Overall survival by *IDH2* mutant allele (R140 or R172) in patients with late-stage mutant-*IDH2* relapsed or refractory acute myeloid leukemia treated with enasidenib or conventional care regimens in the randomized, open-label, phase 3 IDHENTIFY trial

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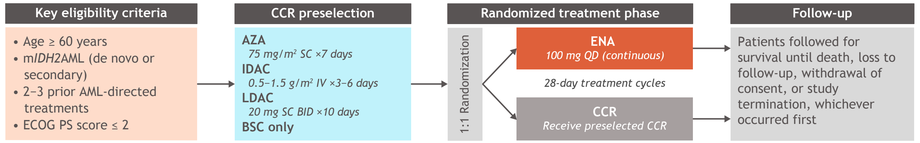
Introduction

- Isocitrate dehydrogenase-2 (*IDH2*) gene mutations occur in ~8%-19% of patients with acute myeloid leukemia (AML)[1]
- The most common *IDH2* variants are R140Q (~75% of patients) and R172K (~25%) point mutations, which have unique functions, co-mutational patterns, and prognostic relevance[1-5]
  - Little is known about prognosis and co-mutational patterns in relapsed/refractory (R/R) AML
- Enasidenib (ENA) is an oral inhibitor of mutant-*IDH2* (m*IDH2*) proteins that promotes myeloid cell differentiation and indirectly reduces DNA methylation by suppressing 2-hydroxyglutarate (2-HG)[6-8]
- The randomized, open-label, phase 3 IDHENTIFY trial (NCT02577406) compared ENA with conventional care regimens (CCR) in an older, heavily pretreated patient population with late-stage m*IDH2* R/R AML[9]
- In the intent-to-treat (ITT) population, ENA did not significantly improve overall survival (OS), the primary endpoint, compared with CCR, but ENA substantially improved morphologic response rate and prolonged time to treatment failure (TTF) and event-free survival (EFS) vs CCR[9]
  - OS was likely confounded by early treatment discontinuation and use of subsequent therapy during OS follow-up, which were more frequent in the CCR arm
- Here, we assess the safety and efficacy of ENA in the IDHENTIFY trial in patient subgroups defined by m*IDH2* variant: R140 or R172

Methods

- IDHENTIFY was an international, randomized, multicenter, open-label trial that enrolled patients aged ≥ 60 years with m*IDH2* R/R AML and 2 or 3 prior AML-directed therapies (**Figure 1**)
- Eligible patients were first preselected to one of four CCR options (azacitidine, intermediate-dose cytarabine, low-dose cytarabine, or best supportive care only), and then randomized 1:1 to ENA 100 mg/day or CCR in repeated 28-day cycles
- Total 2-HG concentration and *IDH2* variant allele frequency (VAF) were assessed at baseline and on-study
  - 2-HG level in peripheral blood was determined by liquid chromatography-tandem mass spectrometry (Covance, Inc; Princeton, NJ)
  - *IDH2* VAF was quantified in DNA from bone marrow mononuclear cells (BMMCs) by digital PCR (Sysmex; Baltimore, MD; lower limit of detection 0.02%–0.04%)
- Co-occurring gene mutations at baseline were identified by targeted next-generation sequencing of BMMC DNA using the 37-gene Archer VariantPlex Core Myeloid Panel (ArcherDx; Boulder, CO)

Figure 1. IDHENTIFY study design



Primary endpoint
- **OS:** Time from randomization until death

Key secondary endpoints
- **EFS:** Time from randomization to disease progression, relapse, or death
- **TTF:** Time from randomization to treatment discontinuation
- **ORR:** CR + CRi/CRp+ PR + MLFS (IWG 2003 criteria[10])
- **HI & TI:** HI in the erythroid, neutrophil, or platelet lineage; RBC or platelet TI (IWG 2006 criteria[11])

AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; BSC, best supportive care; CCR, conventional care regimens; CR, complete remission; CRi/CRp, CR with incomplete blood count or platelet recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; ENA, enasidenib; EFS, event-free survival; HI, hematologic improvement; HR, hazard ratio; IDAC, intermediate-dose cytarabine; *IDH2*, isocitrate dehydrogenase-2; IV, intravenous; IWG, International Working Group; LDAC, low-dose cytarabine; mIDH2, mutant-IDH2; MLFS, morphologic leukemia-free state; ORR, overall response rate; OS, overall survival; PR, partial remission; QD, once daily; RBC, red blood cell; SC, subcutaneous; TI, transfusion independence; TTF, time to treatment failure. Figure adapted from de Botton S, et al. *Blood* 2022;in press.

Results

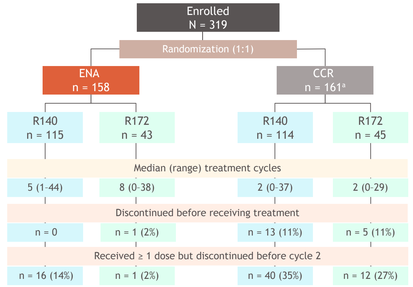
Enrollment and patient characteristics

- Overall, 319 patients were randomized to ENA (n = 158) or CCR (n = 161) (**Figure 2**)
- Most patients (72%) had the R140 variant subtype and 28% had the R172 variant (subtype information was missing for 2 patients)
- Early treatment discontinuation was more common in the CCR arm[9]
  - 20 patients randomized to CCR and 1 patient randomized to ENA discontinued before receiving any allocated treatment
- Baseline demographic and disease characteristics were generally balanced between treatment arms and m*IDH2* variant subgroups (**Table 1**)

Baseline 2-HG, *IDH2* VAF, and co-mutational profiles

- Baseline 2-HG levels were similar between treatment arms and *IDH2* variant subgroups (**Figure 3**)
- Individual *IDH2* VAFs were highly variable, but median *IDH2* VAFs were similar between arms and variant subgroups (**Figure 4A**)

Figure 2. Patient enrollment and disposition[9]



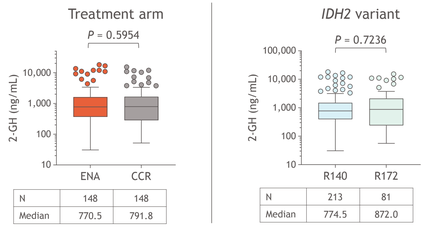
[a]mIDH2 subtype was missing for 2 CCR-randomized patients. CCR, conventional care regimens; ENA, enasidenib.

Table 1. Baseline characteristics by treatment arm and *IDH2* variant subtype

	ENA		CCR	
	R140 n = 115	R172 n = 43	R140 n = 114	R172 n = 45
Age, years, median (range)	72.0 (60-85)	70.0 (60-85)	70.5 (60-86)	71.0 (61-84)
ECOG PS score, n (%)				
0-1	93 (81)	38 (88)	93 (82)	32 (71)
2-3	22 (19)	5 (12)	21 (18)	13 (29)
Prior AML therapies, n (%)				
≤ 2	92 (80)	36 (84)	97 (85)	27 (60)
≥ 3	23 (20)	7 (16)	17 (15)	18 (40)
Prior stem cell transplant, n (%)	9 (8)	5 (12)	14 (12)	5 (11)
Primary refractory AML,[a] n (%)	48 (42)	17 (40)	50 (44)	12 (27)
ELN risk status, n (%)				
Favorable	12 (10)	1 (2)	9 (8)	1 (2)
Intermediate	15 (13)	10 (23)	14 (12)	9 (20)
Adverse	71 (62)	25 (58)	74 (65)	30 (67)
Not evaluable	17 (15)	7 (16)	17 (15)	5 (11)
Transfusion dependence, n (%)				
RBC-TD	76 (66)	28 (65)	69 (61)	28 (62)
Platelet-TD	66 (57)	22 (51)	58 (51)	16 (36)

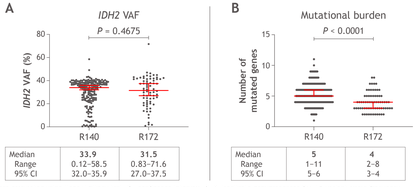
[a]Includes patients who had never attained prior morphologic CR/CRi/CRp before study entry.
AML, acute myeloid leukemia; CCR, conventional care regimens; CR, complete remission; CRi/CRp, CR with incomplete blood count or platelet recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; ENA, enasidenib; RBC, red blood cell; TD, transfusion-dependent.

Figure 3. Baseline 2-HG concentrations by treatment arm and *IDH2* variant



P values were calculated using Mann-Whitney test. 2-HG, 2-hydroxyglutarate; CCR, conventional care regimens; ENA, enasidenib; *IDH2*, isocitrate dehydrogenase-2.

Figure 4. Baseline *IDH2* VAF and mutational burden by *IDH2* variant



P values were calculated using Mann-Whitney test. CI, confidence interval; *IDH2*, isocitrate dehydrogenase-2; VAF, variant allele frequency.

- Baseline mutational burden was significantly greater in the R140 subgroup vs R172 (median 5 vs 4 gene mutations, respectively; P < 0.0001) (**Figure 4B**)
- The genes most commonly co-mutated with R140 were *SRSF2* and *RUNX1* (59% each), whereas *DNMT3A* (57%) and *RUNX1* (43%) were the most common co-mutations in the R172 cohort
- Compared with R172, the R140 cohort was enriched with poor-risk mutations, including *FLT3* (-ITD and -TKD), *NRAS*, and *RUNX1* (**Table 2**)

Clinical responses and survival

- ORR was greater with ENA vs CCR within each m*IDH2* variant subgroup (*P* < 0.0001 in each group), as were rates of CR, HI, RBC TI, and platelet TI (**Table 3**)
- Median OS was 5.7 months in both treatment arms in the R140 subgroup (*P* = 0.612), and was prolonged by 6.8 months with ENA in the R172 subgroup (median 14.6 months, vs 7.8 months with CCR; *P* = 0.039) (**Figure 7**)
- ENA prolonged median EFS and median TTF compared with CCR in both the R140 and R172 subgroups (**Figure 5**)

Table 2. Genes preferentially co-mutated with *IDH2*-R140 or R172 at baseline

	R140 n = 181	R172 n = 68	R140 / R172 preference
Gene mutation	n (%)		*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
TP53	20 (11)	14 (21)	R172; 0.0624
NRAS	30 (17)	5 (7)	R140; 0.0676
STAG2	36 (20)	7 (10)	R140; 0.0905

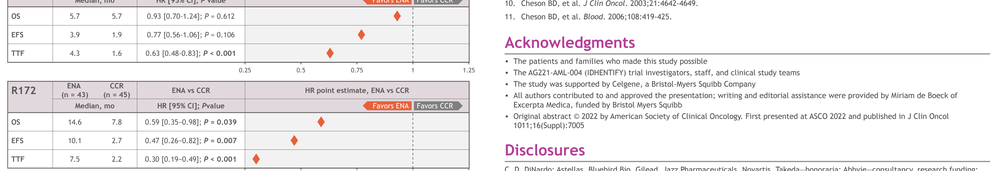
DNMT3A, DNA methyltransferase 3 alpha; FLT3, fms-like tyrosine kinase 3; IDH2, isocitrate dehydrogenase-2; ITD, internal tandem duplication; NPM1, nucleophosmin-1; RUNX1, RUNX family transcription factor 1; SRSF2, serine and arginine rich splicing factor 2; STAG2, stromal antigen 2; TKD, tyrosine kinase domain; TP53, tumor protein p53.

Table 3. Clinical responses in the R140 and R172 subgroups

	R140		R172	
	ENA n = 115	CCR n = 114	ENA n = 43	CCR n = 45
ORR,[a] n (%)	42 (36.5)	13 (11.4)	22 (51.2)	3 (6.7)
OR [95% CI]; *P* value	4.3 [2.2, 8.6]; *P* < 0.0001		15.0 [3.9, 56.9]; *P* < 0.0001	
CR rate,[a] n (%)	21 (18.3)	4 (3.5)	16 (37.2)	2 (4.4)
P value	0.0005		0.0001	
TI,[b,c] n/N (%)				
RBC	15/76 (19.7)	4/69 (5.8)	18/28 (64.3)	5/28 (17.9)
Platelet	14/66 (21.2)	7/58 (12.1)	12/22 (54.5)	1/16 (6.3)
Any HI,[b] n (%)	42 (36.5)	14 (12.3)	25 (58.1)	4 (8.9)

[a]ORR includes CR, CRi/CRp, PR, and MLFS, defined according to the IWG 2003 response criteria for AML[10]. [b]Defined according to the IWG 2006 response criteria for myelodysplastic syndromes[11]. [c]n/N = number of patients who attained TI, divided by the number of patients who were transfusion-dependent at baseline.
CCR, conventional care regimens; CI, confidence interval; CR, complete remission; CRi/CRp, CR with incomplete hematologic or platelet count recovery; ENA, enasidenib; HI, hematologic improvement; IWG, International Working Group; MLFS, morphologic leukemia-free state; OR, odds ratio; ORR, overall response rate; PR, partial remission; RBC, red blood cell; TI, transfusion independence.

Figure 5. OS, EFS, and TTF in the R140 and R172 subgroups



CCR, conventional care regimens; CI, confidence interval; ENA, enasidenib; EFS, event-free survival; HR, hazard ratio; mo, months; OS, overall survival; TTF, time to treatment failure.

Safety

- Median treatment duration was substantially longer with ENA compared with CCR overall (142 vs 36 days, respectively) and within each variant subgroup
- There were no notable differences in rates of common adverse events between the R140 and R172 subgroups in either treatment arm
- Thrombocytopenia was the most common treatment-related grade ≥ 3 adverse event in both arms (**Table 3**)
- ENA-related, all-grade hyperbilirubinemia and IDH differentiation syndrome (IDH-DS) each occurred at similar frequencies between m*IDH2* variant subgroups
  - Increased blood bilirubin: R140 21%, R172 17%
  - IDH-DS: R140 14%, R172 14%

Table 4. Grade ≥ 3 treatment-related AEs in ≥ 10% of patients in the R140 and R172 subgroups[a]

	R140		R172	
	ENA n = 115	CCR n = 101	ENA n = 42	CCR n = 40
Preferred term, n (%)				
Thrombocytopenia	8 (7)	8 (8)	8 (19)	4 (10)
Neutropenia	4 (3)	10 (10)	5 (12)	5 (13)
Febrile neutropenia	2 (2)	12 (12)	2 (5)	5 (13)
Increased blood bilirubin	12 (10)	0	1 (2)	0

[a]AEs were assessed among patients who received 1 or more dose of randomized study drug (Safety population). AE, adverse event; CCR, conventional care regimens; ENA, enasidenib.

Conclusions

- The R140 variant was associated with poor-risk mutations and significantly greater baseline mutational burden compared with the R172 variant
- In these exploratory post hoc analyses, ENA improved morphologic and hematologic response rates vs CCR in both the R140 and R172 subgroups, with similar safety profiles between the variant subgroups
- Survival benefits with ENA vs CCR were more evident in the R172 subgroup
  - Overall, OS was confounded by early dropout and use of subsequent AML-directed treatment (including commercially available ENA), most frequently in the CCR arm[10]
- Additional research is needed to clarify the impact of the distinct co-mutational profiles of *IDH2*-R140 and *IDH2*-R172 on treatment outcomes in R/R AML

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