Real-world effectiveness of enasidenib in older patients with relapsed/refractory isocitrate dehydrogenase-2-mutated acute myeloid leukemia

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Introduction

- For patients with relapsed/refractory (R/R) acute myeloid leukemia (AML), older age (typically defined as ≥ 60 years at first relapse) and Black race have been recognized as prognostic indicators of worse survival[1,2]
- In August 2017, orally administered enasidenib was approved by the US Food and Drug Administration (FDA) for the treatment of patients with R/R AML with an isocitrate dehydrogenase-2 (IDH2) mutation,[3] which occurs in 8%–19% of patients with AML[4]
  - Approval was based on a phase 2 trial in which 23% of patients experienced a complete remission (CR) or a CR with partial hematologic recovery (CRh) lasting a median of 8.2 months[5]
- To date, few published studies have assessed the real-world outcomes of patients with IDH2-mutated R/R AML and studies comparing disease response and survival benefits associated with enasidenib and other R/R AML therapies among older and Black R/R AML patients are completely lacking

Objective

- This study aimed to assess real-world outcomes (ie, response to therapy, survival) in a subgroup of patients with IDH2-mutated R/R AML who were aged ≥ 60 years at the time of R/R disease onset and treated with enasidenib or other therapies in the first-line (1L) setting; assessments included survival outcomes among Black patients within this broader patient subgroup

Methods

- A retrospective, observational cohort study was conducted in patients with R/R AML and IDH2 mutations who were treated 1L with enasidenib between January 2018 and June 2019, or 1L with another approved R/R AML therapy between January 2016 and July 2017
  - Patients were required to have ≥ 6 months of follow-up time post-initiation of 1L R/R therapy at the time of data abstraction/collection (which lasted from February 13, 2020 to April 01, 2020), except in cases of death within 6 months after the initiation of 1L R/R therapy
  - Patients who participated in a clinical trial for 1L therapy in the R/R AML setting were ineligible for study participation
- Data were collected from patient medical records abstracted by physicians in the Cardinal Health Oncology Provider Extended Network (OPEN)
  - OPEN research community is > 800 private-practice and hospital-based oncologists and hematologists across the United States (US)
  - Patient characteristics, treatment patterns, physician-reported response to 1L therapy for R/R AML, date of progression, and date of death were collected
- Bivariate comparisons of demographic, clinical, and treatment characteristics across R/R AML 1L therapy cohorts were conducted using chi-square or Fisher's exact tests and t-tests
- Binomial logistic regression was used to estimate the likelihood of disease response (ie, CR, CRh, CR with incomplete hematologic recovery [CRi], partial remission [PR] or morphological leukemia-free state [MLFS]) adjusted for demographic, clinical, and treatment-related variables
- The Kaplan–Meier method was used to estimate time-to-event outcomes (ie, progression-free survival [PFS] and overall survival [OS])
  - Adjusted risk of disease progression and death (ie, hazard ratio [HR] of progression and death) were estimated using Cox proportional hazard models to control for potential confounders (eg, sex, insurance, Eastern Cooperative Oncology Group performance status [ECOG PS], cytogenetic risk, *TP53* mutation, and comorbidities of interest [eg, chronic kidney disease, liver disease])
- All analyses were conducted in a subgroup of patients aged ≥ 60 years receiving 1L therapy for R/R AML, with $P < 0.05$ as the threshold for statistical significance
  - PFS and OS were also estimated and compared across R/R AML 1L therapy cohorts using the log-rank test among a subgroup of Black patients with AML ≥ 60 years of age

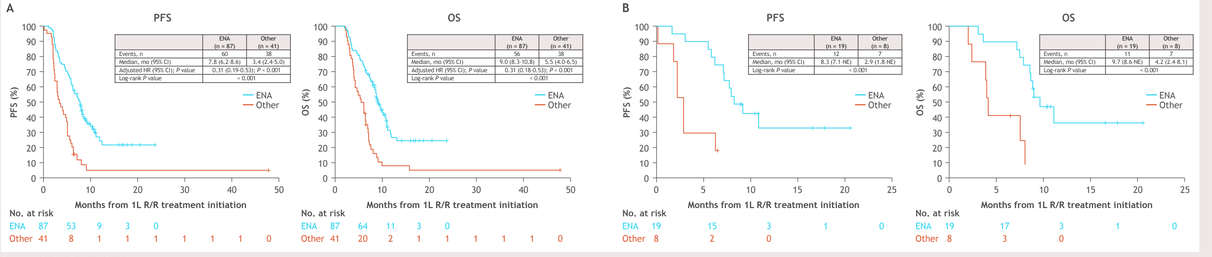
Results

Patient demographic, clinical, and treatment characteristics

- In total, 87 patients treated with 1L enasidenib and 41 patients who received another 1L R/R treatment aged ≥ 60 years were identified by 20 abstracting physicians
  - Participating physicians had a broad geographic distribution across the US, with 30% practicing in the Northeast, 20% in the Midwest, 25% in the South, and 25% in the West
- Patients with R/R AML treated with 1L enasidenib were more likely to have Medicare advantage/supplemental insurance plans (59.8% vs 31.7%, respectively; $P = 0.003$ [chi-square]), an ECOG PS of 0–1 (50.6% vs 31.7%; $P = 0.045$ [chi-square]), mutation of the *TP53* gene (24.1% vs 7.3%; $P = 0.023$ [Fisher's exact]), and moderate to severe chronic kidney disease (29.9% vs 7.3%; $P = 0.004$ [Fisher's exact]) compared with patients treated with other 1L R/R therapy **(Table 1)**

- After a mean follow-up of approximately 9 and 7 months from treatment initiation for patients with R/R AML treated with 1L enasidenib and other 1L therapy, respectively (**Table 1**), median PFS was 7.8 and 3.4 months (adjusted HR = 0.31 [95% CI, 0.19-0.53]; $P < 0.001$), and median OS was 9.0 and 5.5 months (adjusted HR = 0.31 [95% CI, 0.18-0.53]; $P < 0.001$; **Figure 2A**)
- Median PFS was 8.3 and 2.9 months (log rank; $P < 0.001$), and median OS was 9.7 and 4.2 months (log rank; $P < 0.001$) among Black patients aged ≥ 60 years with 1L enasidenib treatment or other 1L therapy for R/R AML, respectively (**Figure 2B**)

Figure 2. PFS and OS in the total population (A) and among Black patients (B) aged ≥ 60 years



ENA, enasidenib; NE, not evaluated.

Table 1. Demographic, clinical, and treatment characteristics

	1L therapy for R/R AML		*P* value
	Enasidenib (n = 87)	Other (n = 41)	
Mean age at initiation of 1L therapy for R/R AML, years (SD)	71.8 (6.7)	69.8 (5.6)	0.086
Male, n (%)	49 (56.3)	25 (61.0)	0.619
Race, n (%)			
White	62 (71.3)	30 (73.2)	0.955
Black/African American	19 (21.8)	8 (19.5)	
Asian	6 (6.9)	3 (7.3)	
Health insurance status at AML diagnosis,[a] n (%)			
Medicare	29 (33.3)	20 (48.8)	0.093
Medicare Advantage/Supplemental	52 (59.8)	13 (31.7)	0.003
Medicaid	2 (2.3)	1 (2.4)	1.000
Commercial	10 (11.5)	7 (17.1)	0.386
Military health insurance (eg, TRICARE/VA)	1 (1.2)	2 (4.9)	0.240
Unknown	1 (1.2)	0 (0.0)	1.000
ECOG PS at diagnosis of R/R disease, n (%)			
0–1	44 (50.6)	13 (31.7)	0.045
≥ 2	43 (49.4)	28 (68.3)	
Cytogenetic risk at diagnosis of R/R disease, n (%)			
Favorable	8 (9.2)	4 (9.8)	0.305
Intermediate	43 (49.4)	20 (48.8)	
Poor	30 (34.5)	10 (24.4)	
Unknown	6 (6.9)	7 (17.1)	
***TP53* mutation, n (%)**	21 (24.1)	3 (7.3)	0.023
Chronic kidney disease (moderate to severe) at diagnosis of R/R disease, n (%)	26 (29.9)	3 (7.3)	0.004
Liver disease at diagnosis of R/R disease, n (%)	14 (16.1)	3 (7.3)	0.172
Mean number of RBC units received ≤ 16 weeks prior to initiation of R/R AML 1L therapy, n (SD)	1.9 (1.4)	2.3 (3.8)	0.329
Induction therapy received, n (%)			
Standard induction	14 (16.1)	18 (43.9)	< 0.001
Venetoclax monotherapy or combination therapy	21 (24.1)	0 (0.0)	
Low-intensity induction, including HMA monotherapy	52 (59.8)	23 (56.1)	
Received R/R 1L therapy for either relapsed or refractory disease, n (%)			
Relapsed	62 (71.3)	24 (58.5)	0.152
Refractory	25 (28.7)	17 (41.5)	
Mean follow-up from initiation of 1L therapy for R/R AML, months (SD)	8.7 (4.3)	6.6 (7.1)	0.086

[a]Not mutually exclusive.
RBC, red blood cell; SD, standard deviation; VA, Veterans Affairs.

- There was a statistically significant difference in the induction regimens received across the R/R AML 1L therapy cohorts ($P < 0.001$ [Fisher's exact]; **Table 1**)
  - Patients who received 1L R/R enasidenib were most commonly prescribed low-intensity induction, including a hypomethylating agent (HMA) monotherapy (59.8%), followed by venetoclax monotherapy or combination therapy (24.1%), and standard induction (16.1%)
  - Patients who received other R/R 1L therapy were most commonly prescribed low-intensity induction, including HMA monotherapy (56.1%), followed by standard induction (43.9%); no patient received venetoclax monotherapy or combination therapy

Physician-reported disease response to 1L therapy for R/R AML

- CR, CRh, CRi, PR, and MLFS rates were higher among patients treated with enasidenib vs other 1L therapies for R/R AML **(Figure 1)**
- After adjusting for other patient characteristics **(Table 2)**, the odds of achieving physician-reported response (CR, CRh, CRi, PR, or MLFS) were almost 12 times greater among patients treated with enasidenib as 1L therapy than among those who received other 1L therapy

Figure 1. Physician-reported disease response to 1L therapy for R/R AML

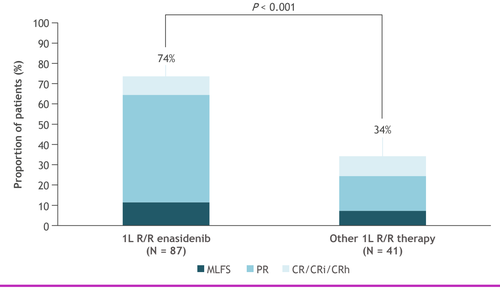


Table 2. Adjusted logistic regression for achievement of physician-reported response[a] during 1L therapy for R/R AML

Effect	Adjusted odds ratio	95% CI	*P* value
Enasidenib vs other R/R AML 1L therapy	11.72	2.80-49.08	0.001
Female vs male	0.49	0.17-1.38	0.175
Insurance (Medicaid vs commercial)	1.73	0.01-572.84	0.853
Insurance (other[b] vs commercial)	1.05	0.25-4.37	0.948
ECOG PS 0-1 vs ≥ 2 at diagnosis of R/R disease	8.56	2.72-26.88	< 0.001
Cytogenetic risk at diagnosis of R/R disease (poor/intermediate/unknown vs favorable)	0.41	0.05-3.55	0.415
TP53 mutation (no vs yes)	0.87	0.25-3.07	0.831
Chronic kidney disease (no vs yes)	0.50	0.14-1.86	0.301
Liver disease (no vs yes)	0.03	0.00-0.32	0.003
Number of RBC units in 16-week pre-index period	0.73	0.56-0.95	0.021
Induction therapy (venetoclax monotherapy or combination therapy vs standard induction)	0.11	0.01-0.86	0.036
Induction therapy (low-intensity induction/HMA monotherapy vs standard induction)	0.12	0.02-0.59	0.009
R/R disease type (refractory vs relapsed)	0.66	0.21-2.04	0.466

[a]Response = CR/CRh/CRi/PR/MLFS. [b]Patients with commercial insurance and any other type of insurance were allocated as commercial insurance patients for regression analysis.

Conclusions

- Results from this real-world cohort study suggest that the disease response and survival benefits of 1L enasidenib among patients with IDH2-mutated R/R AML demonstrated in the trial setting are conferred to patients in routine clinical practice with poor prognostic indicators, such as older age at R/R disease onset and Black race
- Superior disease response rates, significantly longer PFS and OS, and significantly reduced risk of disease progression and death, after adjusting for patient characteristics, were observed among patients aged ≥ 60 years with R/R AML who received 1L enasidenib compared with those who received other 1L therapy
- Among Black patients aged ≥ 60 years with R/R AML, median PFS and OS were significantly longer in those who received 1L enasidenib compared with those who received other 1L therapy
- Unmeasured confounding (eg, differences in patient-level factors not collected) may have occurred, resulting in biased estimates of treatment effects; however, given the magnitude of the treatment effect, unmeasured confounding likely would not change these findings
- Further research with a larger sample size and a longer follow-up time is needed to confirm response and survival outcome findings among older adult and Black patients with IDH2-mutated R/R AML

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