



HAVE WE OPTIMIZED THERAPY YET FOR PATIENTS WITH AML?

The future paradigm of HMA + VEN or targeted inhibitor approaches: sequencing or triplet combinations in AML therapy

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The routine use of next-generation sequencing methods has underscored the genetic and clonal heterogeneity of acute myeloid leukemia (AML), subsequently ushering in an era of precision medicine-based targeted therapies exemplified by the small-molecule inhibitors of *FLT3*, *IDH1/IDH2*, and *BCL2*. This advent of targeted drugs in AML has broadened the spectrum of antileukemic therapies, and the approval of venetoclax in combination with a hypomethylating agent has been a welcome addition to our AML patients unable to tolerate intensive chemotherapy. Mounting evidence demonstrates that molecularly targeted agents combined with epigenetic therapies exhibit synergistic augmented leukemic cell kill compared to single-agent therapy. With such great power comes greater responsibility in determining the appropriate frontline AML treatment regimen in a molecularly defined subset and identifying safe and effective combination therapies with different mechanisms of action to outmaneuver primary and secondary resistance mechanisms in AML.

LEARNING OBJECTIVES

- Compare frontline treatment approaches in IC-ineligible *IDH1*-mutant AML and explain how to sequence targeted therapies upon relapse
- Evaluate frontline AZA-VEN therapy and targeted treatment options for IC-ineligible AML patients with *IDH2*, *FLT3*, *NPM1*, or *TP53* mutations

Introduction

The approval of venetoclax (VEN) and a hypomethylating agent (HMA; azacitidine [AZA] or decitabine) combination therapy for older adults (aged ≥ 75 years or not eligible to receive intensive chemotherapy [IC]) with newly diagnosed (ND) acute myeloid leukemia (AML) denotes a paradigm shift in the AML treatment landscape.¹ In the registrational VIALE-A trial for ND AML patients unable to receive IC (median age, 76 years), AZA-VEN combination therapy showed significantly improved composite complete remission (CRc; CR + CR with incomplete hematologic recovery [CRi], 66.4% vs 28.3%) and overall survival (OS) rates (14.7 vs 9.6 months) compared to AZA-placebo.² Long-term follow-up (43.2 months) of VIALE-A confirmed an ongoing survival benefit, albeit more pronounced in those who achieved measurable residual disease negativity.³

Nevertheless, this golden era of rationally targeted AML therapy is plagued by primary resistance and clonal evolution leading to adaptive resistance.⁴ Specifically, in AML patients receiving frontline VEN-based therapy, kinase-

activating mutations such as *FLT3*-ITD and *TP53* alterations appear to be the major drivers of adaptive drug resistance, while patients enriched for *NPM1* and/or *IDH1/IDH2* mutations appear particularly sensitive to VEN, with durable responses.⁵ Sequential single-cell sequencing of diagnosis-remission-relapse samples of AML patients treated with HMA-VEN has illuminated confounding patterns of treatment resistance such as the expansion or acquisition of new *FLT3*-ITD clones or the parallel outgrowth of triple-mutant *FLT3*-ITD/*IDH1*/*NPM1* treatment-resistant subclones.⁵ Furthermore, the emergence of *RAS* pathway mutations appears to be the leitmotif of AML treatment failure across the spectrum of HMA-VEN,⁵ *IDH* inhibitors,^{6,7} and *FLT3* inhibitors (*FLT3i*).⁸ In addition to the mutational spectrum and clonal hierarchy, other primary and acquired mechanisms of resistance, such as cell of origin/differentiation state (e.g., monocytic AML), pro- and antiapoptotic protein dynamics/*BAX* mutations, and mitochondrial metabolism alterations may also be at play.⁹ This innate and treatment-induced selective pressure on AML clones has prompted

Table 1. Comparison of baseline demographics and efficacy outcomes in patients with ND *IDH1*^{mut} AML treated on the pivotal registrational trials of VIALE-A (pooled analysis) and AGILE

Efficacy-evaluable population	AZA with VEN N=33	IVO with AZA N=72
Age, median (range or IQR)	76 (64–90)	76 (58–84)
Response outcomes		
Composite CR (CRc*) rate	67%	53%
CR rate	27%	47%
Duration of response (mo)		
Median time to CRc (range)	1.2 (0.8–8.1)	4.0 (1.7–8.6)
Median duration of CRc (95% CI)	21.9 (7.8–NE)	NE (13.0–NE)
Survival outcomes (mo or percentage)		
Median OS (95% CI)	15.2 (7.0–NE)	24 (11.3–34.1)
Estimated 12-mo survival probability (95% CI)	57.6% (39.1–72.3)	~64%

IQR, interquartile range.

*Here defined as CR plus CRi in VIALE-A (pooled analysis) and CR/CRh in AGILE. CR plus CRi in AGILE was 54%.

Data derived from Pollyea et al¹¹ and Montesinos et al.²

unresolved questions regarding the categorical frontline treatment approach; namely, do we combine, add on, or sequence HMA-VEN and molecularly targeted therapies? Here we present case studies that illustrate the genomic complexity of AML and how we approach treatment in different settings.

Clinical scenario: older adult with ND *IDH1*-mutant AML

Mr. X, a 79-year-old man who dislikes hospitals, presented with a white blood cell (WBC) count of $1.0 \times 10^9/L$, hemoglobin level of 7.4 g/dL, and platelet count of $120 \times 10^9/L$ during his periodic cardiac checkup. Bone marrow biopsy confirmed AML with 28% myeloblasts and trisomy 12, and molecular studies identified *NPM1* (variant allele fraction [VAF], 40%), *DNMT3A* (VAF, 35%), and *IDH1*-R132C (VAF, 48%) mutations. What is the appropriate frontline treatment option for this patient?

The National Comprehensive Cancer Network® version 3.2023 AML guidelines endorse either AZA-VEN or ivosidenib (IVO, an orally administered *IDH1*-targeted inhibitor) plus AZA as a category 1 recommendation (Table 1). Preclinical data have shown that *IDH1/2*-mutant cells exhibit BCL2 dependence, thus rendering them sensitive to VEN, a BCL2 inhibitor.¹⁰ In the pooled analysis of AZA-VEN studies,¹¹ 44 patients with ND AML (n=498, 8%) harbored *IDH1*^{mut}. Among those who received AZA-VEN (n=33), the CRc and CR rate was 66.7% and 27%, respectively. Most patients achieved CR or CRi in the first cycle, the median duration of objective response (DoR) was 21.9 (95% CI, 7.8–NE [not estimable]) months, and median OS was 15.2 months (95% CI, 7.0–NE). In this pooled analysis of *IDH1/2*^{mut} AML patients treated with AZA-VEN (n=81), 87% had grade 3 or higher hematological adverse events (AEs); 42%, febrile neutropenia; and 46%, thrombocytopenia.¹¹

In the phase 3 AGILE trial, IVO (500 mg daily) plus AZA (parenterally for 7 days) was compared to AZA-placebo in ND, IC-ineligible *IDH1*^{mut} AML patients.² In the intention-to-treat population (n=146), 72 patients received IVO-AZA: among those, the rate of CR or CR with partial hematological recovery (CRh) was 53%, including a CR rate of 47%. The median time to CR was 4.3 months (range, 1.7–9.2), and the median DoR was 22.1 months

(95% CI, 13.0–NE). With a median follow-up of 12.4 months, median OS in the IVO-AZA arm was 24.0 months (95% CI, 11.3–34.1), compared to 7.9 months with AZA-placebo ($P=.001$). Among patients treated with IVO-AZA, 70% had grade ≥ 3 hematological AEs; 28%, febrile neutropenia; and 24%, thrombocytopenia. AEs of special interest (grade ≥ 3) included 10% QTc prolongation and 4% differentiation syndrome, which resolved with conservative management.²

In this case scenario, we will propose either AZA-VEN or IVO-AZA as a frontline treatment for IC-ineligible *IDH1*^{mut} AML after carefully considering the patient's comorbidities and the AE profile of the treatment regimen. Depending on test availability and institutional turnaround time for molecular studies, practical issues may arise with obtaining *IDH1* mutation status prior to initiating therapy, particularly in proliferative patients who may require more urgent treatment.

Relapsed/refractory *IDH1*-mutant AML

IVO or olutasidenib (OLU) is approved to treat relapsed/refractory (R/R) *IDH1*^{mut} AML (Table 2).¹² In the phase 1b study evaluating IVO in R/R *IDH1*^{mut} AML,¹³ the rate of CR plus CRh was 30.4% (95% CI, 22.5–39.3), including a 21.6% CR rate in the primary efficacy population. With a median follow-up of 14.8 months (range, 0.2–30.3), the median duration of CR or CRh was 8.2 months (95% CI, 5.5–12.0), and the median OS was 8.8 months (95% CI, 6.7–10.2). AEs of special interest (grade ≥ 3) included QTc prolongation (7.8%) and IDH differentiation syndrome (3.9%). Of note, this study did not include patients exposed to VEN due to their contemporaneous approvals.¹³

OLU (FT-2102), an oral, selective *IDH1*^{mut} inhibitor, was approved in 2022 for R/R *IDH1*^{mut} AML. The phase 1 study evaluated OLU monotherapy and a combination with AZA (OLU-AZA) in both treatment-naïve and R/R *IDH1*^{mut} AML/MDS, and a signal of efficacy was observed in all cohorts.¹² In the pivotal phase 2 cohort in R/R *IDH1*^{mut} AML, 153 *IDH1* inhibitor-naïve patients received OLU at 150mg twice daily.¹² In this cohort the CR plus CRh rate was 35% (95% CI, 27.0–43.0), with a 32% CR rate. The

Table 2. Comparison of baseline demographics and efficacy outcomes in patients with R/R *IDH1*^{mut} AML treated on the pivotal registrational trials of IVO and OLU

Efficacy-evaluable population	IVO N=125	OLU N=147
Age, median (range or IQR)	67 (18–87)	71 (range, 32–87)
ECOG PS, n (%)		
0	27 (22)	45 (31)
1	64 (51)	76 (52)
2	32 (26)	23 (16)
3	2 (1)	0
AML type, n (%)		
De novo	83 (66)	97 (66)
Secondary	42 (34)	50 (34)
Cytogenetic risk, n (%)		
Favorable	–	6 (4)
Intermediate	66 (53)	107 (73)
Poor	38 (30)	25 (17)
Missing/unknown	21 (17)	9 (6)
Co-mutations, n (%)		
<i>NPM1</i>	24 (20)	31 (21)
<i>FLT3</i>	9 (8)	15 (10)
<i>CEBPA</i>	3 (3)	<10%
Prior regimens, median (range)	2 (1–6)	2 (1–7)
VEN, n (%)	0	12 (8)
HSCT, n (%)	36 (29)	17 (12)
Bone marrow blast percentage, median (range)	56 (0–98)	42 (4–98)
Response outcomes		
Composite CR (CR plus CRh) rate	30%	35%
CR rate	21%	32%
Duration of response (mo)		
Median time to CR/CRh (range)	2.7 (0.9–5.6)	1.9 (0.9–5.6)
Median duration of CR/CRh (95% CI)	8.2 (5.5–12.0)	25.9 (13.5–NE)
Survival outcomes (mo or percentage)		
Median OS (95% CI)	8.8 (6.7–10.2)	11.6 (8.9–15.5)*
Estimated 18-mo survival probability in patients with CR/CRh	50%	78%

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PS, performance status.

*In the 153-patient safety population (which included the 147-patient efficacy-evaluable population plus 6 patients with a lack of a centrally confirmed *IDH1* mutation).

Adapted from Venugopal and Watts.⁴¹

median duration of CR plus CRh was 25.9 months (95% CI, 13.5–NE), and median OS was 11.6 months (95% CI, 8.9–15.5). AEs of special interest (grade ≥3) included hepatic enzyme elevation (15%) and IDH differentiation syndrome (9%). In updated results from all phase 2 cohorts, 17 patients (15 receiving OLU monotherapy and 2 in combination with AZA) had prior exposure to VEN, of which 7 achieved a CR, CRh, or CRi (41%), and the median duration of CR/CRh (5 patients) was 18.5 plus months at the data cutoff date.^{14,15} OLU-AZA was evaluated in multiple subcohorts on the phase 2 study and demonstrated durable clinical activity in

treatment-naïve AML and R/R patients without prior exposure to an HMA or *IDH1* inhibitor.¹⁶ The activity of OLU after IVO treatment failure is unknown, although preclinical studies suggest it may have activity in second-site mutations.¹⁷

In R/R *IDH1*^{mut} AML, the management decision is dictated by the first-line treatment. Given available data, we would propose IVO or OLU monotherapy or an HMA-VEN regimen (prospective data are with decitabine) for patients with prior exposure to IC and consider OLU monotherapy for patients with prior exposure to AZA-VEN, given the limited prospective data.^{18,19}

Clinical scenario: older adult with *IDH2*-mutant AML, treatment-naïve and relapsed settings

For treatment-naïve patients with *IDH2*^{mut} AML ineligible for IC, AZA-VEN is standard therapy. Enasidenib (ENA), an oral, selective *IDH2*^{mut} inhibitor, is approved in the R/R setting (Table 3.²⁰ In the pooled analysis of AZA-VEN studies,¹¹ 68 patients with ND AML (n=498, 14%) harbored *IDH2*^{mut}. Among those who received AZA-VEN (n=50), the CRc rate was 86% with a 56% CR rate. Most patients achieved their response (CR or CRi) in the first cycle, and the median DoR (95% CI, 16.7-NE) and median OS (95% CI, 17.6-NE) were not reached. The AG221-AML-005 trial evaluated ENA-AZA against AZA monotherapy in ND, IC-ineligible *IDH2*^{mut} AML (N=107). Among the efficacy-evaluable population (n=101), rates of CR plus CRh (57% vs 18%; *P*=.0002), CR (54% vs 12%; *P*<.0001), and median DoR (24.1 vs 9.9 months) were significantly higher in the ENA-AZA arm compared to AZA monotherapy. Nevertheless, there was no difference in median OS (15.9 vs 11.1 months; *P*=.11) between treatment arms, perhaps influenced by a lack of placebo control and the subsequent use of ENA in patients on the AZA monotherapy arm. Serious AEs included febrile neutropenia (13%) and differentiation syndrome (10%).²¹ In a single institutional study of ENA-AZA in patients with *IDH2*^{mut} AML, outcomes were better in those with early vs late relapse, and a small group of R/R patients with prior exposure to ENA or AZA showed a signal of activity with ENA-AZA-VEN triplet therapy.²²

IC-ineligible adults with treatment-naïve *IDH2*^{mut} AML are highly sensitive to AZA-VEN, and we would strongly recommend this approach as first-line therapy. In the relapsed setting post AZA-VEN, ENA monotherapy is the standard of care, and in R/R patients without prior exposure to HMA or VEN, ENA or an HMA-VEN regimen may be considered.

Future directions in *IDH1/2*^{mut} AML: triplet (AZA-VEN-*IDH1/2* inhibitor) vs. sequencing with *IDH1/2* inhibitors

In a phase 1b study evaluating the safety and efficacy of IVO-VEN plus or minus AZA (IVO-VEN-AZA) in *IDH1*^{mut} myeloid malignancies

(n=31),²³ the AE profile was similar to that of IVO or AZA monotherapy, and the maximum tolerated dose was not reached. Of note, VEN was given for 14 days starting with cycle 1 and was studied at both 400 mg and 800 mg daily given potential pharmacokinetic interactions with IVO. Clinical activity was observed with IVO-VEN and IVO-VEN-AZA (CRc, 83% and 90%, respectively) with no difference in survival between IVO-VEN and IVO-VEN-AZA (42.1 months vs not reached [NR]; *P*=.13), and enrollment continues on the IVO-VEN-AZA cohort.²³ In another nonrandomized study evaluating total oral therapy with cedazuridine-decitabine (days 1-5), VEN (days 1-14), and IVO or ENA, robust treatment response was observed in treatment-naïve patients. In the R/R setting, responses were more pronounced in those without prior VEN exposure.²⁴ Triplet regimens may increase the likelihood of receiving a curative-intent hematopoietic stem cell transplant in a selected subset of older adults. The I-DATA study (NCT05401097) comparing the order of treatment with IVO-ENA monotherapy and AZA-VEN in treatment-naïve, IC-ineligible patients should offer some clarity on the sequencing of these agents. Ultimately, randomized studies of AZA-VEN-*IDH* inhibitor vs AZA-VEN (possibly followed by an *IDH* inhibitor) are needed, and differences in sensitivity to AZA-VEN by the *IDH*^{mut} subtype and the unique clinical profiles of available *IDH* inhibitors should be considered. Switch maintenance studies (AZA-VEN followed by *IDH1* inhibitor-AZA once remission is achieved) are also under consideration.

Clinical scenario: older adult with relapsed *NPM1*^{mut} AML

Mr. X, now 81 years of age, presents with prolonged pancytopenia prior to starting his 14th cycle of IVO-AZA. The bone marrow biopsy evaluation confirmed relapsed AML, and molecular studies identified *NPM1* (VAF, 50%), *DNMT3A* (VAF-40%), and *BCOR* (VAF, 25%) mutations. What is the appropriate treatment regimen for this patient?

Approximately 10% to 40% of patients with *NPM1*^{mut} AML relapse, depending on various factors, and a single-center report suggests that adding VEN to either high- or low-intensity salvage

Table 3. Comparison of baseline demographics and efficacy outcomes in patients with *IDH2*^{mut} AML treated on the VIALE-A (pooled analysis), AG221-AML-005, and ENA (registrational trial)

Efficacy-evaluable population	AZA with VEN N=50	ENA with AZA N=68	ENA N=109
Age, median (range or IQR)	76 (64–90)	75 (70–79)	67 (19–100)
Trial design and setting	Phase 3, ND	Phase 1b/2, ND	Phase 1/2, relapsed/refractory
Response outcomes			
Composite CR (CRc*) rate	86%	57%	26.8%
CR rate	56%	54%	20.2%
Duration of response (mo)			
Median time to CRc (range or IQR)	1.1 (0.7–8.8)	4.6 (2.3–6.7)	3.7 (0.7–11.2)
Median duration of CRc (95% CI)	NE (16.7-NE)	NE (10.2-NE)	8.8 (0.7–11.2)
Survival outcomes (mo or percentage)			
Median OS (95% CI)	NE (17.6-NE)	22.0 (14.6-NE)	9.3 (8.2–10.9)
Estimated 12-mo survival probability (95% CI)	75.6% (61–85.3)	72% (60–82)	39%

IQR, interquartile range.

*Here defined as CR plus CRi in VIALE-A (pooled analysis) and enasidenib and CR plus CRh in AG221-AML-005. CR plus CRi in AG221-AML-005 was 63%. Data derived from Pollyea et al¹¹; DiNardo et al²¹; and Stein et al.²⁰

regimens may improve outcomes in these patients.²⁵ In addition, preclinical studies have shown that deregulation of the *HOXA9/MEIS1* axis drives leukemogenesis in *NPM1*^{mut} AML and that menin-*MLL* inhibition abrogates this phenotype.²⁶ In a phase 1 study evaluating patients with R/R AML including *NPM1*^{mut}, revumenib (SNDX-5613), a selective oral menin inhibitor, demonstrated tolerability and clinical activity (CRc, 36% in *NPM1*^{mut} AML) in a heavily pretreated population. AEs of special interest included QTc prolongation (53%) and differentiation syndrome (16%).²⁷ In the absence of a clinical trial evaluating targeted therapies in *NPM1*^{mut} AML, we would recommend a VEN-based regimen for this patient with relapsed *NPM1*^{mut} AML after prior treatment with IVO-AZA.

Clinical scenario: older adult with *FLT3*^{mut} AML

Mr. Z, a 78-year-old man, presents with a WBC of $40 \times 10^9/L$, a hemoglobin level of 7.4 g/dL, and a platelet count of $70 \times 10^9/L$. Bone marrow biopsy confirms AML with 67% myeloblasts and a normal karyotype, and the molecular studies identify *NPM1* (VAF, 40%), *FLT3*-ITD (allele ratio, 0.83), and *IDH2* (VAF, 22%) mutations. What is the appropriate frontline treatment option for this patient?

Currently, there are no approved targeted options for treatment-naïve patients with *FLT3*^{mut} AML who are IC ineligible. In the pooled analysis of AZA-VEN studies,²⁸ 64 patients with ND AML (n=498, 13%) harbored *FLT3*^{mut}. Among those who received AZA-VEN (n=42), 30 had *FLT3*-ITD and 12, *FLT3*-TKD mutations. The CRc rates in patients with *FLT3*-ITD and *FLT3*-TKD were 63.3% and 77%, respectively. Among these patients, median OS was longer in those with *FLT3*-TKD (19.2 months; 95% CI, 1.8-NE) compared to *FLT3*-ITD (9.9 months; 95% CI, 5.3-17.6).²⁸ In a proof-of-concept study allowing the addition of an FLT3i to a decitabine-VEN backbone (n=25), CRc rates were 92% (polymerase chain reaction/next-generation sequencing negativity, 91%) and 62% (polymerase chain reaction/next-generation sequencing negativity, 100%) in ND (IC-ineligible) and R/R *FLT3*^{mut} AML (including prior FLT3i exposed), respectively.²⁹ Triplet therapy combining the FLT3i gilteritinib (GILT) with AZA-VEN, with modified dosing for myelosuppression, is also being evaluated in this population,³⁰ and a multicenter study is planned (VICEROY).

In the R/R setting, the VEN-GILT doublet has shown promising clinical activity in a phase 1b study (n=61 patients with R/R *FLT3*^{mut} AML). The primary end point was a modified CRc rate (mCRc, CR minus CRi plus CRp plus morphologic leukemia-free state), and prior VEN or FLT3i (other than GILT) was allowed (64% had prior FLT3i exposure). VEN at 400 mg plus GILT at 120 mg/day was chosen as the recommended phase 2 dose based on clinical activity (75% mCRc rate) and tolerability. Cytopenias of grade 3 or above were observed in 80% of patients, and approximately 50% required dose interruptions secondary to VEN or GILT-related AEs. While VEN-GILT demonstrated activity even in patients with prior FLT3i exposure (67% mCRc rate), myelosuppression can be prolonged, and dose modifications for tolerability were common, highlighting the need for robust clinical trials to further examine the safety and efficacy of VEN-based combinations.³¹

In IC-ineligible patients with *FLT3*^{mut} AML, we recommend AZA-VEN in the frontline setting and GILT monotherapy in the R/R setting, outside of a clinical trial.

Clinical scenario: older adult with *TP53*^{mut} AML

Ms. Y, a 76-year-old woman with a previous history of large-cell lymphoma treated with chemotherapy 5 years ago, presents

with a WBC of $2.5 \times 10^9/L$, a hemoglobin level of 7.9 g/dL, and a platelet count of $45 \times 10^9/L$. Bone marrow biopsy confirms AML with 67% myeloblasts and a complex karyotype with 17p deletion, and molecular studies identified a *TP53* R282W (VAF, 73%) mutation. What is the appropriate frontline treatment option for this patient?

Improving the short-lived remissions and inferior survival in *TP53*^{mut} AML remains the Sisyphean endeavor of the leukemia research community. In particular, *TP53* multihit status is notoriously refractory to treatment.³² Retrospective and prospective studies have shown that adding VEN to HMA or chemotherapy does not improve survival in *TP53*^{mut} AML.^{33,34} In the pooled analysis of AZA-VEN studies, there was no difference in OS between those who received AZA-VEN and AZA (5.2 vs 4.9 months).³⁵ Magrolimab (MAGRO) is a first-in-class humanized anti-CD47 antibody that blocks CD47 binding to signal-regulatory protein- α and promotes phagocytosis of leukemic cells.³⁶ MAGRO-AZA has been evaluated in patients with untreated higher-risk myelodysplastic syndrome (n=95),³⁷ of which 26.3% harbored a *TP53* mutation (n=25). Anemia was the most common MAGRO-related AE (37.9%), which resolved with subsequent cycles. Among those with *TP53*^{mut}, 10 (40.0%) achieved CR. At the median follow-up of 12.5 months, DoR was 7.6 months (95% CI, 3.1-13.4), and median OS was 16.3 months (95% CI, 10.8-NR) in *TP53*^{mut} patients.³⁷ Given this encouraging activity, the phase 3 ENHANCE-2 study is evaluating MAGRO-AZA vs AZA-VEN or IC in treatment-naïve patients with *TP53*^{mut} AML (NCT04778397). Triplet therapy with MAGRO-AZA-VEN is underway and has demonstrated preliminary activity in frontline and R/R AML, *TP53*^{mut} and wild type,³⁸ and the phase 3 ENHANCE-3 study is evaluating triplet MAGRO-AZA-VEN vs AZA-VEN in all-comers with ND, IC-ineligible AML (NCT05079230). Immunotherapy approaches such as anti-CD3/CD123 bispecific antibodies, with or without an AZA-VEN backbone, may also have a role,^{39,40} and other therapies exploiting CD47/signal-regulatory protein- α are under investigation.

Conclusions

Increased biological understanding of AML has translated into an expansion of the AML treatment landscape with rational combinations incorporating molecularly targeted therapies. In the era of precision medicine, tolerable regimens combining targeted agents with an HMA-VEN backbone may improve outcomes in IC-ineligible patients across various molecular subsets (*IDH1/2*, *NPM1*, *FLT3*, *TP53*). Ongoing and future clinical trial evaluations should guide us in the choice of treatment regimens, answering critical questions about topics such as the use of frontline triplet combinations, compared with the sequencing of targeted therapies. Triplet regimens may be associated with increased toxicity, and equipoise is needed to optimize treatment approaches and delineate survival advantages in multicenter trials. Despite unresolved questions, having these tailored treatment options available for our patients represents a major advance compared to less than a decade ago.

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For all our patients, who teach us so much every day. Visual abstract created with biorender.com.

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