Molecular predictors of response and survival following IDH1/2 inhibitor monotherapy in acute myeloid leukemia

Mutations in the isocitrate dehydrogenase gene (*IDH1*/2) are present in approximately 20% of patients with acute myeloid leukemia (AML), with a higher incidence in older patients.[1] The prognostic impact of *IDH1*/2 mutations is context-dependent, given their frequent association with diploid or other intermediate-risk karyotype, *FLT3*-internal tandem duplications (ITD) and *NPM1* mutations.[2] Three IDH inhibitors are currently Food and Drug Administration-approved for *IDH*-mutated AML; ivosidenib and olutasidenib (IDH1 inhibitors) and enasidenib (IDH2 inhibitor). Ivosidenib ± azacitidine is approved for frontline therapy and all three IDH inhibitors for relapsed/refractory disease. Complete remission with (CR) or without (CRi) blood count recovery rates in newly diagnosed *IDH*-mutated AML patients treated with ivosidenib or enasidenib were reported at 42.4%,[3] and 21%,[4] respectively; the corresponding CR/CRi rate in the relapsed/refractory setting were 30.4% and 26.6%.[5,6] Hypomethylating agent and venetoclax combination therapy (HMA-Ven) is also a therapeutic consideration for elderly/unfit *IDH*-mutated AML.[7] There is limited comparative data on the outcomes of patients treated with IDH inhibitors *versus* HMA-Ven. We have previously described our experience with HMA-Ven in treatment-naïve and relapsed/refractory AML and identified molecular predictors of response and survival.[8,9] In the current study, our primary objective was to determine the impact of mutations and karyotype on response and survival in *IDH*-mutated AML patients receiving IDH1/2 inhibitor monotherapy in routine clinical practice and retrospectively compare the findings with those of *IDH*-mutated patients treated with HMA-Ven.

The current study includes a total of 59 consecutive patients with *IDH*-mutated AML treated with single-agent IDH1/2 inhibitor (ivosidenib or enasidenib), outside of clinical trials, at the Mayo Clinic (Rochester MN, Jacksonville FL, Scottsdale, AZ), between 2017 and 2023. Study patients were retrospectively recruited after Institutional Review Board approval. Cytogenetic and molecular studies were performed at the time of diagnosis by conventional karyotype and next-generation sequencing (NGS) of a 42-gene panel, respectively. Four-gene panel NGS (*FLT3*, *IDH1*/2 and *TP53*) was obtained at relapse. Disease risk and response were assessed according to the 2022 European LeukemiaNet (ELN) criteria.[10] Timing of response assessment was based on treating physician discretion. Determinants of treatment response were assessed by X^2 or Fisher's exact test for nominal data and Wilcoxon rank sum test for continuous variables. Overall survival was calculated from the time of initiation of IDH1/2 inhibitor to last follow-up or death without censoring for transplant and evaluated by the Kaplan–Meier method. Analyses were performed using JMP Pro 16.0.0 software package, SAS Institute, Cary, NC.

A total of 59 patients with *IDH*-mutated AML (median age 74 years, range 54-91; 59% males; 54% secondary or therapy-related) received ivosidenib (n=16) or enasidenib (n=43), of which 11 (19%) and 48 (81%) patients were treated in the frontline and relapsed/refractory setting, respectively. Patients with relapsed/refractory disease had received either one (n=24), two (n=15), three (n=6), or four (n=3) prior therapies which included cytarabine + idarubicin (7+3) (n=24), HMA-Ven (n=11), mitoxantrone, etoposide, cytarabine (MEC) (n=5), liposomal daunorubicin/cytarabine (n=4), cladribine, cytarabine, granulocyte colony-stimulating factor (G-CSF), mitoxantrone (CLAG-M)/fludarabine, cytarabine, G-CSF, idarubicin (FLAG-IDA) (n=4), and 7+3+ midostaurin (n=3). Seven patients had relapsed following allogeneic hematopoietic stem cell transplant (alloHSCT). ELN cytogenetic risk was evaluable in 57 patients and included intermediate (75%, n=43) or adverse (25%, n=14) risk. Mutations detected included *DNMT3A* in 22 patients (37%), *SRSF2* in 21 (36%), *RUNX1* in 15 (25%), *ASXL1* in 12 (20%), *BCOR* in seven (12%), *NPM1* in seven (12%), *K/NRAS* in six (10%), *FLT3*-ITD in six (10%), and *TP53* in four (7%). A comparison of *IDH1- versus IDH2*-mutated patients revealed a higher incidence of *RUNX1* mutations (44% *vs*. 19%; *P*=0.05) and adverse karyotype (50% *vs*. 14%; *P*=0.01) in *IDH1*-mutated patients. Treatment-emergent toxicities included differentiation syndrome (n=17), hyperbilirubinemia (n=11), and Qtc prolongation (n=6); treatment was discontinued due to toxicity in six patients. Table 1 provides information regarding patient characteristics at the time of initiation of IDH inhibitor, response rates, and overall outcome.

Fifteen (25%) patients achieved CR (n=10; 17%) or CRi (n=5; 8%); median time to response was 2.2 months (range, 1.0-7.1) and median response duration 3.6 months (range, 1.0-33). In addition, two (3%) patients experienced partial remission and eight (14%) hematological improvement. Measurable residual disease (MRD) assessement was performed in a subset of patients; MRD negativity was confirmed in three (75%) of four patients, evaluable by multiparametric flow cytometry, and in one (17%) of six patients, evaluable by *IDH* mutation analysis. Among the 15 patients with CR/CRi, relapse was documented in four (27%), and six (40%) patients were bridged to alloHSCT.

Table 1. Clinical characteristics at time of treatment initiation with single agent IDH1/2 inhibitor for 59 patients with acute myeloid leukemia stratified by achievement of complete response or complete response with incomplete count recovery.

Variables	All patients N=59	Patients in CR/CRi N=15 (25%)	Patients not in CR/CRi N=4 (75%)	*P*/Multivariate *P*
Age in years, median (range)	74 (54-91)	71 (54-84)	74 (55-91)	0.37
>60 years, N (%)	53 (90)	12 (80)	41 (93)	0.17
Male, N (%)	35 (59)	9 (60)	26 (59)	0.95
AML type, N (%)				
De novo	27 (46)	6 (40)	21 (48)	0.60
Secondary or therapy-related	32 (54)	9 (60)	23 (52)	
Treatment setting, N (%)				
Upfront	11 (19)	3 (20)	8 (18)	0.88
Relapsed/refractory	48 (81)	12 (80)	36 (82)	
Number of prior treatments, median (range)	1 (1-4)	1.5 (1-4)	1 (1-4)	0.86
IDH mutation, N (%)				
IDH-1	16 (27)	1 (7)	15 (34)	0.02
IDH-2	43 (73)	14 (93)	29 (66)	
	N=52	N=14	N=38	0.38
IDH (VAF), median (range)	38 (5-50)	38 (10-50)	36 (5-49)	
Hemoglobin, g/dL, median (range)	8.8 (6-14.7)	8.6 (7.5-14.7)	8.8 (6-12.8)	0.88
Leukocyte count, x10^9/L, median (range)	1.92 (0.3-71.9)	1.05 (0.3-6.5)	2.35 (0.3-71.9)	0.01/0.06
Leukocyte count >2x10^9/L*, N (%)	27 (46)	3 (20)	24 (55)	0.02/0.12
Platelet count, x10^9/L, median (range)	53 (5-510)	74 (12-360)	46 (5-510)	0.79
Circulating blasts %, median (range)	10 (0-83)	2 (0-30)	16 (0-83)	0.01/0.09
Circulating blasts >5%,* N (%)	32 (54)	4 (27)	28 (64)	0.01/0.07
2022 ELN cytogenetic risk stratification, N (%)	N=57	N=15	N=42	
Intermediate	43 (75)	14 (93)	29 (69)	0.04/0.01
Adverse	14 (25)	1 (7)	13 (31)	
Mutations on NGS, N (%)				
DNMT3A	22 (37)	8 (53)	14 (32)	0.14
SRSF2	21 (36)	5(33)	16 (36)	0.83
RUNX1	15 (25)	7 (47)	8 (18)	0.03/0.04
ASXL1	12 (20)	1 (7)	11 (25)	0.09
BCOR	7 (12)	5 (33)	2 (5)	0.01/0.01
NPM1	7 (12)	3 (20)	4 (9)	0.28
K/NRAS	6 (10)	2 (13)	4 (9)	0.65
FLT3-ITD	6 (10)	2 (13)	4 (9)	0.65
TP53	4 (7)	0(0)	4 (9)	0.12
TET2	4 (7)	1 (7)	3 (7)	1.0

*Cut-off was determined by receiving operating characteristic (ROC) analysis. CR: complete response; Cri: CR with incomplete count recovery; AML: acute myeloid leukemia; HMA: hypomethylating agent; Ven: venetoclax; VAF: variant allele frequency; ELN: European LeukemiaNet; NGS: next-generation sequencing; ITD: internal tandem dublication.

Four of the five remainder patients are alive and in continuing response for a median duration of 22.2 months (range, 2.1-44.4), while one patient in ongoing response for 6.9 months, has died from sepsis. An additional two patients, one with hematological response and one non-responder, proceeded to alloHSCT following HMA-Ven and cladribine-cytarabine-Ven, respectively. CR/CRi rates were higher with *IDH2 versus IDH1* mutation (33% *vs*. 6%; *P*=0.02). Among *IDH2*-mutated patients, CR/CRi was more likely with R140 *versus* R170 mutation (14/34, 41% *vs*. 0/6, 0%; *P*=0.02). In addition, CR/CRi rates were higher with *BCOR* mutation (CR/CRi 71% *vs*. 19%; *P*=0.01), and *RUNX1* mutation (47% *vs*. 18%; *P*=0.03); CR/CRi rates were lower in the presence of ELN adverse karyotype (7% *vs*. 33%; *P*=0.04), *ASXL1* (8% *vs*. 30%; *P*=0.09) or *TP53* mutations (0% *vs*. 27%; *P*=0.12). Multivariable analysis confirmed superior response in the presence of *BCOR* (*P*=0.01; overall response to odds ratio [OR]=19.5) or *RUNX1* mutations (*P*=0.04; OR 5) and inferior response in the presence of ELN adverse karyotype (*P*=0.01; OR=13.5). CR/CRi rates were not significantly different in the frontline *versus* relapsed/refractory setting (27% *vs*. 25%; *P*=0.88), *de novo versus* secondary AML (22% *vs*. 29%; *P*=0.55), presence or absence of *NPM1* (43% *vs*. 23%; *P*=0.28), *FLT3*-ITD (33% *vs*.

Table 2. Predictors of complete response or complete response with incomplete count recovery and post-treatment survival in 59 patients with acute myeloid leukemia treated with IDH1/2 inhibitor monotherapy.

Variables	CR/CRi Univariate *P* CR/CRi rates	CR/CRi Multivariate *P*/OR	Overall survival Univariate *P* Median survival	Overall survival Multivariate *P* HR (95% CI)
Age	0.37		0.27	
ELN adverse karyotype	0.04 7% *vs*. 33% Presence *vs*. absence	0.01/13.5	0.04 9 *vs*. 11 months Presence *vs*. absence	<0.01 3.2 (1.5-6.7)
BCOR mutation	0.01 71% *vs* 19% Presence *vs*. absence	0.01/19.5	0.01 9.5 *vs*. NR Absence *vs*. presence	<0.01 4.8 (1.4-16.5)
RUNX1 mutation	0.03 47% *vs*. 18% Presence *vs*. absence	0.04/5.0	0.05 9.5 *vs*. 14.6 months Absence *vs*. presence	0.04 2.4 (1.1-5.4)
ASXL1 mutation	0.09 8% *vs*. 30% Presence *vs*. absence	-	0.09	-
NPM1 mutation	0.28	-	0.07	-
FLT3-ITD mutation	0.65	-	0.42	-
TP53 mutation	0.12 0% *vs*. 27% Presence *vs*. absence	-	0.15	-
K/NRAS mutation	0.65	-	0.87	-
Presence of CR/CRi	NA	NA	<0.01 NR *vs*. 9.3 months	-
AlloHSCT after IDH inhibitor	NA	NA	<0.01 NR *vs*. 9.5 months	-

NR: not reached; NA: not applicable; CR: complete response; Cri: CR with incomplete count recovery; OR: odds ratio; HR: hazard ratio; CI: confidence interval; ELN: European LeukemiaNet; ITD: internal tandem duplication; alloHSCT: allogeneic stem cell transplant.

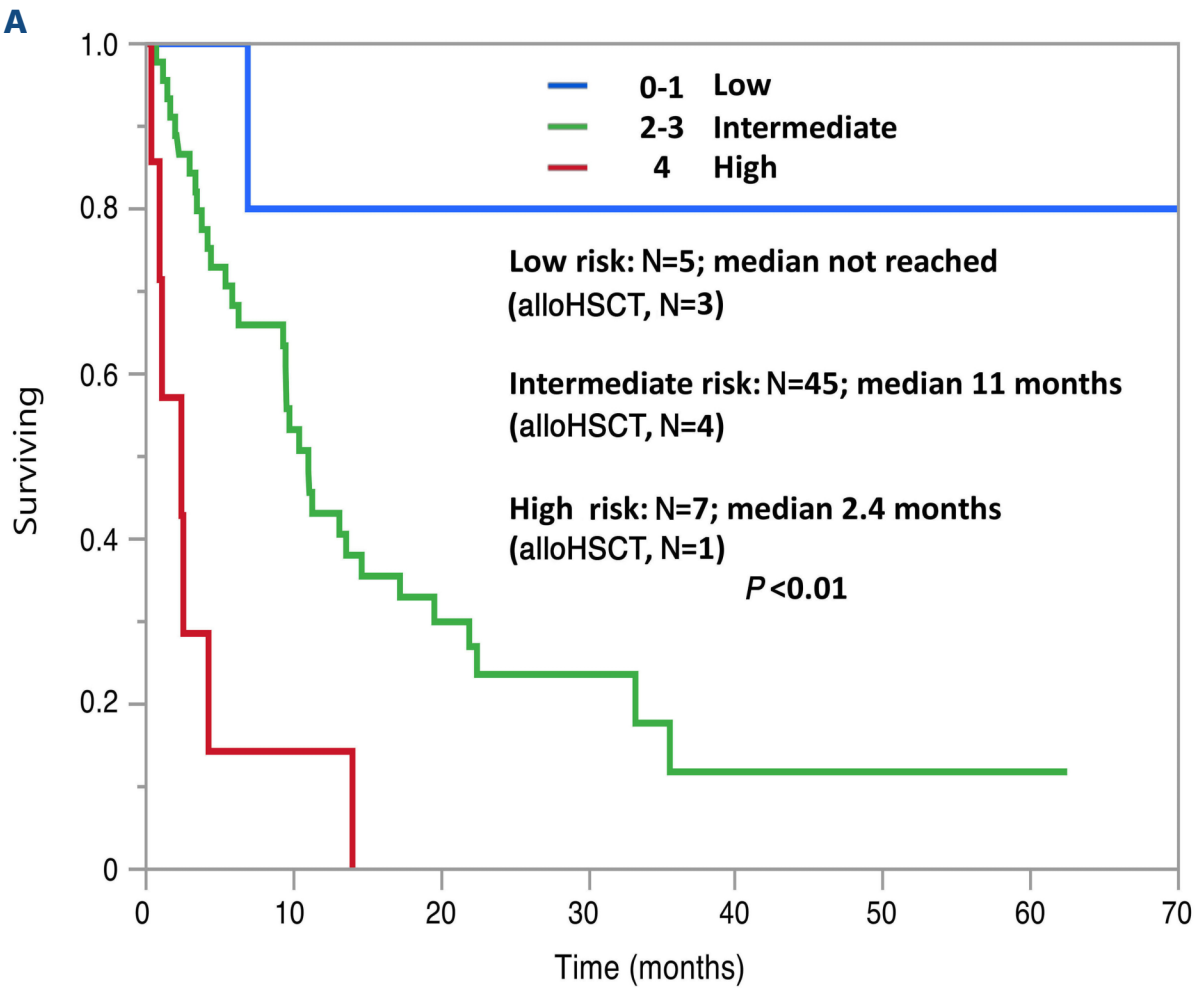
25%; *P*=0.65), *DNMT3A* (36% *vs*. 19%; P=0.14), *TET2* (25% *vs*. 25%; *P*=1.0), *SRSF2* (24% *vs*. 26%; *P*=0.83), or *K/NRAS* (33% *vs*. 25%; *P*=0.65) mutations (Table 2). Response was also not influenced by *IDH* mutation variant allele frequency (median-38%; range, 5-50; *P*=0.38) and number of prior therapies (*P*=0.86). Only one (9%) of 11 patients previously treated with HMA-Ven (n=8, frontline HMA-Ven) responded to IDH inhibitor therapy compared to 14 of 48 (29%) patients without prior HMA-Ven exposure (*P*=0.13).

At a median follow-up of 9.5 months (range, 0.4-70), from initiation of IDH inhibitor, 43 (73%) patients have died and eight (14%) underwent alloHSCT. Median survival following IDH inhibitor therapy was 10.4 months (range, 3.4-33.1) and superior in *IDH2- versus IDH1*-mutated patients (13.1 *vs*. 5.1 months; *P*<0.01), in the presence *versus* absence of CR/CRi (not reached [NR] *vs*. 9.3 months; *P*<0.01) and in patients receiving alloHSCT (NR *vs*. 9.5 months; *P*<0.01). The survival differences in *IDH1- versus IDH2*-mutated patients remained significant after accounting for karyotype, mutations, response and alloHSCT. Univariate survival analysis identified adverse karyotype (*P*=0.04), absence of *BCOR* (*P*=0.01) and absence of *RUNX1* mutations (*P*=0.05) as predictors of inferior survival. Multivariable analysis, adjusted for alloHSCT, confirmed the survival impact of *BCOR* and *RUNX1* mutations and adverse karyotype; corresponding hazard ratio (HR) and 95% confidence interval (CI) were HR=4.8, 95% CI: 1.4-16.5; HR=2.4, 95% CI: 1.1-5.4; HR=3.2, 95% CI: 1.5-6.7 (Table 2). A three-tiered survival model was subsequently generated by using HR-weighted risk point assignment; two points for absence of *BCOR* mutation and one point each for absence of *RUNX1* mutation and presence of adverse karyotype, resulting in high (4 points, n=7; median survival 2.4 months), intermediate (2-3 points, n=45, median 11 months) and low (0–1 point, n=5; median NR) risk categories (*P*<0.01; Figure 1A). The aforementioned observations were confirmed when survival analysis was restricted to *IDH2*-mutated patients; the small number of *IDH1*-mutated patients precluded similar analysis.

Response rates and survival in the 59 *IDH*-mutated patients treated with IDH inhibitors were retrospectively compared to *IDH*-mutated Mayo Clinic patients treated with HMA-Ven (n=32; median age 69 years; treatment-naïve n=20 and relapsed/refractory n=12); CR/CRi rates were not different in HMA-Ven treated frontline *versus* relapsed/refractory patients (70% *vs*. 75%; *P*=0.76). Similarly,

CR/CRi rates were comparable in IDH inhibitor-treated frontline *versus* relapsed/refractory patients (27% *vs*. 25%; *P*=0.87). CR/CRi rates were superior with HMA-Ven compared to IDH inhibitor (72% vs. 25%; *P*<0.01) while survival was similar between the two treatment regimens (17.8 *vs*. 10.4 months; *P*=0.24; Figure 1B). CR/CRi with HMA-Ven was higher in the presence of *SRSF2* mutation (100% *vs*. 65%; *P*=0.03) while not influenced by adverse karyotype (63% *vs*. 73%; *P*=0.59) or *RUNX1* (57% *vs*. 76%; *P*=0.34) or *BCOR* mutations (100% *vs*. 69%; *P*=0.14).

The current study confirms activity of IDH inhibitor monotherapy in treatment-naïve and relapsed/refractory *IDH*-mutated AML[3-6] and unveils unique molecular predictors of response and survival. The study also provides comparative information in *IDH*-mutated patients treated with HMA-Ven. Salient observations include the favorable impact of *BCOR* and *RUNX1* mutations on IDH inhibitor treatment response and survival and were most apparent in



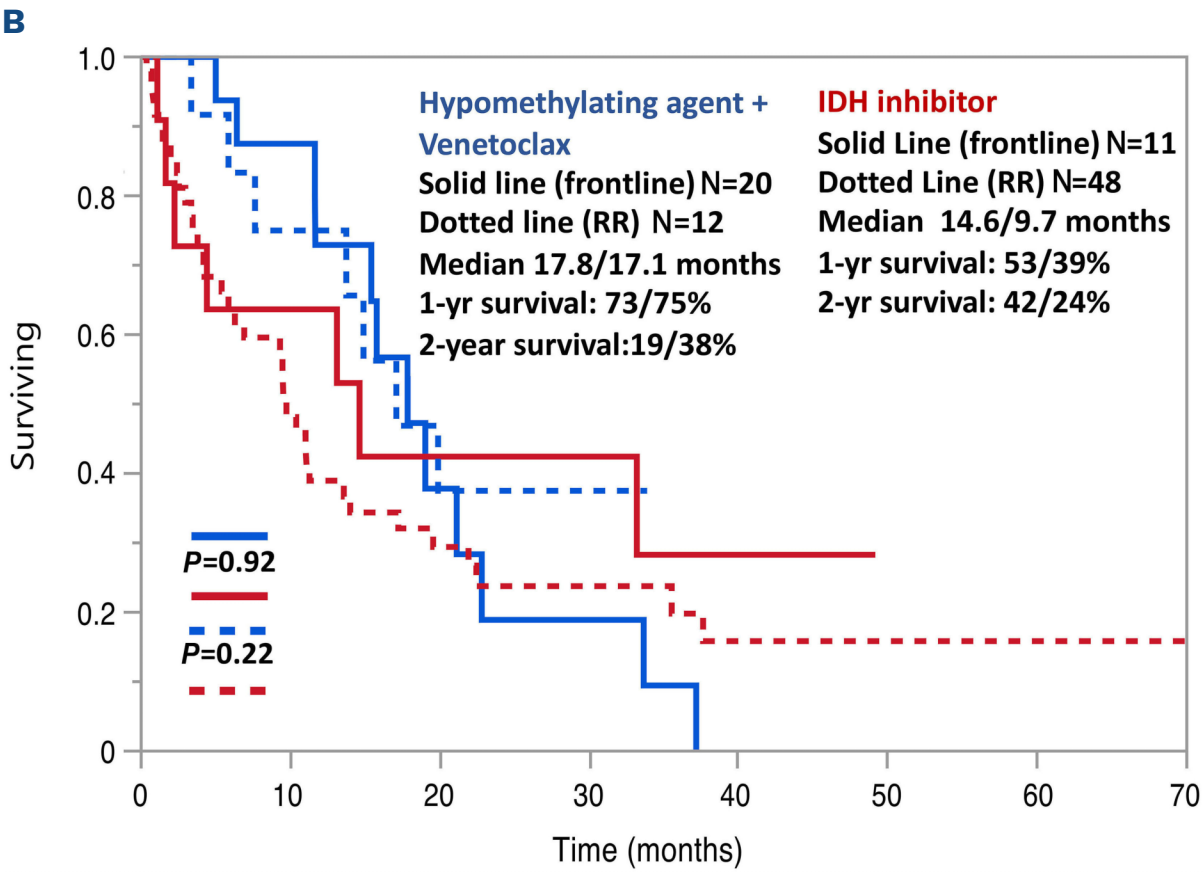


Figure 1. Overall survival in patients with *IDH1/2*-mutated acute myeloid leukemia. (A) Overall survival in 57 patients with acute myelod leukemia (AML) treated with IDH inhibitor, stratified by hazard ratio (HR)-weighted scoring system, absence of *BCOR* mutation, HR=4.8, 95% confidence interval (CI): 1.4-16.5; presence of adverse karyotype, HR=3.2, 95% CI: 1.5-6.7; and absence of *RUNX1* mutation, HR=2.4, 95% CI: 1.1-5.4, allocating 2 adverse points for absence of *BCOR* mutation, 1 adverse point for adverse karyotype, and 1 adverse point for absence of *RUNX1* mutation. Median overall survival stratified by low risk (0-1 points), intermediate risk (2-3 points) and high risk (4 points) is shown. (B) Overall survival in 91 patients with *IDH*-mutated AML treated with either IDH inhibitor (N=59) or hypomethylating agent + venetoclax (N=32). alloHSCT: allogeneic stem cell transplantation; RR: relapsed refractoryrefractory; yr: years.

IDH-2 mutated patients. In previously reported enasidenib clinical trials, responses were negatively affected by the presence of *FLT3* (overall response rate [ORR] 8.3%) or *NRAS* (ORR 29%) mutations, and high co-mutational burden (≥ 6 *vs*. ≤3 mutations; ORR 31% *vs*. 55%);[11] in addition, as was the case in the current study, adverse karyotype was associated with inferior response (ORR 18% *vs*. 46%) and survival (ORR 7 *vs*. 9.3 months).[11] In ivosidenib-treated patients, treatment response was lower in the presence of receptor tyrosine kinase pathway mutations (CR/CRh 7% *vs*. 43%) and higher with *JAK2* mutation (CR/CRh 64% *vs*. 32%).[12]

The observations from the current study are particularly relevant in light of the adverse prognosis assigned to *BCOR* and *RUNX1* mutations, in the latest ELN 2022 risk stratification, which was, however, derived from intensively treated patients.[10] Our findings differ from a prior study on *IDH*-mutated AML patients treated with IDH inhibitors (n=60), in which *RUNX1* mutation was associated with inferior CR rate, in addition, among patients in whom pre-treatment and relapsed samples were analyzed (n=18), *BCOR* and *RUNX1* mutations were frequently acquired at the time of relapse in four and three cases, respectively.[13] The discrepancies stem from key differences in the study populations, unlike the current study, the former study included patients with myelodysplastic syndrome and chronic myelomonocytic leukemia (n=5) and was enriched with patients harboring complex karyotype (22% *vs*. 11%).[13] It should be noted that response prediction is different than survival prediction and frequency of mutations at time of relapse might actually suggest that a higher proportion of patients with the specific mutations achieved response and thus were at risk for relapse. In other words, one has to respond first, in order to relapse. Regardless, the current study provides a practical prognostic model for use in *IDH*-mutated patients with AML receiving IDH inhibitor therapy. The study also suggests superiority of HMA-Ven to IDH inhibitor, in *IDH*-mutated AML, irrespective of karyotype or mutational profile. The favorable responses seen with HMA-Ven were also evident in a prior study of 81 *IDH1/2*-mutated AML patients treated with HMA-Ven with reported CR/CRi rate of 79%.[14] Recently, "doublet therapy" with IDH inhibitor + HMA and "triplet therapy" with IDH inhibitor + Ven + HMA have garnered interest due to higher responses with composite CR rates of 53%,[15] and 90%,[16] respectively. Nonetheless, controlled studies are needed to determine the optimal combination therapy and associated molecular determinants of response and survival.

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Disclosures

No conflicts of interest to disclose.

Contributions

KM, NG and AT designed the study, collected data, performed analysis and co-wrote the paper. MA, OK and MP collected data. AA, HA, KHB, AM, AS, MH, MRL, WH, MS, MMP, AP, TB, JF, JP, LS and CA contributed patients. All authors reviewed and approved the final draft of the paper.

Data-sharing statement

Data will be shared upon reasonable request to the corresponding author.

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