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Frontline isocitrate dehydrogenase inhibitor therapy in isocitrate dehydrogenase-mutated myelodysplastic neoplasms

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Running title

IDH Inhibitors in MDS

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Author contributions

A.A & Z.A: Study design, data collection, analysis, manuscript writing and review.
U.I, N.A, S.S.K: Data collection, manuscript review.
E.P, O.C, A.K, Z.X, A.W, R.S, J.L: Analysis and manuscript review.
R.K & D.S: Study design, analysis, manuscript writing and review.

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To the Editor:

Mutated isocitrate dehydrogenase (m*IDH*) enzymes result in the aberrant conversion of α-ketoglutarate (αKG) to D-2-hydroxyglutarate (2HG), leading to epigenetic dysregulation, impaired hematopoietic differentiation and leukemogenesis (1). *IDH* mutations are less frequently observed in myelodysplastic neoplasms (MDS, ~5%), compared with up to 20% in acute myeloid leukemia (AML). Targeted inhibition of mutant *IDH* enzymes with small-molecule inhibitors has been shown to reduce intracellular 2HG levels, reversing the hypermethylation signal and restoring cellular differentiation (2, 3).

Ivosidenib, a first-in-class mutant *IDH1* inhibitor, has demonstrated clinical efficacy in patients with AML with FDA approval as monotherapy in frontline and relapsed/refractory (R/R) disease as well as frontline therapy in combination with azacitidine (4-6). Ivosidenib was approved for R/R MDS after demonstrating a high overall response rate (ORR) of 83.3%, a complete response (CR) rate of 38.9% (7/18), a median overall survival (OS) of 36 months, and a median duration of response that was not reached (7). Notably, the majority of patients had intermediate or higher-risk disease and had received prior hypomethylating agents (79%) or intensive chemotherapy (15.8%) (7). Enasidenib, a selective mutant *IDH2* inhibitor, is currently approved by the FDA for the treatment of R/R AML and has also shown activity in MDS. In a phase II study evaluating enasidenib in high-risk MDS, composite CR rates were 70% and marrow CR rate were 33% in treatment-naïve patients receiving enasidenib in combination with hypomethylating agents (HMA) and 22% in patients with R/R disease receiving enasidenib monotherapy (8).

Despite these encouraging results in R/R settings, data evaluating the use of *IDH* inhibitors in the frontline treatment of m*IDH* MDS remain limited. In this study, we present our institutional experience with frontline *IDH* inhibitor therapy in patients with treatment-naïve m*IDH* MDS. We conducted a retrospective cohort study of patients diagnosed with m*IDH* MDS who received *IDH*-directed therapy at Moffitt Cancer Center between January 2017 to July 2024 with clinical follow-up continued through April 2026. Clinical, laboratory, and molecular data were obtained through systematic chart review. The primary indication for treatment in the lower-risk group was neutropenia, and the decision to use *IDH* inhibitors rather than standard-of-care therapy was based on their favorable safety profile and the treating physician's clinical experience and expertise. Treatment responses were assessed according to the International Working Group (IWG) 2023 response criteria. Overall response (ORR) was defined as the achievement of hematological improvement or better response per IWG 2023. Descriptive statistical methods were used to summarize patient characteristics and treatment outcomes. This study was approved by the Moffitt Cancer Center Scientific Review Committee and institutional review board.

Ten patients with MDS had *IDH* mutations and were treated with *IDH*-directed therapy. Among these, 70% (7/10) had an *IDH1* mutation and 30% (3/10) had an *IDH2* mutation. All patients received *IDH*-directed therapy as frontline treatment.

Baseline demographics and risk stratification are shown in Table 1. Of the cohort, 20-30% of patients had higher-risk disease based on clinical and molecular risk stratification models. Median number of mutations detected on Next Generation Sequencing (NGS) was 3 and the most common co-mutations were *SRSF2(*4), *DNMT3A*(3), and *ASXL1*/*SF3B1*/*STAG2*(2; Supplemental Figure 1).

Among patients with *IDH1* mutations, 86% (6) received single agent ivosidenib and 14% (1) received combination of ivosidenib with azacitidine (Figure 1). The median baseline blood counts are highlighted in Table 1. The CR or CR-equivalent (full peripheral blood count recovery with <5% blasts at baseline) rate was 100% (7) per IWG 2023 criteria, and 57% (4) achieved undetected *IDH1* mutation based on serial NGS (VAF ≤ 5%). The median time to best response based on IWG 2023 was 14 days (range, 11–143). The median duration of best response was 39 months (range, 11–79) and the median duration of therapy was 40 months (range, 12–80). One patient (#3 in Figure 1) lost response approximately 11 months after achieving CR-equivalent and although alternative therapy was initiated, the patient passed away prior to reassessment because of complications related to COVID-19 infection. One patient with very high-risk disease by IPSS-R treated with combination therapy developed *IDH1*-mutated AML relapse after undergoing allogeneic stem cell transplant (ASCT) while on maintenance ivosidenib post-transplant (Figure 1). The remaining 71% (5) are alive and in ongoing remission.

Among patients with *IDH2* mutations, 67% (2) received single agent enasidenib and 33% (1) received combination azacitidine with enasidenib (Figure 1). The median baseline blood counts are highlighted in Table 1. Two patients had CR-equivalent and one patient CR-bilineage per IWG 2023. One patient achieved undetected *IDH2*, one patient had >50% reduction in *IDH2* allele burden, and third patient did not have molecular assessment at follow-up. One patient underwent ASCT and remains in remission without additional therapy. Two remain on active therapy maintaining response until the date of analysis. The median duration of best response was 23 months (range, 12–43) and the median duration of therapy was 27 months (range, 16–44). In patients who achieved

molecular clearance of the total cohort (5/10), the median time to clearance was 11 months (range, 3-37) although prospective study is required to further define the kinetics of clearance.

Our results suggest that frontline *IDH* inhibition in treatment-naïve m*IDH* MDS is associated with very high clinical and molecular response rates with durable remissions including a duration of >6 years on active therapy. In comparison to R/R MDS patients, both the composite CR and duration of remission are substantially improved in our cohort of patients treated with frontline therapy. Specifically with a median follow-up of 34 months, 70% of patients continue on active therapy with a median duration of response not reached. Notably, the median OS was 36 months with ivosidenib and 20 months with enasidenib in the R/R setting (7, 8), while in our study has not been reached (Supplemental Figure 2), and this is inclusive of 30% of patients with higher risk disease. Further, the totality of data to date have suggested improved durations of response and survival with utilization of *IDH* inhibitors in MDS than in the respective AML studies (4, 5, 9). The data suggests that early intervention with *IDH* inhibitors prior to AML transformation is disease modifying although future translational studies are required to better elucidate these findings. For our lower-risk MDS patients, indication for therapy was predominantly G4 neutropenia as we have previously shown *IDH* mutations are strongly enriched in LR-MDS patients with severe neutropenia (10). Notably, normalization of ANC was rapid leading to absence of any infectious complications during follow up (Figure 2). In our cohort, *IDH1* mutations were exclusively R132C and *IDH2* mutations R140Q (Table 1; Supplemental Figure 1), which may partly explain the observed responses and differential outcomes, as other *IDH* isoforms (e.g *IDH1* R132H

and *IDH2* R172) are strongly associated with AML (11). The safety of *IDH* inhibitor monotherapy was excellent with transient cytopenias observed only in patients receiving HMA. For patients on ivosidenib, Grade 1 QTc prolongation occurred in 14%. Importantly, differentiation syndrome of any grade occurred in 0% of patients, and no patient required a treatment interruption or discontinuation related to an adverse event.

Moreover, our group previously demonstrated that treatment with azacitidine without *IDH*-directed therapy yielded an ORR that did not exceed 50%, CR rate of approximately 14%, and mOS of no more than 31 months for the entire cohort (12). *Sebert et al.,* found that patients who did not respond to *IDH* inhibitors showed no additional responses when HMA was later added (13). The majority of our patients in this study received *IDH* inhibitor monotherapy (8/10), supporting the potential role of single-agent *IDH*-directed therapy particularly in patients with neutropenia given the robust ANC recovery observed in all patients, and raising questions about the benefit of HMA therapy without an *IDH* inhibitor in this population, both in the frontline and subsequent-line settings. Notably, the one patient with early AML transformation following ASCT was treated with combination therapy. We thus eagerly await the prospective phase 3 PyramIDH study comparing ivosidenib monotherapy versus HMA in treatment-naïve m*IDH1* MDS (clinicaltrials.gov #NCT06465953). It is also important to recognize that therapeutic decision-making should account for the specific *IDH* isoform, relevant co-mutations, and the patient's overall risk profile. Further supporting the potent efficacy of m*IDH* inhibition in early disease course, Bolton et al. demonstrated hematological response rates of 82% in patients with m*IDH1* clonal cytopenias of undetermined significance (CCUS) treated with ivosidenib monotherapy (n=20) with a median duration of response not reached (14). Recent data

highlight similar outcomes of higher risk CCUS patients and lower-risk MDS patients which together support for consideration of uniform treatments across this continuum of disease (15). Recognizing the limitations imposed by our sample size and heterogenous treatment approaches across different risk groups, significant caution is required in drawing broader conclusions. Given the rarity of these molecular subgroups, international, real-world datasets along with continued follow-up of the above clinical trials should further strengthen the disease modifying impact of early *IDH* inhibition. However, questions remain if indefinite vs fixed duration of therapy is required as well as if molecular clearance should impact this decision.

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Table 1: Baseline patient characteristics and treatment responses

	Overall (N = 10)	*IDH1* (n = 7)	*IDH2* (n = 3)
Median age (range)	71 (49 – 84)	73 (58 – 84)	68 (49 – 76)
Male, n (%)	4 (40)	3 (43)	1 (33)
IPSS-R high/very high, n (%)	2 (20)	2 (29)	1 (33)
IPSS-M mod-high/high/very high, n (%)	3 (30)	2 (29)	1 (33)
Abnormal karyotype, n (%)	3 (30)	2 (29)	1 (33)
IDH Variant	—	p.R132C	p.R140Q
Median VAF%* (range)	—	32.1 (9.6 – 43.7)	24.7 (24.7 – 24.7)
≥3 co-mutations on NGS, n (%)	9 (90)	6 (86)	3 (100)
Median ANC ×10³/μL (range)	0.34 (0.15 – 1.10)	0.29 (0.15 – 0.77)	0.52 (0.33 – 1.10)
Median hemoglobin g/dL (range)	10.0 (8.5 – 15.4)	9.8 (8.5 – 12.5)	14.9 (9.0 – 15.4)
Median platelets ×10³/μL (range)	168 (95 – 849)	202 (111 – 849)	108 (95 – 194)
Overall response, n (%)	10 (100)	7 (100)	3 (100)
CR or CR-equivalent†, n (%)	9 (90)	7 (100)	2 (67)
CR‡, n (%)	8 (80)	6 (86)	2 (67)

*One IDH1 patient and one IDH2 patient had unknown VAF.
† Per International Working Group 2023.
‡ Per International Working Group 2006. 100% of patients achieved hematologic improvement.
Abbreviations: ANC, absolute neutrophil count; CR, complete response; IDH, isocitrate dehydrogenase; IPSS-M, Molecular International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; VAF, variant allele frequency.

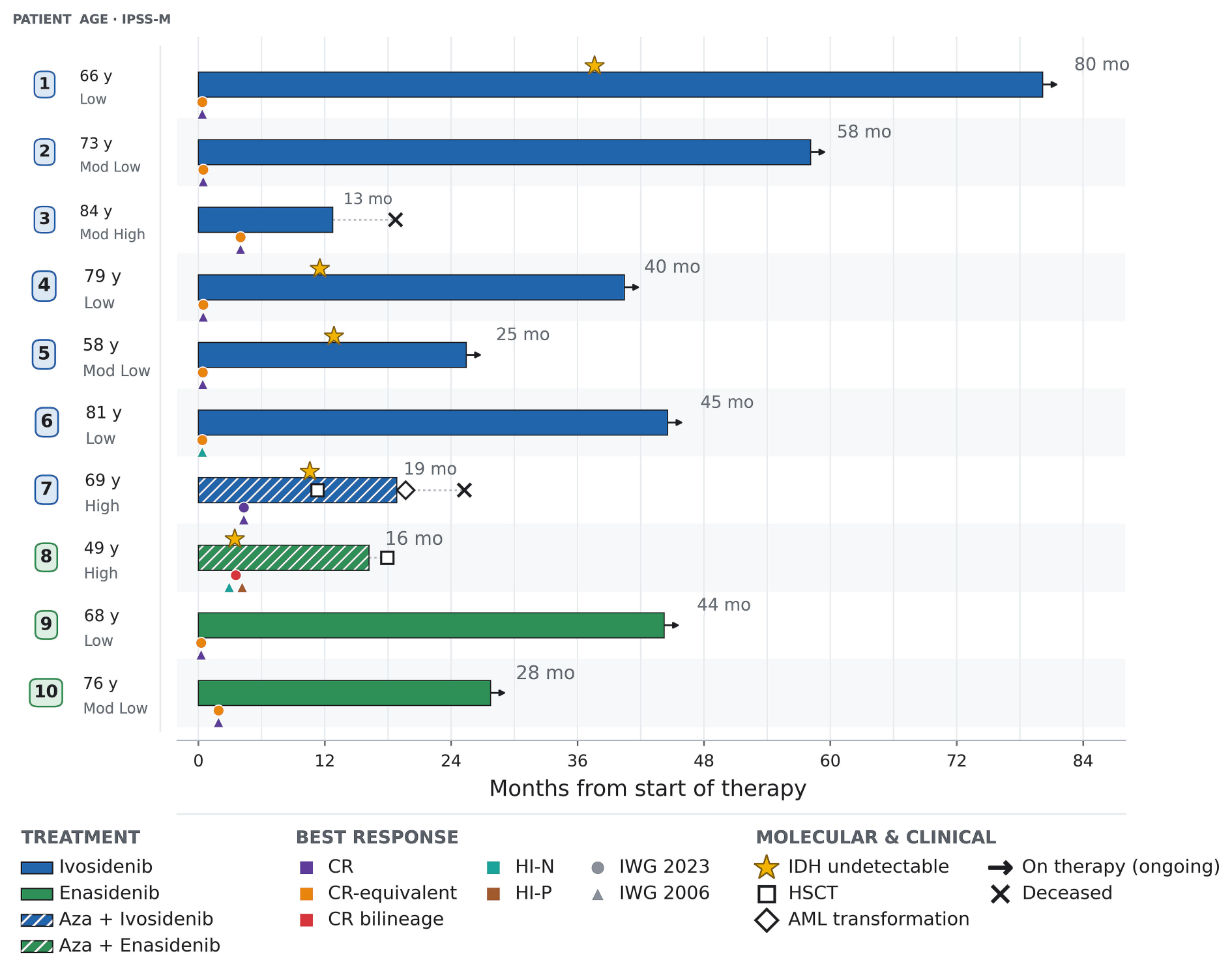
Figure Legends

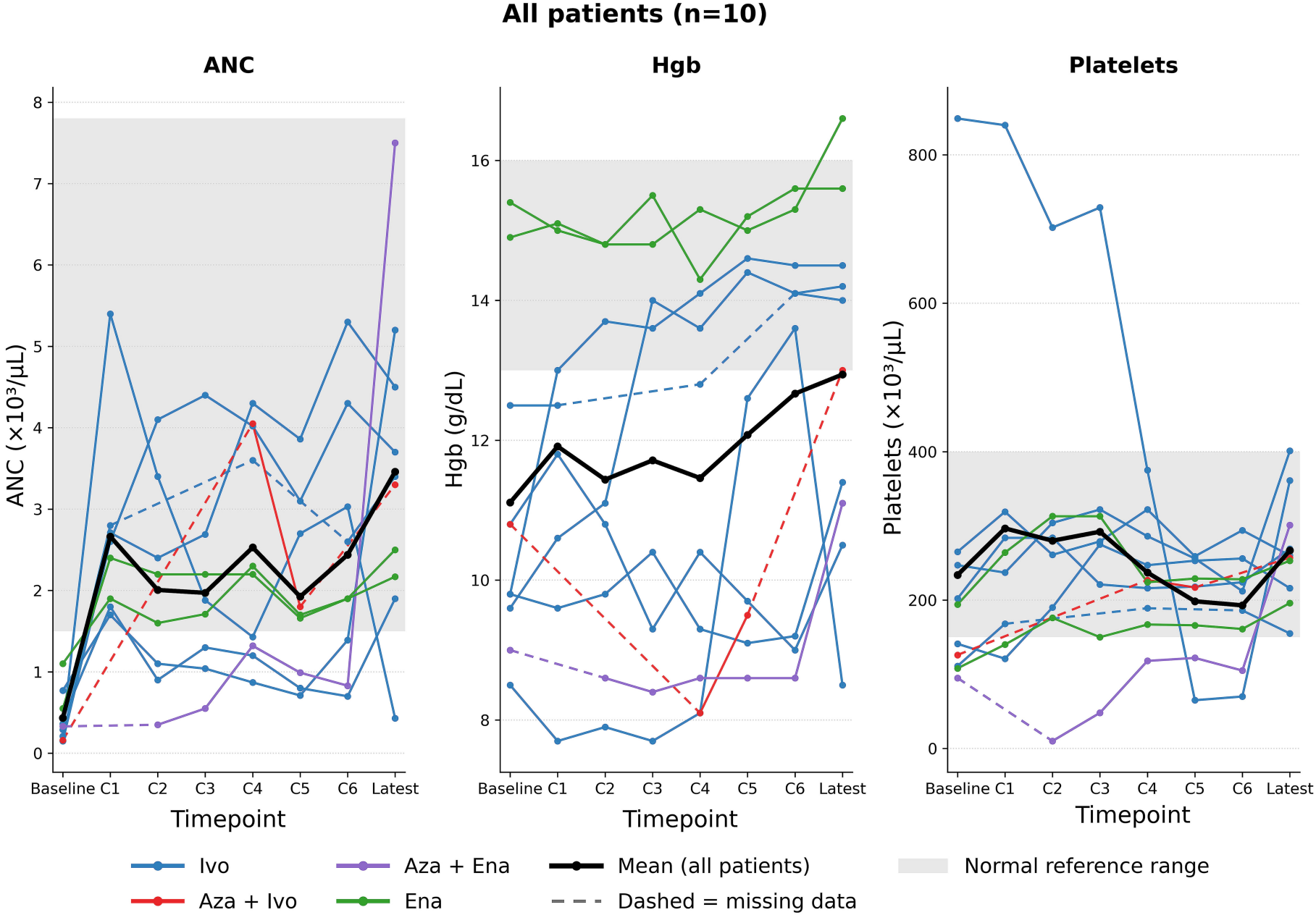
Figure 1: Swimmer plot of treatment duration, response, and outcomes in patients receiving *IDH* inhibitor-based therapy

Abbreviations: AML, acute myeloid leukemia; Aza, azacitidine; CR, complete remission; HI-E, hematologic improvement–erythroid; HI-N, hematologic improvement–neutrophil; HI-P, hematologic improvement–platelet; HSCT, hematopoietic stem cell transplantation; IDH, isocitrate dehydrogenase; IPSS-M, Molecular International Prognostic Scoring System; IWG, International Working Group; Ivo, ivosidenib; Ena, enasidenib.

Figure 2: Peripheral blood count trends in all patients

Abbreviations: ANC, absolute neutrophil count; Aza, azacitidine; Ena, enasidenib; Hgb, hemoglobin; Ivo, ivosidenib; Plts, platelets; C1–C6, treatment cycles 1–6.

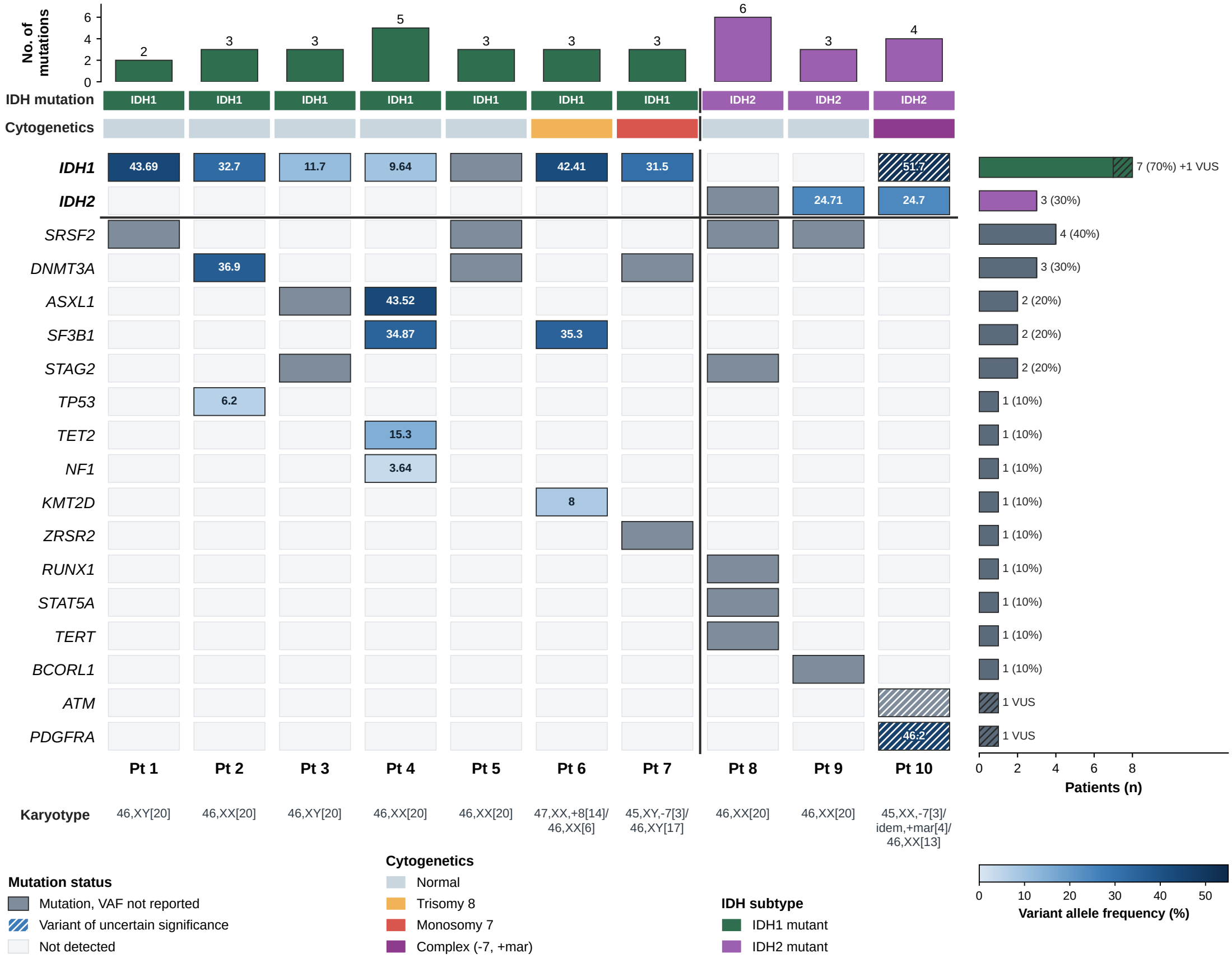

PATIENT AGE · IPSS-M
1
66 y
Low
80 mo
2
73 y
Mod Low
58 mo
3
84 y
Mod High
13 mo
4
79 y
Low
40 mo
5
58 y
Mod Low
25 mo
6
81 y
Low
45 mo
7
69 y
High
19 mo
8
49 y
High
16 mo
9
68 y
Low
44 mo
10
76 y
Mod Low
28 mo
0
12
24
36
48
60
72
84
Months from start of therapy
TREATMENT
Ivosidenib
Enasidenib
Aza + Ivosidenib
Aza + Enasidenib
BEST RESPONSE
CR
CR-equivalent
CR bilineage
HI-N
HI-P
IWG 2023
IWG 2006
MOLECULAR & CLINICAL
IDH undetectable
HSCT
AML transformation
On therapy (ongoing)
Deceased



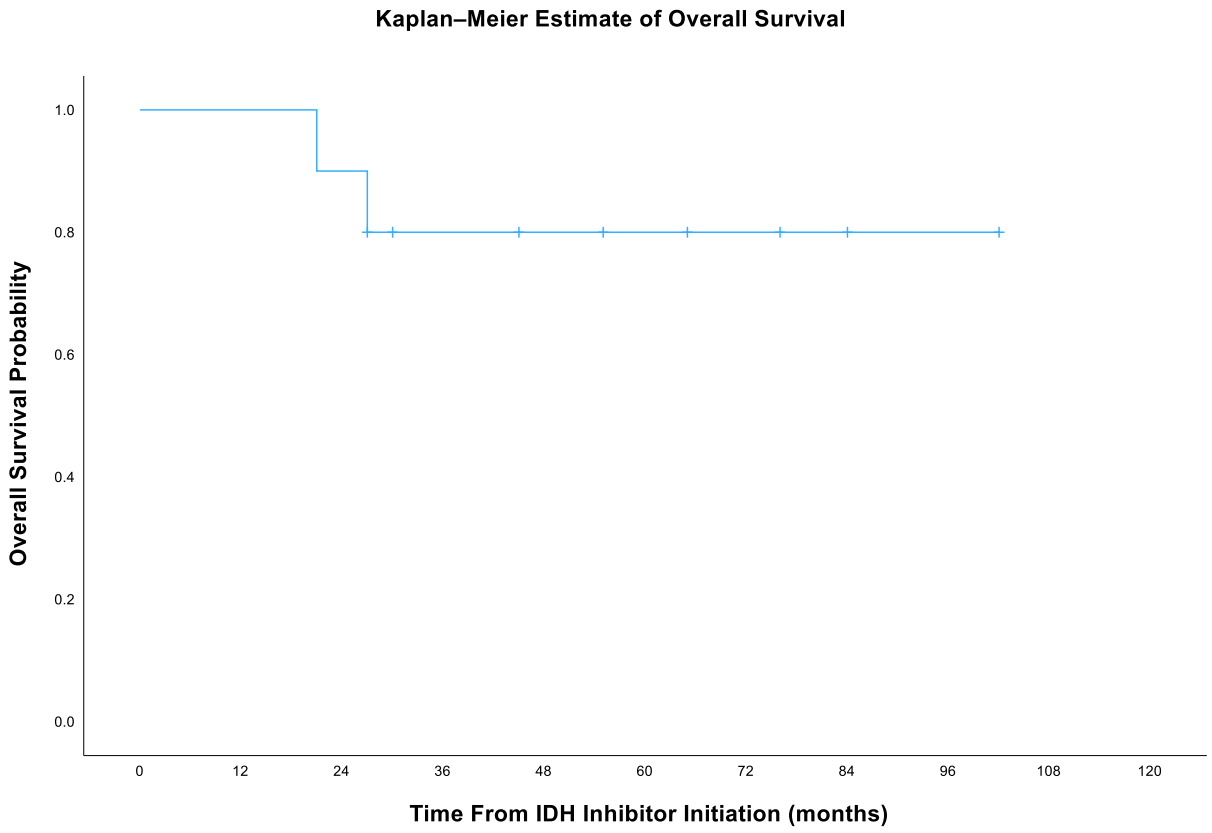
Abbreviations: ANC, absolute neutrophil count; Aza, azacitidine; Ena, enasidenib; Hgb, hemoglobin; Ivo, ivosidenib; Plts, platelets; C1–C6, treatment cycles 1–6.

Supplementary

Co-mutations and cytogenetics



VAF, variant allele frequency; VUS, variant of uncertain significance. Numerals within cells denote VAF (%). Karyotypes are given in ISCN nomenclature.


Kaplan–Meier Estimate of Overall Survival
Overall Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
108
120
Time From IDH Inhibitor Initiation (months)

Figures Legends

Supplemental Figure 1: Co-mutations and cytogenetics

Abbreviations: ISCN, International System for Human Cytogenomic Nomenclature; VAF, variant allele frequency; VUS, variant of uncertain significance.

Supplemental Figure 2: Kaplan-Meier Estimate of Overall Survival

Tick marks indicate censored observation.