How I Treat

Clinical Advances in Hematology & Oncology November 2026

How I Treat MDS/AML: Individualizing Therapy Based on Disease Biology, Patient Fitness, Molecular Features, and Treatment Goals



Courtney D. DiNardo, MD, MSCE
Professor of Medicine, The University of Texas MD Anderson Cancer Center
Associate Member, The University of Texas Graduate School of Biomedical Sciences at Houston
Houston, Texas

ON THE WEB:
hematologyandoncology.net

MILLENNIUM MEDICAL PUBLISHING, Inc.

Indexed through the National Library of Medicine (PubMed/MEDLINE) and EMBASE

How I Treat MDS/AML: Individualizing Therapy Based on Disease Biology, Patient Fitness, Molecular Features, and Treatment Goals

Courtney D. DiNardo, MD, MSCE

In the Clinic . . .

Consider the following patient cases encountered in my clinic.

Case 1: Secondary AML With Adverse-Risk Genetics

A 65-year-old male presents with pancytopenia identified by their primary care physician at the time of an upper respiratory infection. Past medical history includes hypertension, obesity, and a smoking history. Eastern Cooperative Oncology Group (ECOG) performance status (PS) is 1. Laboratory values include a white blood cell (WBC) count of 2500 cells/μL, absolute neutrophil count (ANC) of 900 cells/μL, a hemoglobin of 8.5 g/dL, and a platelet count of 65,000/μL. A bone marrow biopsy shows 28% blasts with a background of underlying trilineage dysplasia. Molecular profiling reveals *TET2*, *ASXL1*, and *U2AF1* mutations.

Although the patient has relative fitness for intensive chemotherapy, he also has underlying myelodysplastic syndrome (MDS)–associated changes and adverse-risk genetics per the European LeukemiaNet (ELN) 2022 criteria.[1] For this type of patient, I would prioritize a hypomethylating agent (HMA) + venetoclax regimen, followed by a stem cell transplant (SCT) in first complete remission (CR1).

Case 2: Proliferative Monocytic AML

A 65-year-old male presents with petechiae and bruising. He also has a history of hypertension, obesity, and smoking, plus an ECOG PS of 1. Laboratory findings include a WBC count of 52,000 cells/μL, circulating blasts, a hemoglobin of 8.5 g/dL, and a platelet count of 35,000/μL. A bone marrow biopsy shows 55% blasts with monocytic features. Molecular profiling reveals deletion (20q) and mutations in *ASXL1* and *NRAS*.

Although there are commonalities between this patient and the prior one, this patient has a proliferative monocytic leukemia with an *NRAS* mutation. This patient is classified as ELN 2022 intermediate risk, and notably *NRAS* mutations are not adverse risk when treated with intensive chemotherapy regimens. However, when treated with lower-intensity regimens including venetoclax, both *RAS* mutations and monocytic disease biology have been associated with primary and secondary resistance. Thus intensive chemotherapy would be my preferred treatment option here, followed by an SCT in CR1.

Case 3: *NPM1*/*FLT3*-ITD AML

A 55-year-old female presents with progressive fatigue and bruising; she has no significant past medical history and has an ECOG PS of 1. Laboratory findings include a WBC count of 25,000 cells/μL, a hemoglobin of 8.5 g/dL, and a platelet count of 25,000/μL. A bone marrow biopsy shows 55% blasts with monocytic features. Molecular profiling reveals *NPM1* and *FLT3*-internal tandem duplication (ITD) mutations.

Given the patient's de novo acute myeloid leukemia (AML) phenotype and the presence of the targetable *FLT3* mutation, the treatment choice here is intensive chemotherapy + a FLT3 inhibitor. Both midostaurin and quizartinib are approved as frontline FLT3 inhibitors in combination with intensive chemotherapy. *NPM1* and *FLT3* should be monitored during treatment, and an SCT in CR1 is indicated if the patient does not attain measurable residual disease

On the Cover

Illustration of acute myeloid leukemia.

Credit: Nemes Laszlo/Science Source

Disclaimer

Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Millennium Medical Publishing, Inc., the supporter, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

©2026 Millennium Medical Publishing, Inc., 611 Broadway, Suite 605, New York, NY 10012. Printed in the USA. All rights reserved, including the right of reproduction, in whole or in part, in any form.

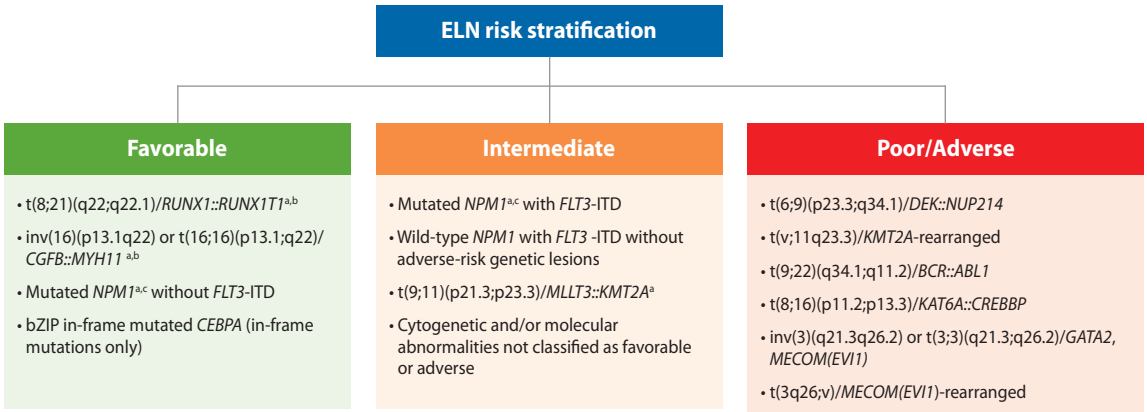


Figure 1. ELN risk stratification according to genetic features at initial AML diagnosis.[1]

[a]Initial risk assignment may change during treatment based on MRD analysis.
[b]Concurrent *KIT* and/or *FLT3* mutations do not alter risk categorization.
[c]AML with *NPM1* mutation and adverse-risk cytogenetic abnormalities is considered adverse-risk.
AML, acute myeloid leukemia; ELN, European LeukemiaNet; ITD, internal tandem duplication; MRD, measurable residual disease; VAF, variant allele frequency.

(MRD)–negative status by both *NPM1* and *FLT3*-ITD.

Case 4: AML in an Older Patient

A 78-year-old female presents with progressive fatigue and bruising. Past medical history includes hypertension, type 2 diabetes, and osteoarthritis, all well controlled. Laboratory findings include a WBC count of 2500 cells/μL, a hemoglobin of 8.2 g/dL, and a platelet count of 55,000/μL. A bone marrow biopsy shows 28% blasts and molecular profiling reveals 2 *DDX41* mutations (DDX41 p.D140fs at 45% variant allele frequency [VAF] and p.R525H at 5% VAF).

In this patient, the primary molecular feature affecting the treatment decision is the lack of an *IDH1* mutation, which would favor the use of azacitidine + ivosidenib.[2] The patient's age will preclude use of SCT, so the optimal treatment will be an HMA + venetoclax regimen that is continued for as long as she benefits. Of note, the presence of a *DDX41* mutation at near-heterozygous frequency (~50% VAF) indicates that this patient likely has a hereditary hematologic malignancy related to inheritance of a germline *DDX41* mutation. Patients with *DDX41* mutations can do quite well with an HMA + venetoclax–based therapy, and are considered ELN 2024 favorable risk.

The Common Thread: Individualizing Therapy Based on Disease Biology, Patient Fitness, Molecular Features, and Treatment Goals

Why do these patients require different treatment approaches? Selection of initial treatment for patients with AML requires a nuanced consideration of disease-related, treatment-related, and patient-related factors. Patient fitness is a primary consideration, and eligibility for intensive induction therapy is still the first dichotomous factor for initial treatment selection in the current National Comprehensive Cancer Network (NCCN) clinical guidelines.[2] However, treatment decisions are increasingly individualized based on disease risk, the presence of molecular alterations, and patient-related factors.

Conventionally, use of allogeneic SCT in patients with AML was limited to patients receiving intensive induction chemotherapy. However, today patients can proceed to SCT after a lower-intensity regimen, typically an HMA + venetoclax. In fact, recent evidence from the PARADIGM trial indicates that some patients, primarily those with adverse-risk AML, may be more likely to successfully proceed to SCT after an HMA + venetoclax regimen than after intensive chemotherapy.[3] However, this trial excluded some patients, including those with core binding factor (CBF)-AML, *FLT3*-mutated AML, and younger adults with *NPM1* mutations, where the curative potential of intensive chemotherapy is well recognized. Therefore, determination of the optimal induction therapy approach in different clinical scenarios remains an important topic of ongoing discussion.

MRD testing is also gaining an increasing role in monitoring treatment responses and guiding therapeutic decisions. The presence of MRD after induction therapy is associated with an increased risk of relapse.[4,5] Accordingly, patients with *NPM1*-, *CBFB::MYH11*-, or *RUNX1::RUNX1T1*-mutated AML with confirmed MRD positivity after induction and/or consolidation therapy

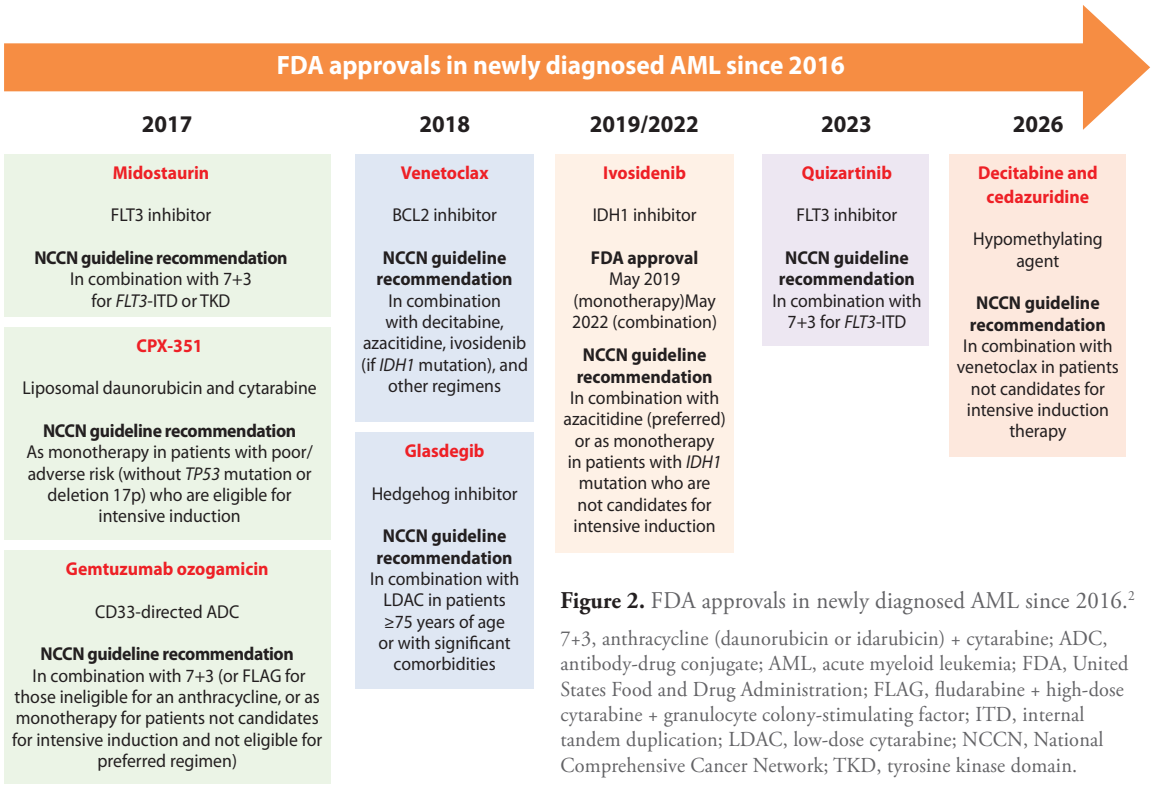


Figure 2. FDA approvals in newly diagnosed AML since 2016.[2]

7+3, anthracycline (daunorubicin or idarubicin) + cytarabine; ADC, antibody-drug conjugate; AML, acute myeloid leukemia; FDA, United States Food and Drug Administration; FLAG, fludarabine + high-dose cytarabine + granulocyte colony-stimulating factor; ITD, internal tandem duplication; LDAC, low-dose cytarabine; NCCN, National Comprehensive Cancer Network; TKD, tyrosine kinase domain.

should be considered for SCT or other further therapies. MRD positivity can also guide the use of post-SCT maintenance therapy in patients with *FLT3*-mutated AML.

AML Overview

AML is a rare, aggressive, hematologic malignancy characterized by clonal expansion of immature myeloid precursors in the peripheral blood and bone marrow leading to myelosuppression and bone marrow failure.[6] AML will be diagnosed in approximately 22,720 individuals in the United States in 2026, accounting for 1.1% of new cancer cases. An estimated 11,500 individuals will die from AML in 2026, representing 1.8% of cancer deaths.[7]

AML is more common in men than in women, with age-adjusted rates of 5.2 vs 3.7 cases per 100,000 persons.[7] Older adults are more likely to be diagnosed with AML; the median age at diagnosis is 70 years. However, younger adults can also be affected, and nearly one-quarter of diagnoses (22.7%) occur in patients younger than 55 years.

Most AML cases are de novo, arising in the absence of known precipitating factors. The remaining 10% to 20% of diagnoses are encompassed in the heterogeneous category of secondary AML (sAML); these include cases of AML occurring after a prior myeloid disease such as MDS or myeloproliferative neoplasm, AML developing subsequent to cytotoxic chemotherapy or radiation for another disease (treatment-related AML), and AML in patients with germline predisposition.[8] sAML is associated with a worse prognosis than de novo AML, although patient age, comorbidities, cytotoxic treatment history, and molecular characteristics all influence prognosis.

AML Treatment Framework

Establishing the Diagnosis and Disease Biology

Criteria for the diagnosis and classification of AML have changed over the years as more became understood about its pathologic and molecular features. In 2022, 2 different classification systems—the World Health Organization (WHO) criteria and the International Consensus Criteria—were published, classifying myeloid diseases and subtypes based on molecular findings, pathologic features, prior cytotoxic exposure, and genetic predisposition.[9,10]

According to the 2022 WHO criteria, a diagnosis of AML requires at least 20% myeloid blasts in the bone marrow except for the presence of defining genetic abnormalities, for which there is no minimum blast threshold.[9,10] The accurate classification of AML requires morphologic analysis, immunophenotyping including immunohistochemistry and flow cytometry, and molecular analyses including cytogenetics, fluorescence in situ hybridization, and mutation sequencing.[2] In order to individualize initial

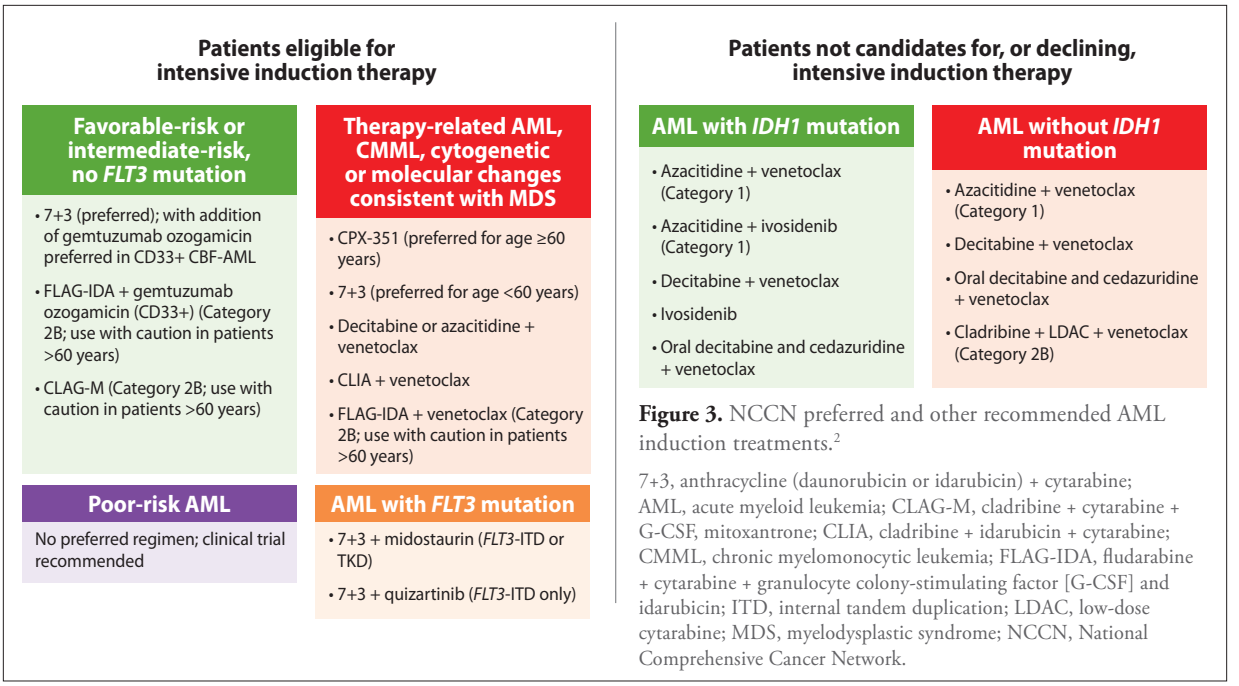


Figure 3. NCCN preferred and other recommended AML induction treatments.[2]

7+3, anthracycline (daunorubicin or idarubicin) + cytarabine; AML, acute myeloid leukemia; CLAG-M, cladribine + cytarabine + G-CSF, mitoxantrone; CLIA, cladribine + idarubicin + cytarabine; CMML, chronic myelomonocytic leukemia; FLAG-IDA, fludarabine + cytarabine + granulocyte colony-stimulating factor [G-CSF] and idarubicin; ITD, internal tandem duplication; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; NCCN, National Comprehensive Cancer Network.

therapy appropriately, molecular and cytogenetic analysis should be expedited to obtain results for immediately actionable mutations or chromosomal abnormalities, with results ideally made available within 1 week.[2]

Assessing the Patient and Defining Treatment Intent

The evaluation for patients with AML includes determination of the ELN 2022 risk category, which stratifies patients based on the risk of recurrence following intensive induction chemotherapy (Figure 1).[1] Adverse-risk AML per the ELN 2022 is significantly more common in older adults vs younger adults and is more common in patients with sAML.[11]

Consideration of patient-related factors, including fitness, PS, goals of care, patient preferences, and social support, are also keys to individualizing AML treatment.[12] This is particularly relevant as additional treatment options are introduced.

Choosing Initial Therapy

The treatment landscape for AML has changed dramatically in recent years, with 8 new agents introduced in newly diagnosed AML alone in the past 10 years (Figure 2).[13] With numerous options available, frontline treatment is selected bases on multiple factors, including disease characteristics, treatment factors, and patient-related factors and preferences.[2] Key determinants include the patient's fitness driven by age and PS and the molecular profile of the disease, which informs the ELN genetic risk classification and guides the use of targeted therapies.[1]

Intensive Chemotherapy: The Clear Choice for Some Patients

Conventionally, intensive induction chemotherapy has been the standard approach for all eligible patients with AML, and it remains the clear choice for selected patients (Figure 3). For example, in younger patients with favorable-risk AML by cytogenetics (CBF-AML) or by molecular mutation profile, intensive chemotherapy is the appropriate strategy as this offers a curative approach.

The standard 7+3 regimen consisting of cytarabine continuous infusion for 7 days with an anthracycline, typically daunorubicin or idarubicin, administered daily for 3 days is frequently used as a standard induction therapy.[2] Gemtuzumab ozogamicin can be added to 7+3 for patients with CD33-positive AML, and is most beneficial in patients with CBF leukemias (t[8;21] or inv[16]). An FLT3 inhibitor is added to 7+3 for patients with *FLT3*-mutated AML. In terms of the FLT3 inhibitors available, midostaurin can be used for patients with *FLT3*-ITD or tyrosine kinase domain mutations, whereas the second-generation FLT3 inhibitor quizartinib should be used only for patients with *FLT3*-ITD mutations.

Intensive Induction for Patients With sAML

As the population is aging, and as the number of individuals exposed to cytotoxic agents for other medical conditions is increasing, the incidence of sAML is also increasing.[14] Outcomes for patients with sAML are poor; patients do not tend to have targetable alterations, and

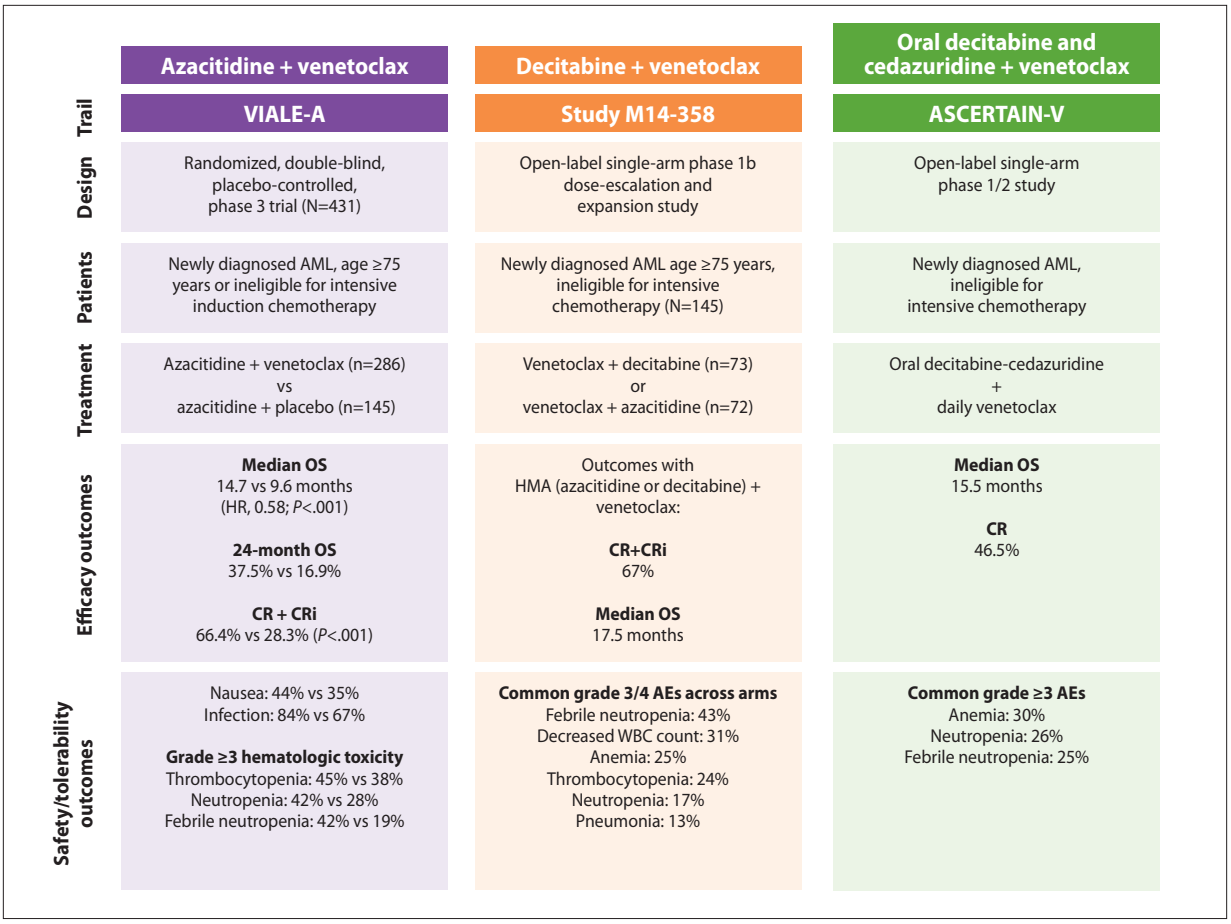


Figure 4. Efficacy and safety of key HMA + venetoclax regimens in newly diagnosed AML.[19-23]

AE, adverse event; AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete count recovery; HMA, hypomethylating agent; HR, hazard ratio; OS, overall survival; WBC, white blood count.

many novel agents have limited efficacy in sAML.

For patients with sAML who are eligible for intensive chemotherapy, the preferred induction therapy for adults is CPX-351, a dual-drug formulation of liposomal cytarabine and daunorubicin that has demonstrated improved response rates and overall survival in patients in this population.[2]

HMA + Venetoclax as a Lower-Intensity Induction Therapy

Approximately one-half of patients with AML are ineligible for intensive induction therapy owing to poor PS, comorbidity, and/or older age.[15] Prior to the introduction of an HMA + venetoclax approach, there were limited treatment options for these patients, and prognosis with an HMA or low-dose cytarabine alone was quite poor. However, the introduction of the HMA + venetoclax combination approach has changed the AML treatment paradigm over the past 5 to 10 years, and it is now the standard treatment for patients who are not candidates for, or who decline, intensive chemotherapy (Figure 3).[2]

Today, 3 HMAs are available for use in combination with venetoclax: the parenterally administered azacitidine and decitabine, and the oral formulation of decitabine and cedazuridine.[16-18] Each of these agents has been evaluated in combination with venetoclax and is an option for patients with newly diagnosed AML (Figures 4 and 5).[19-23]

Early Evidence for HMA + Venetoclax

The US Food and Drug Administration initially granted accelerated approval for the use of azacitidine or decitabine + venetoclax based on response rates demonstrated in the open-label, nonrandomized study M14-358 in patients with newly diagnosed AML who were at least 75 years of age or had comorbidities precluding the use of intensive induction chemotherapy.[19] In that trial, venetoclax + either azacitidine or decitabine was associated with a complete remission (CR) or CR with incomplete blood count recovery (CRi) of 67%. The median overall survival (OS) was 17.5 months.

Parenteral administration

Azacitidine

Lyophilized powder, 100-mg single-dose vials

Starting dose: 75 mg/m^2 by SC or IV injection daily for 7 days. Repeat cycles every 4 weeks.

Dose may be increased to 100 mg/m^2 if no beneficial effect is seen after 2 treatment cycles and no toxicity other than nausea and vomiting has occurred.

Warnings/precautions: Risks of substitution with other azacitidine products; anemia, neutropenia, and thrombocytopenia; hepatotoxicity; renal toxicity; tumor lysis syndrome; embryo-fetal toxicity

Decitabine

Lyophilized powder, 50-mg single-dose vial for reconstitution

5-day regimen: 20 mg/m^2 by continuous IV infusion over 1 hour repeated daily for 5 days. Repeat cycle every 4 weeks.

Warnings/precautions: Neutropenia and thrombocytopenia; embryo-fetal toxicity

Oral administration

Decitabine/cedazuridine

Tablets contain 35 mg decitabine and 100 mg cedazuridine; 1 tablet taken once daily on days 1-5 of each 28-day cycle

Warnings/precautions: Severe myelosuppression, including fatal adverse reactions and infectious complication; embryo-fetal toxicity

Dose modification approach to reduce prolonged myelosuppression with DEC-C + venetoclax (based on phase 2B of ASCERTAIN-V)

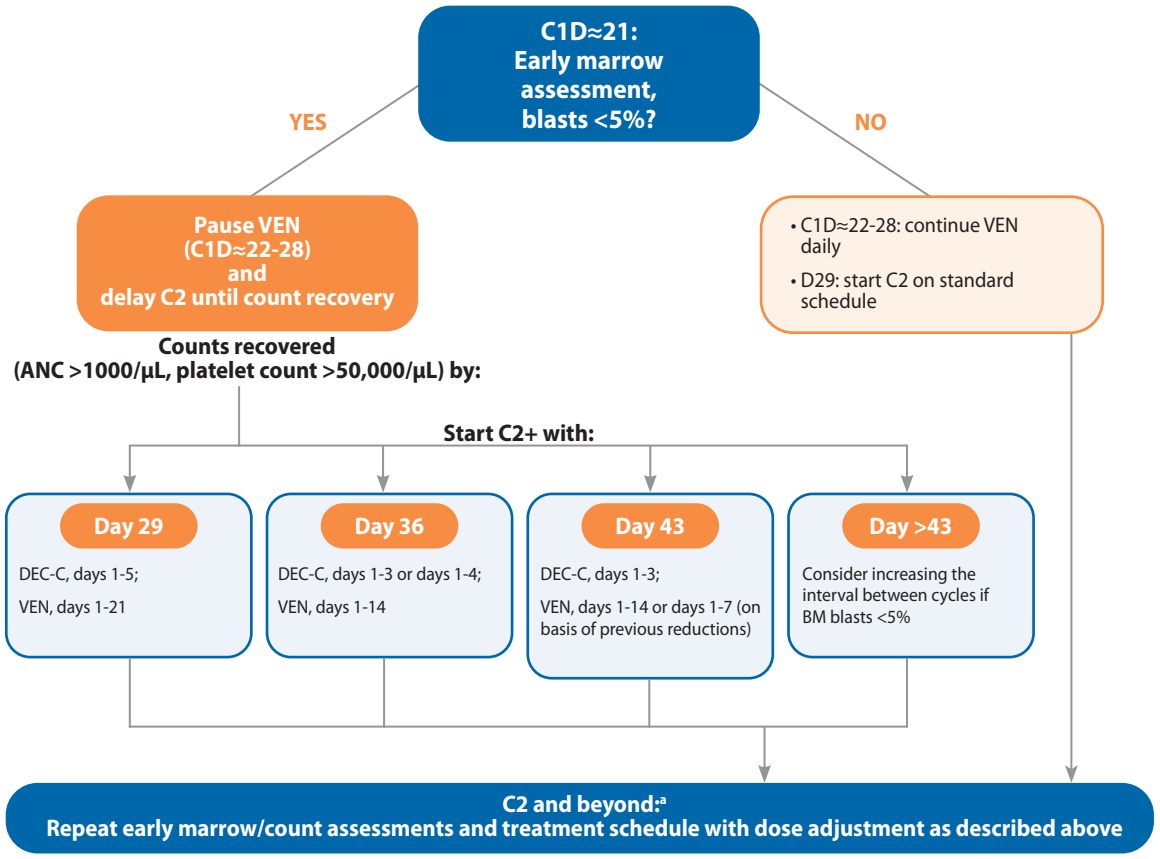


Figure 5. In the clinic dosing summary of HMAs used in newly diagnosed AML.[16-18]

AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; C, cycle; D, day; DEC-C, decitabine and cedazuridine; HMA, hypomethylating agent; IV, intravenous; SC, subcutaneous; VEN, venetoclax.

[a]Ongoing cycles of treatment continued until disease progression, unacceptable toxic effects, or patient withdrawal.

Table. Overview of PARADIGM Trial Comparing Intensive Chemotherapy vs Lower-Intensity Therapy in Patients With Newly Diagnosed AML[3]

Trial design	**Multicenter, randomized, phase 2 trial**	
Patient population	Adults with newly diagnosed AML eligible for intensive induction; excluded CBF-AML, *FLT3*-mutated AML, and *NPM1*-mutated AML (except in patients age ≥60 years)	
Treatment groups	**Azacitidine + venetoclax (n=86)**	**Intensive chemotherapy (n=86)**
Primary endpoint: median EFS	14.5 months	6.2 months
	HR: 0.57 (95% CI, 0.39-0.84; *P*=.002)	
Grade ≥3 infection	28%	41%
Grade ≥3 hemorrhage	2%	12%
Patients proceeding to transplant	68%	40%

AML, acute myeloid leukemia; CBF, core binding factor; EFS, event-free survival HR, hazard ratio.

VIALE-A: Azacitidine + Venetoclax

These findings provided a rationale for the randomized, phase 3 VIALE-A trial, which compared azacitidine + venetoclax against azacitidine + placebo in 431 patients with newly diagnosed AML who were at least 75 years of age or otherwise ineligible for intensive induction chemotherapy.[20,21] In that trial, azacitidine + venetoclax was associated with a significant improvement over azacitidine + placebo in OS (14.7 vs 9.6 months; hazard ratio [HR], 0.58; 95% CI, 0.52-0.85; *P*<.001) and an improvement in the composite CR rate, including CR and CRi (66.4% vs 28.3%; *P*<.001).

Adverse events (AEs) in VIALE-A included nausea, reported in 44% of patients receiving azacitidine + venetoclax and 35% of patients receiving azacitidine + placebo, and grade 3 or higher thrombocytopenia (45% vs 38%), neutropenia (42% vs 28%), and febrile neutropenia (42% vs 19%). The rate of any-grade infections was 84% and 67%, respectively.

ASCERTAIN-V: Oral Decitabine and Cedazuridine + Venetoclax

More recently, results were reported from the phase 1/2 open-label, multicenter ASCERTAIN-V trial evaluating the all-oral regimen of decitabine and cedazuridine + venetoclax in patients with AML who were 75 years of age or older or otherwise ineligible for intensive chemotherapy.[22] Decitabine and cedazuridine, available in a fixed-dose formulation, has been shown to have a pharmacokinetic exposure equivalent to that of intravenous decitabine.[23]

The ASCERTAIN-V trial enrolled 189 patients across its phase 1 (n=30), phase 2a (n=58), and phase 2b (n=101) portions. Following the observation of myelosuppression in phase 1, the phase 2b study used early bone marrow assessments to help mitigate myelosuppression through individualized dose modifications. Blast reductions and the timing of count recovery were used to guide the subsequent dosing schedule.[22] Implementation of the early bone marrow assessment was associated with a trend toward reduced dosing of venetoclax over time and subsequent reductions in decitabine and cedazuridine over time. No drug-drug interactions between decitabine and cedazuridine and venetoclax were observed.

In the pivotal phase 2b trial, oral decitabine and cedazuridine + venetoclax was associated with a CR rate of 47%, a CR + CRi rate of 63%, and a median OS of 15.5 months. The median OS improved over time in the trial, which investigators attributed to the implementation of individualized dose and schedule changes to mitigate myelosuppression.

In the phase 2b study, serious AEs (SAEs) occurred in 84% of patients overall and in 62% of patients with a response in cycle 1 or 2. Common grade 3 or higher AEs included anemia (30%), neutropenia (26%), and febrile neutropenia (25%). The 30-day and 60-day mortality rates were 3% and 10%, respectively.

Considerations for Patients With *IDH1*-Mutated AML

Mutations in *IDH1* occur in approximately 10% of patients with AML.[21] For patients receiving intensive chemotherapy, IDH1 inhibitors are currently not added to induction therapy. A large randomized study of intensive chemotherapy +/- ivosidenib should have a report out within the year. However, for patients receiving lower-intensity induction therapy, the presence of an *IDH1* mutation is considered in the treatment decision, as there are 2 approved standard-of-care combinations for this genomically defined subset.[2]

The VIALE-A trial included patients with *IDH1* and *IDH2* mutations. Subset analyses reported particularly

In the Clinic...

Data from the PARADIGM trial suggest that just because a patient can tolerate intensive chemotherapy does not mean that intensive chemotherapy is necessarily the best induction regimen for them. Some patients may be able to bridge to transplant with an HMA + venetoclax, allowing them to forgo the toxicity and burden of intensive chemotherapy. Moreover, according to the PARADIGM trial, some patients may in fact be more likely to proceed to SCT after an HMA + venetoclax than with intensive chemotherapy.

As a result, a key question in AML management today is who should optimally receive an HMA + venetoclax and who should receive intensive chemotherapy. Use of the HMA + venetoclax approach is increasingly being utilized in the real world in patients who could tolerate intensive chemotherapy. It is essential that in younger, fitter patients, an HMA + venetoclax is used as a bridge to remission to proceed to a curative transplant. In contrast, for older patients who are not eligible for SCT, an HMA + venetoclax can be continued indefinitely, as long as the therapy is beneficial.

favorable outcomes with azacitidine + venetoclax in patients with *IDH2* mutations.[24] Azacitidine + venetoclax does remain a Category 1–recommended option in NCCN guidelines for patients with *IDH1*-mutated AML.[2]

The other Category 1 recommendation for patients with *IDH1*-mutated AML is the combination of the IDH1 inhibitor ivosidenib + azacitidine. In the randomized, phase 3 AGILE trial, ivosidenib + azacitidine was associated with significant improvements over placebo + azacitidine in event-free survival (EFS; 12-month EFS rate, 37% vs 12%; HR, 0.33; 95% CI, 0.16-0.69; *P*=.002) and in OS (24.0 vs 7.9 months; HR, 0.44; 95% CI, 0.27-0.73; *P*=.001).[25]

Common grade 3 or higher AE rates were febrile neutropenia (reported in 28% of patients receiving ivosidenib + azacitidine and 34% receiving placebo + azacitidine) and neutropenia (27% vs 16%). Rates of any-grade infection were 28% and 49%, respectively; differentiation syndrome occurred in 14% and 8% of patients, respectively.

Lower-Intensity Therapy as a Bridge to Allogeneic SCT: A New PARADIGM in AML?

Conventionally, patients intending to proceed to potentially curative allogeneic SCT receive intensive chemotherapy as induction therapy for AML. However, the introduction of reduced intensity conditioning regimens has allowed for consideration of SCT in a wider patient population. There are also significant downsides to intensive chemotherapy in terms of toxicity and its requirements for extended hospitalizations. Moreover, there is a need for more effective induction therapy for patients with adverse-risk genetic factors such as MDS-associated mutations (eg, *ASXL1*, splicing factor mutations), complex cytogenetics, and *TP53* mutations.

Retrospective and real-world data have shown that patients can successfully proceed to allogeneic SCT following induction therapy with an HMA + venetoclax.[26,27] However, data prospectively comparing an HMA + venetoclax against intensive chemotherapy were lacking, until the randomized, phase 2 PARADIGM trial compared the 2 approaches in patients with AML eligible for intensive chemotherapy (Table).[3]

In the randomized, phase 2 PARADIGM trial, 172 patients with newly diagnosed AML who were eligible for intensive chemotherapy were randomly assigned to azacitidine + venetoclax (n=86) or intensive chemotherapy (n=86).[3] The median age of enrolled patients was 64 years; 72% of patients had adverse-risk AML according to the ELN 2022 classification. The trial excluded patients with CBF-AML, *FLT3* mutations, and patients with *NPM1* mutations who were younger than age 60.

After a median follow-up of 21.9 months, azacitidine + venetoclax was associated with a significant improvement over intensive chemotherapy in EFS (14.5 vs 6.2 months; HR, 0.57; 95% CI, 0.39-0.84; *P*=.002) and an improvement in the percentage of patients proceeding to allogeneic SCT (68% vs 40%). In the safety analysis, azacitidine + venetoclax was associated with reductions over intensive chemotherapy in rates of grade 3 or higher infection (28% vs 41%) and grade 3 or higher hemorrhage (2% vs 12%).

MRD for Monitoring Response to Therapy

Patients receiving intensive chemotherapy should be monitored for MRD, which detects the presence of leukemic cells more sensitively than morphologic methods.[2] MRD positivity is associated with a higher risk of relapse, even in those with favorable risk features such as CBF or an *NPM1* mutation.[4,5]

The most common methods for assessing MRD are quantitative assays such as real-time quantitative PCR (RQ-PCR) and multicolor flow cytometry to detect specific MRD immunophenotypes. Optimally, the initial MRD assessment should be conducted on a dedicated bone marrow aspirate pull.[2] After an MRD-negative

In the Clinic...

In patients who are not eligible for SCT, an HMA + venetoclax regimen is administered as long as the regimen is effective and tolerable. Some patients in my practice have been on these regimens for multiple years, which speaks to the potential long-term tolerability of these regimens.

The availability of an all-oral HMA + venetoclax regimen with the use of oral decitabine and cedazuridine is an important option for patients, as this reduces the need for intravenous therapies, and the time and resources involved, while preserving therapeutic efficacy.

It has been reported that among older adults with AML receiving azacitidine- or venetoclax-based regimens, approximately 42% of their days after the diagnosis are spent at an oncology/infusion clinic or an emergency department with the median duration of infusion visits being 194 minutes.[31] If we as physicians can help patients have more good days at home, and spend less time at infusion centers, that will help improve patients' quality of life.

remission in the bone marrow is attained, MRD can be assessed in peripheral blood by monitoring for the presence of *PML::RAR* alpha, *NPM1*, *CBFB::MYH11*, and *RUNX1T1.*

NCCN guidelines recommend RQ-PCR for detecting *PML::RAR* alpha, *NPM1*, *CBFB::MYH11*, and *RUNX1::RUNX1T1,* and a next-generation sequencing–based targeted deep-sequencing assay to detect *FLT3*-ITD. The threshold of detection should be considered, as these vary based on the technique used and the AML subgroup.

For patients with *NPM1*-mutated AML, *CBFB::MYH11*, and *RUNX1:RUNX1T1* AML, MRD assessment should be performed after 2 cycles of intensive chemotherapy and every 6 to 12 weeks for 24 months. For patients receiving venetoclax-based lower-intensity regimens, MRD negativity may take longer, including up to 4 to 6 cycles of therapy.

In patients with *NPM1*-mutated AML receiving venetoclax-based lower-intensity therapy, *NPM1* MRD is strongly prognostic.[28] Accordingly, *NPM1* monitoring by RQ-PCR should be performed every 6 to 12 weeks using bone marrow or peripheral blood in patients receiving venetoclax-based therapy.[2] In patients with *NPM1*-mutated, *CBFB::MYH11*, and *RUNX1::RUNX1T1*-mutated AML, the presence of persistently positive MRD after induction and/or consolidation warrants consideration of alternative therapies such as allogeneic SCT or a clinical trial.[2] Postinduction MRD positivity has also been shown to identify patients with *NPM1*-mutated AML who obtain a significant OS benefit from allogeneic SCT in first remission.[29]

Looking ahead, triplet therapy incorporating an HMA or low-dose cytarabine, venetoclax, and a targeted therapy (directed against FLT3, IDH, or menin) is emerging as potential advancement.[30] Triplets are associated with an increased risk of myelosuppression, and triplet therapy will likely require careful selection, particularly in older patients, and proactive use of dose adjustments.

Dose Modification and Practical Management: Managing HMA + Venetoclax

Proactive monitoring, including the use of early bone marrow assessments, to guide use of dose and schedule adjustments are critical for optimizing the use of an HMA + venetoclax in practice.[19] Patients may require extended treatment cycles (5 to 6 weeks) and may also require granulocyte colony-stimulating factor (G-CSF) support to minimize periods of neutropenia. These proactive approaches allow the patient to maximize time on therapy and minimize toxicity.

For patients receiving oral decitabine and cedazuridine + venetoclax, an algorithm for managing dosing based on early bone marrow assessments at the end of cycle 1 has been proposed (Figure 5). The recommended dosage of decitabine and cedazuridine in combination with venetoclax is 1 tablet once daily on days 1 to 5 each cycle. I tend to administer venetoclax for 21 days in the first cycle, then do a bone marrow assessment at around days 21 to 28. This will often reveal a blast reduction (<5%), in which case the treatment should be held in order for counts to recover. The timing of count recovery guides the starting schedule for subsequent cycles.

I sometimes find that, after several cycles of oral decitabine and cedazuridine + venetoclax, platelet counts are not recovering to the same extent, or patients are requiring more G-CSF support to reach sustained neutrophil counts. In these patients, I will reduce the number of days that patients receive each agent. Many of my patients who have been receiving the all-oral regimen for a year or longer receive decitabine and cedazuridine for 3 days per cycle rather than 5 days, and the duration of venetoclax is reduced to 14 days per cycle. However, the specific schedules vary across individual patients.

Back to the Clinic . . .

Let's revisit our initial cases and consider the factors that influence treatment decisions in each of these scenarios. For

younger patients who are eligible for intensive chemotherapy, intensive chemotherapy followed by SCT in first remission is the preferred therapy. This includes the patient described with proliferative monocytic AML with a *RAS* mutation.

For a younger patient with *NPM1/FLT3*-mutated AML, the treatment choice would also be intensive chemotherapy. Although the PARADIGM trial demonstrated superior efficacy with an HMA + venetoclax compared with intensive chemotherapy in fit patients with newly diagnosed AML, the trial excluded patients younger than age 60 with *NPM1* mutations and all patients with *FLT3*-mutated AML.

Thus the findings are not broadly applicable to the fit AML population. Conversely, the PARADIGM trial does suggest that an HMA + venetoclax followed by allogeneic SCT in first remission could be a consideration for patients with adverse-risk AML and may increase the likelihood of proceeding to SCT.

An HMA + venetoclax remains the standard of care for patients not eligible for intensive induction therapy. Three HMAs are now available for use in combination with venetoclax: the parenterally administered azacitidine and decitabine, and the oral formulation of decitabine and cedazuridine. The oral formulation of decitabine and cedazuridine provides the distinct advantages of reducing the need for intravenous therapies, and the time and resources involved, while preserving therapeutic efficacy. Appropriate mitigation and management of toxicities, including the use of dose and schedule adjustments and supportive care, maximizes the therapeutic benefit of an HMA + venetoclax regimens. Looking ahead, triplet regimens may provide additional more effective induction options in the future.

Disclosures

Dr DiNardo has received research support (funds directly to the institution) from AbbVie, Astex, Auron Therapeutics, Bristol-Myers Squibb, BeiGene, Ellipses Pharma, Jazz, Kura, PMV, Remix, Rigel, Servier, Schrödinger, SillaJen, and SystImmune; and is a consultant for and has served on the advisory boards of (all approved and within institutional COI policy limits) AbbVie, Astellas, AstraZeneca, BeiGene, Bristol-Myers Squibb, Ellipses Pharma, Genentech, Genmab, GlaxoSmithKline, Molecular Partners, Rigel, Ryvu, Schrödinger, Servier, Solu, and Syndax.

References

1. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377.
2. NCCN guidelines: acute myeloid leukemia. V2026.
3. Fathi AT, Perl AE, Fell GG, et al. Azacitidine-venetoclax or induction chemotherapy for acute myeloid leukemia. *N Engl J Med*. 2026;395(9):845-858.
4. Ivey A, Hills RK, Simpson MA, et al. Assessment of minimal residual disease in standard-risk AML. *N Engl J Med*. 2016;374(5):422-433.
5. Short NJ, Zhou S, Fu C, et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. *JAMA Oncol*. 2020;6:1890-1899.
6. Vakiti A, Reynolds SB, Mewawalla P. Acute Myeloid Leukemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing; April 27, 2024.
7. National Cancer Institute. Cancer stat facts: leukemia – acute myeloid leukemia (AML). https://seer.cancer.gov/statfacts/html/amyl.html Accessed October 13, 2026.
8. Marconi G, Rondoni M, Zannetti BA, et al. Novel insights and therapeutic approaches in secondary AML. *Front Oncol*. 2024;14:1400461.
9. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*. 2022;36(7):1703-1719.
10. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228.
11. Rausch C, Rothenberg-Thurley M, Dufour A, et al. Validation and refinement of the 2022 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. *Leukemia*. 2023;37(6):1234-1244.
12. Venditti A, Palmieri R, Maurillo L, et al. Fitness assessment in acute myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood Adv*. 2025;9(9):2207-2220.
13. Shimony S, Stahl M, Stone RM. Acute myeloid leukemia: 2025 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2025;100(5):860-891.
14. Green SD, Wang ES. How I treat secondary acute myeloid leukemia. *Blood*. 2025;145(12):1260-1272.
15. Garcia-Manero G, Zhao R, LeBlanc TW. Treatment outcomes and unmet needs in patients with acute myeloid leukemia (AML) who are ineligible for intensive induction chemotherapy (IC): a systematic literature review (SLR). *J Clin Oncol*. 2026;44(16_suppl):e18517.
16. INQOVI (decitabine and cedazuridine) full prescribing information. Princeton, NJ: Taiho Oncology, Inc. Revised May 2026.
17. VIDAZA (azacitidine for injection) full prescribing information. Summit, NJ: Celgene Corporation. Revised May 2022.
18. DACOGEN (decitabine for injection) full prescribing information. Dublin, CA: Astex Pharmaceuticals, Inc. Revised December 2018.
19. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood*. 2019;133(1):7-17.
20. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.
21. Pratz KW, Jonas BA, Pullarkat V, et al. Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. *Am J Hematol*. 2024;99(4):615-624.
22. Roboz GJ, Zeidan AM, Mannis GN, et al. All-oral treatment of newly diagnosed acute myeloid leukemia. *N Engl J Med*. 2026;394(21):2107-2116.
23. Garcia-Manero G, McCloskey J, Griffiths EA, et al. Oral decitabine-cedazuridine versus intravenous decitabine for myelodysplastic syndromes and chronic myelomonocytic leukaemia (ASCERTAIN): a registrational, randomised, crossover, pharmacokinetics, phase 3 study. *Lancet Haematol*. 2024;11(1):e15-e26.
24. Huber S, Goessweiner F, Walter W, et al. IDH1- and IDH2-mutated myeloid neoplasms: mutational pattern, clonal hierarchy, and the role in AML transformation. *Blood Adv*. 2026;10(10):3554-3564.
25. Pollyea DA, DiNardo CD, Arellano ML, et al. Impact of venetoclax and azacitidine in treatment-naïve patients with acute myeloid leukemia and *IDH1/2* mutations. *Clin Cancer Res*. 2022;28(13):2753-2761.
26. Rautenberg C, Stelljes M, Bug G, et al. Pretransplantation hypomethylating agents and venetoclax in acute myeloid leukemia patients: a real-world analysis from the Cooperative Transplant Study Group. *Transplant Cell Ther*. 2026;32(5):565-574.
27. Winters AC, Bosma G, Abbott D, et al. Outcomes are similar after allogeneic hematopoietic stem cell transplant for newly diagnosed acute myeloid leukemia patients who received venetoclax + azacitidine versus intensive chemotherapy. *Transplant Cell Ther*. 2022;28(10):694.e1-694.e9.
28. Othman J, Tiong IS, O'Nions J, et al. Molecular MRD is strongly prognostic in patients with NPM1-mutated AML receiving venetoclax-based nonintensive therapy. *Blood*. 2024;143(4):336-341.
29. Othman J, Potter N, Ivey A, et al. Postinduction molecular MRD identifies patients with NPM1 AML who benefit from allogeneic transplant in first remission. *Blood*. 2024;143(19):1931-1936.
30. Jen WY, Lachowiez CA, Marvin-Peek J, et al. Optimizing lower intensity triplet therapy in acute myeloid leukemia: a practical guide. *Blood Cancer J*. 2025;16(1):6.
31. Jensen CE, Heiling HM, Beke KE, et al. Time spent at home among older adults with acute myeloid leukemia receiving azacitidine- or venetoclax-based regimens. *Haematologica*. 2023;108(4):1006-1014.

