated with enasidenib compared with *IDH2*-R140, though this result should be interpreted with caution as 179/239 (74.9%) of patients enrolled in the IDHENTIFY study had the *IDH2*-R140 variant [14]. Furthermore, in line with this result, the *IDH2*-R172 variant has been identified as an independent predictor of improved relapse-free survival and OS compared with *IDH2*-R140 (and other *IDH1/2* mutations) [17].

These data suggest possible novel associations between molecular profile and clinical outcome following enasidenib monotherapy in heavily pretreated patients with late-stage R/R AML bearing *IDH2* mutations. Specifically, the results provide novel insights into how co-mutations and mutational burden may influence treatment outcomes in older patients with *IDH2*-mutated AML, in an *IDH2* variant-specific manner. Additional research is needed to clarify the impact of distinct co-mutational profiles as they relate to disease etiology, patterns of clonal evolution, treatment resistance, and disease progression.

CRediT authorship contribution statement

Paresh Vyas: Data curation, Writing – review & editing. **Pau Montesinos:** Writing – review & editing, Data curation. **Wendy L See:** Writing – review & editing, Formal analysis. **Maroof Hasan:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Alberto Risueño:** Data curation, Formal analysis, Writing – review & editing. **Anita Gandhi:** Writing – review & editing. **Thomas Prebet:** Writing – review & editing. **Amir T Fathi:** Data curation, Writing – review & editing. **Courtney D DiNardo:** Data curation, Writing – review & editing. **Stéphane de Botton:** Data curation, Writing – review & editing. **Iryna Bluemmert:** Writing – review & editing. **Andre C Schuh:** Data curation, Writing – review & editing.

Declaration of Competing Interest

AR reports current employment, equity ownership, and patents with Bristol Myers Squibb.

WLS is a contractor with Bristol Myers Squibb.

IB, **TP**, **AG**, and **MH** report current employment and equity ownership with Bristol Myers Squibb.

SdB reports receiving honoraria from AbbVie, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, Loxo, and Servier; serving in a consultancy position with Bristol Myers Squibb, GlaxoSmithKline, Remix, Servier, and Syndax; speakers' bureau participation for AbbVie, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, and Servier; receiving research funding from Auron and Forma; and having travel expenses paid by AbbVie and Servier.

CDD is a V Foundation Lloyd Family Scholar and Scholar in Clinical Research of The Leukemia & Lymphoma Society receiving research funding from AbbVie, Astex, Bristol Myers Squibb, Cleave, Forma, Foghorn, ImmuneOnc, Loxo, and Servier; receiving honoraria from Astellas, bluebird bio, Bristol Myers Squibb, Foghorn, Gilead, ImmuneOnc, Jazz Pharmaceuticals, Kura, Novartis, Servier, and Takeda; receiving support as a LLS Scholar in Clinical Research; serving in an advisory position for GenMab, GlaxoSmithKline, Kura, and Notable Labs; serving in a consultancy position for AbbVie and Servier; and equity ownership with Notable Labs.

ATF reports receiving clinical trial support from AbbVie, Agios/Servier, and Celgene/Bristol Myers Squibb; advisory board participation with AbbVie, Agios/Servier, Amgen, Astellas, Blueprint, Celgene/Bristol Myers Squibb, Daiichi Sankyo, EnClear, Foghorn, Genentech, Immunogen, Kite, Kura Oncology, Mablytics, Menarini, Morphosys, Novartis, Orum, Pfizer, PureTech, Remix, Rigel, Seattle Genetics, Takeda, and Trillium; and serving in a consultancy position for Daiichi Sankyo, Forma, Ipsen, Menarini, Remix, and Rigel.

ACS reports advisory board membership with AbbVie, Amgen, Astellas, Bristol Myers Squibb, GlycoMimetics, Jazz Pharmaceuticals, Kite/Gilead, Loxo, Novartis, Paladin, Pfizer, Servier, Syndax, and Teva; and serving as Chair of the Canadian Leukemia Study Group (CLSG).

PM reports serving in a consultancy position with Astellas, Agios, Glycomimetics, Celgene/Bristol Myers Squibb, and Daiichi Sankyo; advisory board participation with AbbVie, Astellas, Celgene/Bristol Myers Squibb, Daiichi Sankyo, Incyte, Janssen, Novartis, and Pfizer; and receiving research support from AbbVie, Astellas, Celgene/Bristol Myers Squibb, Daiichi Sankyo, Janssen, Novartis, and Pfizer.

PV reports receiving research funding from Bristol Myers Squibb.

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Authorship contributions

MH designed the study. Data were collected by **AR**, **SdB**, **CDD**, **ATF**, **PM**, **PV**, and **MH**. Data analysis was performed by **AR**, **WLS**, and **MH**. **MH** wrote the first draft of the manuscript. All authors contributed to data interpretation, revised the manuscript, and reviewed and approved the final version.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.leukres.2024.107497.

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