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Tailoring intensive and less-intensive treatment in acute myeloid leukemia ☆

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ABSTRACT

After decades of therapeutic inertia, the treatment of acute myeloid leukemia (AML) has seen remarkable improvements over the past ten years. Scientific discoveries have substantially enhanced the understanding of AML disease biology. The improved knowledge about leukemic transformation and disease mechanisms in this heterogeneous group of aggressive blood cancers has resulted in enhanced biologically defined risk prognostication and the development of novel targeted therapeutic agents. Many of these mechanism-based therapeutics have entered clinical development, with some getting approval for the treatment of specific genetically defined AML subgroups in patients fit or unfit for intensive chemotherapy-based treatment. As a result, the European LeukemiaNet (ELN) expert panel has established a distinct genetic risk stratification for AML patients undergoing less-intensive treatment, which incorporates targeted drugs (ELN 2024). The ELN 2022 risk categories, designed for predicting outcomes following intensive chemotherapy, did not adequately assess responses to these new regimens. In this review, we discuss the current state-of-the-art approaches in both intensive and less-intensive front-line treatments for AML, highlighting the most promising therapeutic innovations.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous and aggressive group of malignant neoplasms that originate from early hematopoietic progenitor cells and are characterized by rapid proliferation and loss of the ability to differentiate.[1] The leukemic cells displace normal hematopoiesis, often causing a dependency on red blood cell and platelet transfusions, alongside life-threatening infections that necessitate immediate therapeutic intervention.

Intensive chemotherapy with cytarabine and anthracyclines has been the standard treatment for AML since the 1970s.[2,3] Aside from the introduction of allogenic stem cell transplantation (allo-SCT), significant therapeutic advancements have been limited for nearly 5 decades (reviewed in[4]). Up until the early 2000s, long-term survival rates remained low, with only minor improvements

Abbreviations: ADC, antibody-drug conjugate; ALLO-SCT, allogenic stem cell transplantation; AML, acute myeloid leukemia; AZA, azacitidine; BLEX, bleximenib; BM, bone marrow; CBF, core-binding-factor; CCR, conventional care regimen; CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DEC, decitabine; DEC–C, decitabine/cedazuridine; DLT, dose-limiting toxicity; DS, differentiation syndrome; EMA, European Medicines Agency; ELN, European LeukemiaNET; FDA, Food and Drug Administration; FLT3i, FLT3 inhibitor; *FLT3* ITD, FLT3 internal tandem duplication; *FLT3* TKD, FLT3 tyrosine kinase domain; GO, Gemtuzumab Ozogamycin; HMA, hypomethylating agents; IC, intensive chemotherapy; IDH-DS, IDH-differentiation syndrome; IDHi, IDH-inhibitor; *IDH1*-mut, isocitrate dehydrogenase 1 mutation; IVO, ivosidenib; ITT, intention-to-treat; *KMT2Ar*, *KMT2A* rearrangement; LDAC, low-dose cytarabine; LISA, lisaftoclax; LTFU, long-term follow-up; mOS, median overall survival; MRD, minimal/measurable residual disease; ND, newly diagnosed; NPM1m, NPM1 mutation; OLU, Olutasidenib; ORR, overall response rate; OS, overall survival; PBO, placebo; PVEK, pivekimab sunirine; R/R, relapsed/refractory; RCT, randomized controlled trial; RFS, relapse-free survival; REV, revumenib; SC, subcutaneous; sNDA, supplemental new drug application; TLS, tumor lysis syndrome; VEN, venetoclax; ZIFTO, ziftomenib.

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mainly due to advancements in allo-SCT and supportive care, including antifungal prophylaxis and management of infections.[5]

Recent scientific discoveries have ushered in a new era after decades of therapeutic stagnation in AML. Genetic sequencing studies have enhanced our understanding of disease pathogenesis, have led to the development of more precise prognostication tools, and have identified new molecular targets for therapy.[3,6-12] Drug developments exploiting these mechanisms have been introduced into clinical investigation since then, culminating in the approval of midostaurin in 2017, which became the first targeted drug shown to improve survival in *FLT3*-mutated AML patients in combination with chemotherapy.[13] Concurrently, targeted therapeutic developments have occurred at an unparalleled pace. Although many developments are still under clinical investigation, AML survival rates have started to improve substantially from only 18.5% in the year 2000 to 32.9% in 2023 in the U.S.[14]

In this review, we explore the evolving frontline treatment landscape for AML, addressing therapies for both fit and unfit patients. We highlight the most promising advancements from ongoing clinical trials that are set to redefine AML treatment protocols and enhance patient outcomes.

AML Patients considered fit for intensive therapy

Fitness assessment, patient selection, and risk stratification

Assessing fitness is required before assigning patients to first-line treatment. It remains a challenge in the usually elderly AML patient population, with a median age at diagnosis of 72 years in 1 registry.[15] While several co-morbidity indices and scoring systems are used in clinical practice,[16] no single assessment tool has been proven to be superior to others.[17] However, the criteria defined by Ferrara and co-workers are widely accepted as reasonably selecting unfit patients for clinical trials.[18] Additional geriatric assessment may facilitate decision making, particularly in elderly borderline-fit patients with moderate-grade co-morbidities.[17,19]

While intensive therapy for AML patients considered fit is generally given with curative intent, the selection of the treatment regimen is based on the most recent 2022 European LeukemiaNET (ELN) genetic risk classification at diagnosis (Table 1).[3] As discussed below in more detail, the baseline stratification at diagnosis is complemented by measurable residual disease (MRD) assessment to assign the post-remission therapy to specific AML subtypes.[20] Initial intensive induction treatment is administered, aiming at inducing a complete remission (CR), followed by consolidation treatment to deepen the response and to eradicate the disease.

Current standard-of-care intensive treatment

Induction treatment

Intensive chemotherapy combining cytarabine and an anthracycline remains a state-of-the-art backbone for induction treatment. It is most commonly administered as a conventional "7 + 3" regimen (cytarabine 100-200mg/m^2/d continuously IV d1-7 and daunorubicin 60 mg/m^2 IV d1-3; or idarubicin 12 mg/m^2 IV d1-3). In US centers, the daunorubicin dosage frequently used is 90 mg/m^2, although 2 prospective randomized trials did not show superiority over 60 mg/m^2.[21,22] For specific AML subtypes, it has become standard-of-care to add targeted agents to the intensive chemotherapy regimens.

FLT3 inhibitors. The multi-kinase inhibitor midostaurin was the first targeted agent shown to improve overall survival (OS) when given with first-line 7 + 3 induction and high-dose cytarabine consolidation followed by 12-month maintenance in younger patients (<60 years of age) with *FLT3*-mutated AML.[13] In the registrational randomized phase III CALGB 10603/ RATIFY trial, median OS was 74.7 months with midostaurin vs 25.6 months. with placebo (HR: 0.78, $P = .009$).[13] Based on these data, midostaurin was approved for AML in this indication in the U.S. and Europe (maintenance not approved in the US). Midostaurin has been used as standard since then, although recently presented long-term follow-up data

Table 1
2022 ELN risk classification by genetics at initial diagnosis.

Risk category[b]	Genetic Abnormality
Favorable (ELN1)	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* • Mutated *NPM1* without *FLT3*-ITD[a] • bZIP in-frame mutated *CEBPA*[b]
Intermediate (ELN2)	• Mutated *NPM1*[b,d] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[c] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse (ELN3)	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[d] • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,[e] monosomal karyotype[f] • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*[g] • Mutated *TP53*[h]

[a] AML with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.
[b] Only in-frame mutations affecting the basic leucine zipper (bZIP) region of *CEBPA*, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.
[c] The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
[d] Excluding *KMT2A* partial tandem duplication (PTD).
[e] Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with 3 or more trisomies (or polysomies) without structural abnormalities.
[f] Monosomal karyotype: presence of 2 or more distinct monosomies (excluding loss of X or Y), or 1 single autosomal monosomy in combination with at least 1 structural chromosome abnormality (excluding core-binding factor AML).
[g] For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
[h] *TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

(10 years) indicate that the sustained OS benefit appears slightly attenuated compared to the earlier reports (43.7% vs 38.6%), likely due in part to aging.[23]

The more potent and selective *FLT3*-ITD inhibitor quizartinib was recently approved in combination with intensive chemotherapy for the treatment of *FLT3*-ITD-positive AML patients based on the randomized phase 3 QuANTUM-First trial.[24] Quizartinib approval in the U.S. and Europe was based on the reported significant OS benefit for the quizartinib vs the placebo arm (median OS: 31.9 months vs 15.1 months, HR 0.78, $P = .032$). While the study also allowed recruitment of elderly patients until 75 years of age a subgroup analysis for OS indicates that quizartinib may be most active in younger patients with high *FLT3*-ITD allelic ratio and *NPM1* co-mutation[24] Available data suggest that higher rates of ≥ grade 3 adverse events, particularly sepsis-related deaths, may have contributed to the smaller OS gain within the elderly patients.[25] These considerations, along with the *FLT3*-ITD allelic-ratio and *NPM1* co-mutation as well as concerns regarding compound-specific adverse effects, such as nausea (midostaurin) or QT-prolongation and myelosuppression (quizartinib), may guide clinicians in choosing one of these FLT3 inhibitors for individual patients in the absence of a head-to-head comparison.

Gemtuzumab Ozogamycin (GO), an anti-CD33 antibody-drug conjugate linked to the cytotoxic agent calicheamicin-, is approved in Europe and the U.S. for first-line treatment of CD33-expressing AML in combination with conventional chemotherapy. Initially approved in the U.S. as a single agent, GO was withdrawn and later re-approved in fractionated lower doses in combination regimens. The re-approval was based on data from the randomized ALFA-0701-trial that found an event-free survival (EFS) benefit for the GO-arm that was limited to patients with favorable or intermediate-risk cytogenetics.[26,27] While 4 other randomized trials failed to demonstrated a survival benefit for the addition of GO to chemotherapy,[28-31] a meta-analysis that integrated all 5 randomized trials found a survival benefit, particularly pronounced in patients with core-binding-factor (CBF) AML (harboring a t(8;21), or inv(16), or t(16;16)); with an absolute survival benefit of 20.7%).[32] However, it has been criticized that in this meta-analysis, the 5-year OS for the patients with CBF-AML not receiving GO was surprisingly low, with 55%. Another randomized trial that assessed GO in addition to intensive chemotherapy in a homogenous cohort of *NPM1*-mutated AML failed to meet the primary endpoints of EFS and OS, likely due in part to a higher early death rate in the GO arm, particularly in patients above the age of 70.[33] However, the addition of GO resulted in a significantly lower cumulative incidence of relapse (CIR at 2-years: 25% vs 37% for the GO and the standard arm, respectively; HR 0.65, $P = .0028$), an observation consistent with the view that the addition of GO may help to avoid the need for salvage treatment options in those patients.[34] No study demonstrated a benefit for the addition of GO in patients with adverse-risk cytogenetics.

CPX-351, a liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 molar ratio, can be considered the current standard-of-care treatment for fit patients with therapy-related AML and AML with myelodysplasia-related changes.[35,36] This is supported by an open-label randomized phase 3 trial demonstrating significantly longer OS of CPX-351 compared with standard 7 + 3 chemotherapy (5-year OS: 18% vs 8%; HR 0.7; $P = .005$) and improved CR rates (47.7% vs 33.3%, $P = .016$) in patients 60 to 75 years of age with high-risk AML.[35,36] Of note, an exploratory landmark survival analysis from the time of transplant favored CPX-351 over 7 + 3 as initial treatment, with an estimated 3-year OS of 56% vs 23%. Although neutrophil and platelet recovery time were longer with CPX-351, there was a trend towards lower 30-day and 60-day mortality with CPX-351 compared to 7 + 3 (5.9% vs 10.6%, and 13.7% vs 21.2%, $P = .097$, respectively).[36] While CPX-351 caused less mucositis, the proportions of patients experiencing grade 1-2 or grade ≥ 3 adverse events were comparable between the groups. However, the longer time that CPX-351 patients remained on study confounded these numbers. Calculating the median rate of adverse events per patient-year on study to normal aimed at normalizing this effect demonstrated a lower number of AEs for CPX-351 (75.68) vs 7 + 3 (87.22).[35] An exploratory subgroup analysis of the UK NCRI AML19 trial comparing CPX-351 with FLAG-Ida in younger adults with high-risk AML suggests that patients with AML with myelodysplasia-related gene mutations benefit from CPX-351, as evidenced by a longer median OS (38.4 vs 16.3 months).[37] Another randomized, open-label phase 3 trial compares CPX-351 to 7 + 3 chemotherapy in patients aged 18 years and older with 2017 ELN intermediate- and adverse-risk AML. Results from this study will provide insights into whether CPX-351 is beneficial for other AML subsets (NCT03897127).

Post-remission consolidation strategies, including allogenic stem cell transplantation

Post-remission strategies for fit patients include conventional consolidation chemotherapy or allo-SCT. The decision for one of these approaches is based on the risk-benefit assessment, weighing the expected relapse risk against transplant-related mortality rates. Allo-SCT-based consolidation is recommended for patients with an estimated relapse risk higher than 35% to 40% (reviewed in[38]), which generally applies to patients assigned to intermediate- or adverse-risk ELN genetic risk categories,[3] except patients with *NPM1*-mutated AML with concurrent *FLT3*-ITD, where the choice to proceed with allo-SCT in CR1 may be guided by molecular MRD measurements.[20]

Also, persistent MRD in remission at specific timepoints, even in patients within favorable ELN risk categories, is recognized as an indication for proceeding with allo-SCT when the estimated relapse-risk exceeds 35% to 40%. The best example for such a scenario is *NPM1*-mutated AML patients, but persistent molecular *NPM1*-mutated MRD in the peripheral blood after 2 cycles of initial therapy.[20,39] In addition, recent studies have shown that paired-end next-generation sequencing (NGS)-based *FLT3*-ITD MRD assays are effective tools for identifying patients at high risk of relapse after intensive chemotherapy with and without midostaurin, and before undergoing allo-SCT.[40-42] These findings suggest that NGS-based *FLT3*-ITD monitoring can help guide post-remission treatment decisions and are therefore expected to be incorporated into routine clinical practice and future treatment guidelines.

Other patients within favorable risk-categories are recommended to receive conventional chemotherapy-based consolidation treatment with regimens that include intermediate-dose cytarabine (IDAC, usually 3-4 cycles at a dose of 1000-1500mg/m^2 IV over 3 h q12h d1-3; in patients <60 years: 1000-1500mg/m^2 IV over 3 h q12h d1-3). Avoidance of alternate day regimens (d1, 3, 5) and administration of G-CSF are associated with shorter time to neutrophil recovery and are therefore recommended.[43,44] Although still being used in some centers, current treatment recommendations argue against high-dose cytarabine regimens (Hi-DAC, 3000 mg/m^2 q12, d1-3) for consolidation treatment.[3] This advice is based on several studies, including a recent randomized trial, demonstrating that post-remission consolidation is associated with higher toxicity and no improvement in survival compared to intermediate-dose regimens (IDAC).[45-47]

For those patients who received FLT3 inhibitors within the induction regimens as outlined above, or for those who received CPX-351, those agents should be included in the consolidation chemotherapy regimens. However, administering GO during consolidation treatment beyond the induction phase does not seem to offer any benefits, based on results from the randomized MRC AML15 trial.[28]

Maintenance treatment

Although there is no standardized definition of the term "maintenance" therapy in AML, various targeted drugs, including the FLT3 inhibitors midostaurin and quizartinib, are being used as single-agent maintenance therapy for patients in remission following consolidation chemotherapy or allogenic SCT.[13,24] Although clinicians administer these treatments according to the registrational trial protocols, it is unclear if maintenance with midostaurin or quizartinib provides a prognostic benefit, and regulatory approval varies between Europe and the U.S. (Europe: midostaurin: after conventional consolidation; quizartinib: after consolidation and allo-SCT; U.S.: only quizartinib after consolidation chemotherapy). Although none of the above-referenced studies randomized patients or had enough power to assess maintenance treatments, the MORPHO trial randomly assigned patients with *FLT3*-ITD-positive AML who underwent allo-SCT in first CR to receive either gilteritinib or placebo. While there was a trend toward improved relapse-free survival (RFS) for the gilteritinib group, this did not reach statistical significance (HR: 0.679, $P = .0518$). However, patients with detectable NGS-based *FLT3*-ITD MRD benefited significantly from gilteritinib maintenance post-allo-SCT compared to those receiving placebo (HR 0.515, $P = .0065$).[48] Two earlier randomized trials evaluated the FLT3 inhibitor sorafenib also in the post-transplant setting and demonstrated a survival benefit for patients who had not previously received FLT3 inhibitors. However, the use of sorafenib in this setting may be challenging due to the toxicity profile of this agent.[49,50] In addition, trials with sorafenib during induction chemotherapy and maintenance therapy in younger (18-60 years) and elderly (>60 years) AML patients did not show improved OS as compared to placebo, including patients with *FLT3* mutations.[51,52]

Evidence for a survival advantage from maintenance treatment is currently only available for CC-486, an orally bioavailable formulation of azacitidine.[53] This drug was approved for maintenance treatment in patients with first CR/CRi following intensive induction chemotherapy who are not eligible for intensive consolidation chemotherapy or allo-SCT. Drug approval was based on a randomized phase-III trial assessing CC-486 given over 14 days in 28-day cycles vs placebo as maintenance treatment in the above-defined population of patients ≥ 55 years of age, demonstrating improved median OS (from 14.8 to 24.7) months ($P < .001$).

Current advances and future directions of intensive treatment

Numerous novel agents targeting leukemic mechanisms are currently under evaluation alongside intensive chemotherapy for AML (Fig. 1). Several of these targeted therapeutics have entered randomized studies, with key efficacy results anticipated soon. This includes whether inhibitors of mutant IDH1 (ivosidenib) or IDH2 (enasidenib) added to an intensive chemotherapy backbone improve survival rates of *IDH1*- or *IDH2*-mutated AML (NCT03839771). Also, a randomized clinical phase-III trial is comparing the FLT3 inhibitors midostaurin and gilteritinib in combination with intensive chemotherapy (NCT04027309). Results may facilitate selecting an FLT3 inhibitor for frontline treatment.

The BCL2 inhibitor venetoclax (VEN) is another drug that shows promise in combination with chemotherapy for AML front-line treatment. One phase 1/2 trial combining VEN with FLAG-IDA reported a 95% combined CR and 90% undetectable flow-cytometry-based MRD in 77 previously untreated AML patients.[54] A recent follow-up indicated 3-year OS and EFS rates of 66% and 64%.[55] A randomized phase III trial is currently evaluating a VEN (14 days initially, then 7 days in following cycles) with standard induction (7 + 3) and consolidation (IDAC) chemotherapy in newly diagnosed AML patients (NCT04628026).

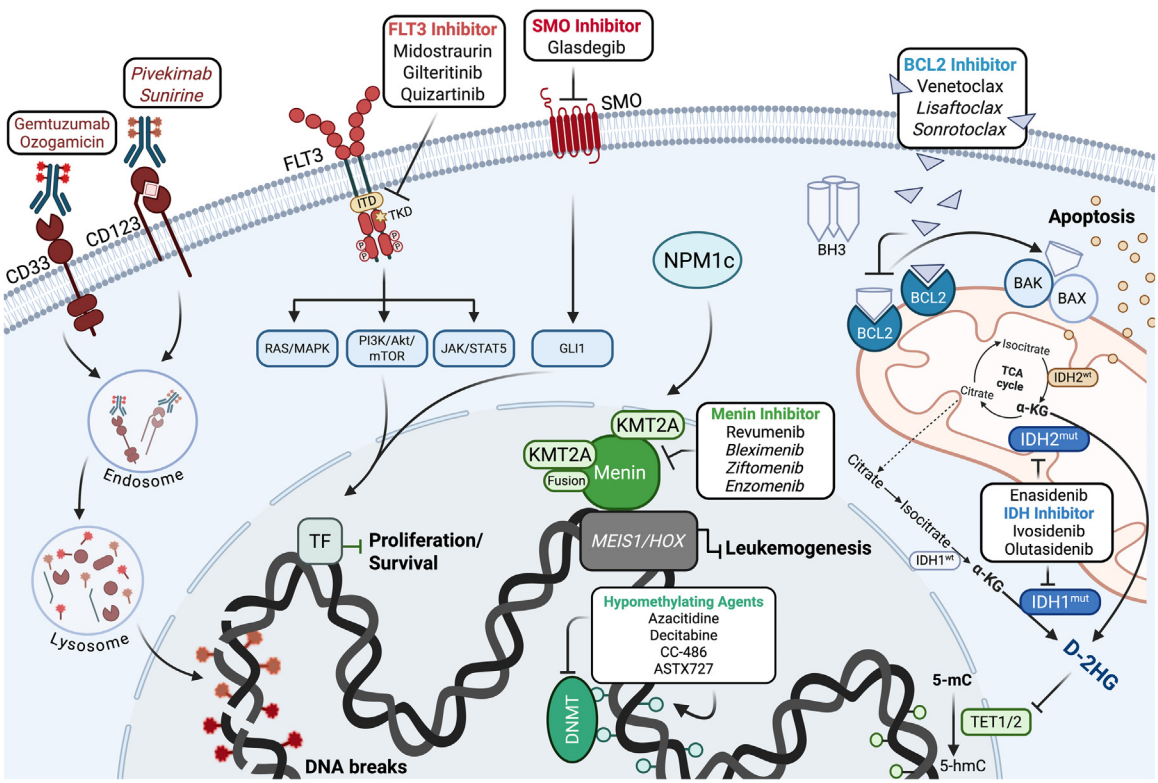

Fig. 1. Targeted drugs for the treatment of AML. Highlighted are targeted drugs and their mechanism of action with approval in the U.S. and / or Europe for the treatment of AML, as well as most promising agents currently under investigation in clinical trials (*italicized*). Abbr: α-KG = alpha-Ketoglutarate, D-2HG = D-2-Hydroxyglutarate, TF = Transcription Factor, 5-mC =5-Methylcytosine, 5-hmC = 5-Hydroxymethylcytosine. Created in BioRender. (2025) https://BioRender.com/t1rqiaw.

Combining VEN with hypomethylating agents (HMAs) versus more intensive regimens like 7 + 3 is currently under investigation. A first randomized trial showed comparable CR rates after 1 cycle of 7 + 3 versus VEN plus decitabine.[56] Further randomized studies assessing survival outcomes in specific AML subtypes are ongoing (NCT04801797 and NCT05904106).

Finally, the success story for the development of menin inhibitors has advanced from target definition to clinical drug approval at an astonishing pace.[57-64] This has led to several early clinical trials assessing individual menin inhibitors in combination with intensive chemotherapy as first-line treatment for *NPM1*-mutated or *KMT2A*-rearranged acute leukemia with and without combination with other targeted drugs, including FLT3 inhibitors (NCT05453903, NCT05735184, NCT05886049, NCT06313437). Based on these trials, some of which have shown promising preliminary efficacy, randomized registration trials are currently being established.[65,66]

AML patients considered unfit for intensive therapy

2024 ELN genetic risk classification ("Less-intensive")

Recent studies have shown that the 2017 and 2022 ELN genetic risk classifications that were developed based on data from patients receiving intensive chemotherapy lack applicability for the population of older or medically unfit patients treated with less-intensity regimens. The newly introduced 2024 ELN genetic risk classification addresses this unmet need by proposing a first molecular risk stratification specifically for patients treated with HMAs alone, HMA plus VEN (HMA/VEN, or azacitidine in combination with ivosidenib (AZA/IVO) for *IDH1*-mutated AML (Table 2).[67]

The 2024 ELN classification largely builds upon the 4-gene classifier that was described for AZA/VEN-treated patients in the VIALE-A and the preceding phase 1b study.[68] Both the VIALE-A classifier and the 2024 ELN classification stratify patients into 3 risk groups. Both classifications highlight the sensitivity of *NPM1*- and *IDH2*-mutated AML to HMA/VEN treatment, if not associated with a signaling gene co-mutation, and presence of a *TP53* mutation as a poor-risk factor. 2024 ELN further extends by including *IDH1*-mutated AML in the favorable-risk group, provided a patient is treated with the combination of AZA/IVO.[69,70] Furthermore, 2024 ELN includes *DDX41* as a favorable marker, supported by studies with HMA monotherapy and HMA/VEN regimens.[71,72]

The 2024 ELN genetic risk classification is supported by an earlier study describing the patterns of molecular response and treatment failure after frontline VEN combination regimens[73] and by a number of more recent genomics studies, although with some variations.[71,74-77] Open questions include, for example, whether *NPM1*-, *IDH2*-, *IDH1*-, and *DDX41*-mutated AML should be regarded separately from other categories currently classified as favorable-risk, which signaling mutations should be included in the model, and whether other abnormalities should be categorized as adverse.

Current standard-of-care non-intensive treatment

This section reviews the current standard-of-care non-intensive treatment regimens approved for AML, highlighting pivotal trial data and real-world evidence in elderly and unfit patient populations (summarized in Table 3).

Hypomethylating agents

With the development of the HMAs AZA and decitabine (DEC) more than ten years ago, a new standard treatment option was introduced for patients with AML who are ineligible for intensive chemotherapy. Although these agents can induce clinical responses ranging from 18% to 30%, their overall efficacy as monotherapy remains limited, with median OS reported between 7.7 and 10.4 months in the pivotal phase 3 trials.[78,79] Data from comparative studies suggest no differences in OS or ORR between AZA and DEC.[80-82]

Guadecitabine is a next-generation HMA that is a dinucleotide of decitabine and deoxyguanosine and is not metabolized by cytidine deaminase, thereby prolonging decitabine exposure.[83] Data from the initial phase 2 trial suggested high clinical activity with a 53% cCR rate in newly diagnosed AML.[84] However, in the subsequent phase 3 trial of 815 treatment-naïve, unfit AML patients (ASTRAL-1), guadecitabine did not improve outcomes compared to standard HMAs or low-dose cytarabine. Median OS was 7.1 months with guadecitabine vs 8.5 months with treatment choice, and CR rates were similar across groups (19.4% vs 17.4%).[85]

The recent development of the oral formulation of decitabine - decitabine/cedazuridine (DEC–C) - represents a clinically relevant advance. By enhancing patient convenience and outpatient administration, it ultimately may considerably improve patient quality of life. In a randomized crossover study of 89 patients with AML ineligible for intensive chemotherapy, the pharmacokinetics and pharmacodynamics of the 2 formulations were similar, and with an ORR of 32.2% and a median OS of 8.9 months, the clinical efficacy of oral DEC–C was consistent with historical data of intravenous DEC.[86] Based on these data, the EMA approved DEC–C as monotherapy for the treatment of adult patients with newly diagnosed AML who are ineligible for standard induction chemotherapy. The development of DEC–C now also opens the way towards completely oral doublet and triplet combination regimens (see below).

Doublet regimens

Currently approved AML doublet regimens include (VEN)-based combinations – HMA/VEN, and low-dose cytarabine (LDAC) plus VEN - as well as HMA combined with the IDH1 inhibitor IVO for patients with *IDH1*-mutated AML. The combination of LDAC and

Table 2
The 2024 ELN genetic risk classification specifically designed for older or medically unfit AML patients receiving less-intensive therapy.

Risk category	Genetic abnormality
favorable	• Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH1* (*TP53*^{wt})[a] • Mutated *DDX41* • Other cytogenetic and/or molecular abnormalities • (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
intermediate	• Other cytogenetic and molecular abnormalities (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
adverse	• Mutated *TP53*

Hypomethylating agents [HMA], HMA plus venetoclax [VEN], or azacitidine plus ivosidenib [AZA + IVO] for *IDH1*-mutated AML).
[a]Favorable risk (median OS time) applies specifically to patients treated with AZA + IVO, irrespective of the presence of activating signaling gene mutations.

Table 3
Overview of approved non-intensive treatment regimens for AML.

Regimen (Dose & Schedule)	Key trial(s)/Design	Population	Efficacy	Comments/Notes	Approval status
AZA-IV/SC	AZA-AML-001 (Phase 3 RCT vs CCR, NCT01074047)[79]	ND-AML, ≥65 y, BM blasts ≥30% (n = 488, median age: 75 y)	CR 19.5% vs 21.9%, CRc (CR+CRi) 27.8% vs 25.1%, mOS 10.4 vs 6.5 mo	Original HMA standard; modest efficacy as monotherapy; important as backbone for combinations	EMA approved, FDA off-label use
DEC-IV	DACO-016 (Phase 3 RCT vs LDAC/BSC, NCT00260832)[78]	ND-AML, ≥65 y, BM blasts ≥20% (n = 485, median age: 73 y)	CR 15.7% vs 7.4%, CRc (CR+Cri) 25.6% vs 10.3%, mOS 7.7 vs 5.0 mo	Alternative HMA; demonstrated OS benefit over LDAC	EMA approved, FDA not approved for AML
DEC–C (oral)	Phase 3 crossover, PK equivalence, NCT03306264)[86]	ND-AML, ineligible for IC (n = 87, median age: 78 y)	CR 23.8%, CRc (CR+Cri) 30.1%, mOS ~8.9 mo	PK and efficacy comparable to IV decitabine; improved convenience	EMA approved, FDA not approved for AML
AZA+VEN (HMA + VEN)	VIALE-A (Phase 3 RCT, NCT02993523)[87]	ND-AML, ≥75 y or unfit (n = 431, median age: 76 y)	CRc 66.4% vs 28.3%, mOS 14.7 vs 9.6 mo	Current standard in unfit AML; not curative; durable responses	EMA and FDA approved
	REVIVE cohort (Israel), multicenter, prospective RWE study (NCT03987958)[120]	ND-AML, ≥18 y, ineligible for IC (n = 207, median age: 75 y)	CR 44.4%, CRc 65.2%, mOS 11.7 mo	VIALE-A trial eligibility strongly predicts clinical outcomes.	
	SEIFEM cohort (Italy), multicenter, prospective RWE study (AZA+VEN vs HMA)[121]	ND-AML, ≥18 y, ineligible for IC (n = 230, median age: 75 y)	CR 44% vs 25.5%, mOS 11 vs 9 mo	Highlights survival benefit and infection risk	
	Gimema AML2320 (Italy), multicenter, prospective RWE study (NCT04589728)[122]	ND-AML, ≥75 y or unfit (n = 178, median age: 74 y)	CRc (CR/Cri) 57% (cycle 1), 64% (cycle 2), mOS 14.2 mo	Early responses predictive of outcomes	
	Johnson et al. (USA), single-center, prospective RWE study[123]	ND-AML, ≥18 y, ineligible for IC (n = 103, median age: 74 y)	CR 39%, CRc (CR/CRi) 85%, mOS 8.5 mo	Consistent CRc rates, lower OS vs trial data	
	US multicenter, retrospective RWE study[124]	ND-AML, ≥18 y, ineligible for IC (n = 439, median age: 75 y)	CR 17%, CRc (CR/CRi) 43%, mOS 11 mo	Confirms efficacy in large RWE cohort	
	AURAML (France) multicenter, retrospective RWE study[125]	ND-AML, ≥18 y, ineligible for IC (n = 186, median age: 74.5 y)	CRc 66.4% (after 6 cycles), OS 12.4 mo	High response rate in real-world setting	
	US multicenter, prospective RWE study (VEN + HMA vs HMA)[126]	ND-AML, ≥18 y, ineligible for IC (VEN + HMA: n = 619, median age: 74.8 y; HMA: n = 480, median age: 75.8 y)	mOS 9.3 mo vs 5.9 mo	Largest RWE cohort to date; OS notably shorter than in pivotal VIALE-A trial	
	German multicenter, prospective RWE study[127]	ND-AML, ≥18 y, ineligible for IC (n = 125, median age: 76 y)	CRc 57%, mOS 7.9 mo	RWE cohort; median OS lower than in VIALE-A	
LDAC + VEN	VIALE-C (Phase 3 RCT + LTFU, NCT03069352)[95,96]	ND-AML, ≥75 y or unfit (n = 211, median age: 76 y)	CR 27% vs 7%, CRc 48% vs 13%, mOS 7.2 vs 4.1 mo (8.4 vs 4.1 mo in LTFU)	OS benefit only in LTFU; alternative if HMA not feasible	FDA approved, not EMA approved
HMA + IVO	AGILE (Phase 3 RCT, NCT03173248)[69,70]	ND-*IDH1*-mut AML, ≥75 y or unfit (n = 146, median age: 76 y)	CR 47% vs 15%, CRc 53% vs 18%, mOS 29.3 vs 7.9 mo (LTFU)	Lower infection rate with IVO; DS in 14%	FDA and EMA approved
	Retrospective, real-word observational study (USA)[100] HMA + IVO vs HMA + VEN	ND-*IDH1*-mut AML, ≥18 y, ineligible for IC (n = 283, median age: 63 y)	CR 42.9% (IVO+AZA) vs 26.7% (VEN+AZA); CRc (CR+CRi/p) 63.2% vs 49.5%	Suggests potential superiority over VEN + AZA in this subgroup	
IVO mono	Phase 1, multicenter, open-label study (NCT02074839)[101]	ND-*IDH1*-mut AML, ≥18 y, ineligible for IC (n = 34, median age: 76.5 y)	CR 30.3%, CRc (CR+CRh) 42.5%, mOS 12.6 mo	Favorable safety; option for frail patients	FDA approved (1st line, *IDH1*-mut, unfit)
OLU mono	Phase 1/2, multicenter, open-label study (NCT02719574)[102]	R/R *IDH1*-mut AML (n = 147, median age: 71 y)	CR 35%, CRc (CR+CRh) 32%, mOS 22.6 mo	Approved for R/R setting only	FDA approved (*IDH1*-mut, R/R only)
Glasdegib + LDAC	BRIGHT AML 1003 (Phase 2, NCT01546038)[128]	ND-AML (de novo/secondary), unfit (n = 116, median age: 77 y)	CR 19.2% vs 2.6%, mOS 8.3 vs 4.3 mo	Limited real-world benefit	FDA approved

This table summarizes pivotal clinical trials and selected real-world evidence (RWE) studies evaluating non-intensive regimens for AML in elderly or unfit patients. Data include regimen details, trial design, patient populations, efficacy outcomes (CR/CRi rates, median OS), key safety and tolerability findings, and regulatory approval status. Abbreviations: AML = acute myeloid leukemia; AZA = azacitidine; BM = bone marrow; CCR = conventional care regimen; CR = complete remission; CRc = composite complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; DEC–*C* = decitabine-cedazuridine; DLT = dose-limiting toxicity; EMA = European Medicines Agency; FDA = Food and Drug Administration; IC = intensive chemotherapy; IDH1-mut = isocitrate dehydrogenase 1 mutation; IVO = ivosidenib; LDAC = low-dose cytarabine; LTFU = long-term follow-up; mOS = median overall survival; ND = newly diagnosed; OLU= Olutasidenib; OS = overall survival; PBO = placebo; PK = pharmacokinetics; R/*R* = relapsed/refractory; RCT = randomized controlled trial; SC = subcutaneous; VEN = venetoclax.

glasdegib also holds approval, though its clinical use remains limited (Table 3).

Hypomethylating Agents + Venetoclax. The combination of HMAs with the BCL2-inhibitor VEN has emerged as the new standard of care for the majority of older or unfit patients with newly diagnosed AML who are ineligible for intensive chemotherapy. This regimen has demonstrated superior outcomes compared to HMA monotherapy, both in clinical trials and real-world settings.

In the pivotal phase 3 VIALE-A trial, 431 patients with newly diagnosed AML ineligible for intensive chemotherapy (median age 76 years) were randomized to receive AZA/VEN or AZA plus placebo (AZA/PBO). The combination significantly improved median OS (14.7 vs 9.6 months; HR 0.66) and composite CR (CR + CRi) rates (66.4% vs 28.3%) compared to AZA alone.[87] Long-term follow-up after a median of 43.2 months confirmed durable benefit, with a maintained OS advantage (median OS: 14.7 vs 9.6 months; HR 0.58); however, the survival curve continues to decline, indicating that the treatment is not curative in the vast majority of patients.[88]

Real-world data have increasingly supported the superiority of HMA/VEN over HMA monotherapy in the frontline treatment of elderly AML patients; however, they also highlight significant discrepancies in outcomes compared to those observed in clinical trials. Median OS reported in the VIALE-A trial using AZA/VEN was not well reproduced in real-world for unfit newly diagnosed AML patients, while CRc rates were more consistent. A recent systematic review of 62 pro- and retrospectively analyzed real-word cohorts including 5,831 patients reported an overall median CRc rate of 56.2%. For patients treated with AZA/VEN, the median CRc was 58.0%, and 55.0% for VEN/DEC. Median OS reported in 54 studies comprising 7,138 patients was 10.4 months overall - 9.8 months for AZA/VEN and 12.0 months for DEC/VEN.[89] Selected pro- and retrospective real-world studies are summarized in Table 3.

HMA/VEN regimens demonstrate consistent clinical activity in routine practice, but real-world outcomes are influenced by patient heterogeneity, treatment variability, and healthcare setting. Notably, in real-world clinical practice, treatment with HMA/VEN is often characterized by considerable variability in dosing and administration. This heterogeneity, primarily driven by dose-limiting toxicities that necessitate individualized dose modifications, likely contributes to the variations in survival and response outcomes observed across several real-world studies when compared to clinical trial data.

Real-world evidence supports that AZA/VEN efficacy can be preserved with individualized, often shortened VEN schedules to manage toxicity without compromising response or survival. Table 4 summarizes findings from retrospective studies comparing VEN durations ranging from 7 to 28 days, demonstrating largely comparable CR/CRi rates and median OS across dosing regimens. While the 28-day VEN schedule remains the approved standard, these results support the feasibility of shorter schedules that may enhance tolerability without compromising response.

To further optimize treatment strategies, prospective trials are underway. A randomized phase 2 study is currently comparing 14-day versus 28-day VEN schedules during both induction and maintenance.[90] Additional studies are investigating response-adapted and MRD-guided VEN tapering strategies.[91] To address the high rate of toxicity-related modifications required with VEN, the next-generation BCL-2 inhibitor lisaftoclax (LISA) is under investigation in AML (and MDS). LISA is designed to reduce myelosuppression while maintaining antileukemic efficacy via an optimized pharmacokinetic profile (GLORA-3; NCT06389292).[92-94]

Low-dose Cytarabine + Venetoclax. The combination LDAC/VEN is an alternative for frail patients not suitable for HMAs and in countries in which HMAs are not available or not reimbursed. In a randomized, placebo-controlled phase 3 study (VIALE-C) of 211 treatment-naïve AML patients ineligible for intensive chemotherapy, the primary analysis showed a 25% reduction in risk of death, although not statistically significant; a subsequent unplanned analysis with additional follow-up then showed a significant OS advantage for LDAC/ VEN compared to LDAC alone.[95,96] Based on the results of VIALE-C, LDAC/VEN is approved by the FDA (but not by EMA) for newly diagnosed AML in adults aged ≥75 or with comorbidities precluding intensive therapy.

Hypomethylating Agents + Ivosidenib. The combination of AZA/IVO has emerged as a targeted, non-intensive treatment option for patients with newly diagnosed *IDH1*-(R132)-mutated AML who are ineligible for intensive chemotherapy. This approach was first evaluated in a dose-finding, open-label phase 1b study, which established the recommended regimen of IVO 500 mg orally once daily in 28-day cycles combined with subcutaneous AZA 75 mg/m² on days 1 to 7. The combination demonstrated a CRc (CR + CRh) rate of 69.6%, with manageable side effects including grade 3 to 4 IDH-differentiation syndrome (IDH-DS) in 8.7% and QT prolongation in 13% of patients.[97]

In the pivotal phase 3, randomized AGILE trial, 146 newly diagnosed patients (median age: 76 years) with *IDH1*-mutated AML were randomized to receive AZA/ IVO or AZA/PBO.[69] The trial was stopped prematurely based on a recommendation by the Independent Data Monitoring Committee that noted a significant difference in outcome between treatment arms. EFS was significantly longer with AZA/IVO compared to AZA/PBO (HR: 0.33; 95%CI, 0.16-0.69; $P = .002$). Median OS was 24 mo and 7.9 mo with AZA/IVO and AZA/PBO (HR: 0.44; 95%CI, 0.27-0.73; $P = .001$), respectively. Of note, the incidence of all-grade infections was lower with AZA/IVO

Table 4
Summary of outcomes from selected retrospective studies with varying venetoclax schedules combined with HMAs in AML.

VEN schedule	Reference	Patients (n)	cCR (CR/CRi) Rate (%)	Median OS (Months)	Key findings
7– vs 28–day VEN	Willekens et al.[91]	82 vs 166 ($n = 248$)	72 vs 72	11.2 vs 10.3	Same CR/CRi as 28–day schedule; lower 8–week mortality (6% vs 16%); fewer platelet transfusions (62% vs 77%)
14– vs 21– vs 28–day VEN	Karrar et al.[129]	40 vs 41 vs 189 ($n = 270$)	68 vs 66 vs 62	18.6 vs 21.3 vs 13.2	Similar CR/CRi rates and OS across schedules; no significant differences in toxicity
14– vs 21– vs 28-day VEN	Kanaya et al.[130]	31 vs 51 vs 18 ($n = 100$)	68 vs 51 vs 39	NR vs 14.3 vs 10.9	CR/CRi declined with shorter duration; variable thrombocytopenia and FN rates
14– vs 21– vs 28–day VEN	Ginosyan et al.[131]	11 vs 43 vs 31 ($n = 85$)	27 vs 72 vs 68	6.1 vs 17.6 vs 15.7	Lower response and survival with 14–day dosing

Includes CR/CRi rates, median OS, and key safety findings from retrospective and prospective studies. Abbreviations: AZA = azacitidine; CR = complete remission; CRc = composite complete remission; CRi = complete remission with incomplete hematologic recovery; FN = febrile neutropenia; HMA = hypomethylating agent; NR = not reached; OS = overall survival; VEN = venetoclax.

(28%) than with AZA/PBO (49%), which may be explained by the initial neutrophil burst observed with AZA/IVO, in particular during the first cycle of therapy. Differentiation syndrome occurred in 14% with AZA/IVO and 8% with AZA/PBO. Long-term efficacy and safety results confirm the benefit of AZA/IVO, with a median OS of 29.3 months, exceeding the primary analysis by more than 5 months.[70] A phase 3b single-arm trial with AZA/IVO is ongoing with the objective to generate additional safety data in a more clinical practice setting (NCT05907057).

With all the caveats of cross-trial comparisons, outcome with AZA/IVO compares favorably to the median OS of 15.2 mo reported for *IDH1*-mut AML treated with AZA/VEN.[67] Furthermore, small retrospective cohorts suggest that AZA/VEN may still retain clinical efficacy when used as salvage following progression on treatment with AZA plus IDH1/2 inhibitors. In contrast, IDH inhibitors appear to have very little efficacy following progression on VEN-based therapy.[98,99]

Supporting these findings, a real-world evidence study including 283 patients with *IDH1*-mutated AML reported composite CR + CRh rates of 63.2% with HMA/IVO compared to 49.5% with HMA/ VEN. The IVO-based regimen was also associated with longer EFS and a higher rate of bridging to allo-SCT, corroborating the efficacy observed in the AGILE trial.[100] These data provide independent clinical validation of *IDH1*-targeted therapy, reinforcing its effectiveness in routine practice within this molecularly defined AML subgroup.

Based on the AGILE trial, AZA/IVO is FDA- and EMA-approved for newly diagnosed *IDH1*-mutated AML in adults ≥75 years or those unfit for intensive chemotherapy.

IDH1-Inhibition as Monotherapy. The approval of IVO monotherapy by FDA for first-line treatment of *IDH1*-(R132)-mutated AML in patients ineligible for intensive chemotherapy is based on the results of a phase 1 study demonstrating a CR/CRh rate of 42.4% and a median OS of 12.6 months.[101] IVO was generally well-tolerated, induced durable remissions, and led to transfusion independence in 42.9% of patients who were previously transfusion dependent. IDH-DS occurred in 9% of patients but did not necessitate treatment discontinuation. IVO monotherapy is a valuable option for frail patients in whom combination treatment with AZA may not be feasible.

Olutasidenib is another active IDH1 inhibitor that is approved by the FDA for relapsed/refractory (R/R) AML based on results of a phase 1/2 trial, showing a CR+CRh rate of 35% and a median OS of 11.6 months.[102] Olutasidenib is currently not approved for frontline treatment.

Current advances and future directions for less intensive treatment

Emerging treatment approaches for unfit AML patients focus on triplet regimens that enhance response depth and durability in genetically defined subgroups, alongside entirely oral therapies designed to improve patient convenience and quality of life (summarized in Table 5).

Triplet approaches

While the HMA/VEN doublet has significantly improved outcomes in unfit AML patients, long-term survival remains constrained by frequent relapses. Emerging evidence suggests that

Table 5
Summary of investigational HMA + venetoclax-based triplet regimens and fully oral doublets/triplets in AML (Elderly, Unfit Patients).

Doublet/Triplet regimen	Target population	Study/Source	CR/CRc rate	Median OS	Key findings	Comments
IVO + VEN + AZA	*IDH1*-mutated ND-AML	Phase 1/2b multicenter study (NCT03471260)[103] 2024 Update[104]	CRc 94%	3-yr OS: 71%	Deep responses in younger patients, 39% underwent allo-HSCT	Single-arm, single-center study; not generalizable to unfit patients
ENA + VEN + HMA	*IDH2*-mutated ND-AML	Phase 1/2b single-center study (NCT04774393)[117]	CRc 100%	35.2 mo	Half of relapses were *IDH2*-wt clones; good tolerability	Prospective comparisons with doublets needed
FLT3i (Gilteritinib/ Quizartinib) + AZA + VEN	*FLT3*-mutated ND-AML (cohort1)	Phase 1/2 single-center study (NCT04140487)[105]; LTFU[106]	CRc 93%	38.5 mo	*RAS* mutations emerged in 24% of relapses	No Phase 3 trial ongoing; early data from fitter cohort
PVEK (CD123 ADC) + VEN + AZA	ND-AML (CD123+)	Phase 1b/2 multi-center study (NCT04086264)[109]	CR 52%; CRc 66%	NR	Novel ADC approach; good tolerability	Further investigation warranted
Menin inhibitor + VEN + AZA	*NPM1*-mut or *KMT2A*-r AML	Refer to Table 6				
DEC–*C* + VEN	Elderly AML (ND/R/R)	Phase 2 single-center study (NCT04746235)[113]	CR 34% (ND), CR 41% (R/R); CRc 57% (ND), CRc 46% (R/R)	11.5 mo (ND), 7.2 mo (R/R)	High response rate, limitation: single-center study	FDA reviewing sNDA for approval
	Elderly ND-AML	ASCERTAIN-V (ASTX727-07) Phase 1/2b multicenter study (NCT04657081)[114]	CR 46.5%; cCR 63.4%	15.5 mo	Comparable safety and efficacy to parenteral regimens.	
DEC–*C* + VEN + IVO	*IDH1*-mutated AML	Phase 1/2 single-center study; 2023 Update (NCT04774393)[116]	CRc 96% (ND), CRc 46% (R/R)	NR	Fully oral triplet; promising MRD clearance	Phase 1/2 data; longer follow-up needed,
DEC–*C* + VEN + ENA	*IDH2*-mutated ND-AML	Phase 1/2 single-center study; 2023 Update (NCT04774393)[116]	CRc 100%	35.2 mo	Low rates of IDHi-related toxicity	Prospective randomized studies warranted
DEC–*C* + VEN + REV	*NPM1*-mut or *KMT2A*-r AML	Phase 1/2 single-center study (SAVE; NCT05360160)[118]	CRc 84% (89% in ND)	NR (ND), 9.3 mo (R/R)	Maintenance-suitable, encouraging efficacy	Phase 1b trial; ongoing

This table outlines emerging clinical strategies for elderly and unfit patients with AML, including triplets with targeted agents (e.g., IDH1/2, FLT3, CD123, menin inhibitors) and oral regimens. Entries include target populations, response rates, survival outcomes, and study highlights. Abbreviations: ADC = antibody-drug conjugate; AZA = azacitidine; CR/CRi = complete remission/complete remission with incomplete hematologic recovery; CRc = composite complete remission; DEC–*C* = decitabine/cedazuridine; ENA = enasidenib; FLT3i = FLT3 inhibitor (e.g., gilteritinib or quizartinib); IDHi = IDH-inhibitor, IVO = ivosidenib; MRD = measurable residual disease; ND = newly diagnosed; OS = overall survival; PVEK = pivekimab sunirine; R/*R* = relapsed/refractory; sNDA = supplemental new drug application; VEN = venetoclax.

triplet regimens may further deepen responses and extend remission durability. These investigational combinations, currently being evaluated in both ND and R/R AML, integrate targeted agents - such as inhibitors of IDH1/2, FLT3, menin, or CD123 antibody-drug conjugates - in treatment backbones. Early-phase studies report enhanced response rates, higher rates of MRD negativity and molecular clearance, indicating the potential for more durable remissions and improved long-term disease control in molecularly defined subsets. One significant challenge will be to find the proper schedule and doses, since triplet combinations may increase myelosuppression.

Ivosidenib + Venetoclax + Azacitidine. Given the sensitivity of *IDH1*-mutated AML to IVO and VEN, a phase 1b/2 study evaluated the doublet IVO/VEN and the triplet AZA/IVO/VEN, both with 2 VEN doses (400 mg and 800 mg) in patients with *IDH1*-mutated myeloid malignancies.[103] After review of safety and efficacy data, ivosidenib (starting on day 15 of cycle 1, then given continuously), VEN 400 (14 days), and AZA (7 days) were chosen as the recommended phase 2 dose. Updated results in 31 patients showed a CRc rate of 94%, and 77% of responders achieved MRD negativity by multiparameter flow cytometry.[104] With a median follow-up of 36 months, the 3-year OS rate was 71%. It is worth noting that these are data from a single-arm, single-institution study; patients included were younger (median age: 70 years), and 39% of patients underwent allo-SCT. Thus, these data cannot automatically be extrapolated to a more typical unfit patient population.

Nonetheless, based on these encouraging findings, a randomized phase 3 trial (EVOLVE-1/HO173/AMLSG 34-23/ ACT-HOV-AML-001) of AZA/IVO ± VEN is ongoing in newly diagnosed *IDH1*-mutated AML or MDS/AML patients ineligible for intensive therapy.

FLT3-inhibitor + Venetoclax + Azacitidine. A randomized, open-label phase 3 trial (LACEWING) evaluated the combination of AZA + gilteritinib versus AZA alone in unfit patients with newly diagnosed *FLT3*-mutated AML. Despite a significantly higher CRc rate with gilteritinib (58.1% vs 26.5% with AZA monotherapy), there was no difference in OS (median OS: 9.82 mo vs 8.87 mo, respectively. The study was closed prematurely based on the protocol-specified boundary for futility.

The triplet combination AZA/VEN + gilteritinib (or quizartinib) is currently being investigated in patients with newly diagnosed *FLT3*-mutated AML.[105] Updated results in 73 patients receiving a triplet combination (mostly gilteritinib or quizartinib) demonstrate a CRc rate of 93% and a median OS of 38.5 months. Relapses were driven mainly by *FLT3*-wildtype clones with the emergence of RAS pathway mutations in 24% of cases.[106] Again, these are single-center data in a more fit (median age 70 years) population of patients, with 40% of patients proceeding to allo-SCT.

A similar triplet approach is being evaluated in the ongoing multicenter, open-label, randomized phase 1/2 trial (VICEROY; NCT05520567), enrolling more unfit adults with newly diagnosed *FLT3*-mutated AML who are ineligible for intensive chemotherapy, to assess the efficacy, safety, pharmacokinetics, and drug-drug interactions of AZA, VEN, and gilteritinib.[107] Currently, no randomized phase 3 study is underway that could potentially lead to registration of this promising triplet combination in the near future.

Pivekimab Sunirine + Venetoclax + Azacitidine. The interleukin-3 receptor (CD123) is overexpressed in hematological malignancies, including AML. Pivekimab sunirine (IMGN632; PVEK) is a first-in-class antibody-drug conjugate (ADC) designed with a high-affinity antibody targeting CD123, a cleavable linker, and a unique indolinobenzodiazepine pseudodimer as its cytotoxic payload. Promising single-agent activity and a manageable safety profile were demonstrated in a phase 1/2 study in R/R AML,[108] providing the rationale for a subsequent open-label, multicenter phase 1/2 trial in ND-AML patients, combining PVEK with AZA + VEN. Patients received PVEK at the recommended phase 2 dose of 0.045mg/kg IV on day 7 + AZA 75mg/m^2 on day 1-7 + VEN up to 400 mg daily on day 14 to 28 in a 28-day cycle. In the intention-to-treat (ITT) population ($n = 50$, median age 74 years), a CR rate of 52% and CRc rate of 66% were observed, with 73% of responders achieving MRD-negativity. Given the encouraging efficacy signals and tolerable safety profile, this triplet regimen warrants further clinical investigation.[109]

Menin Inhibitor + Venetoclax + Azacitidine. The rationale for combining menin inhibitors with AZA/VEN stems from preclinical synergy, with VEN emerging as a promising partner in drug screens aimed at disrupting menin-KMT2A–mediated leukemogenesis.[110]

Three menin inhibitors, revumenib (REV), ziftomenib (ZIFTO), and bleximenib (BLEX), are currently being investigated in triplet combinations in patients with R/R as well as newly diagnosed *NPM1*-mutated and *KMT2A*-rearranged AML (Table 6).[111,112] All trials reported the feasibility and safety of the triplet combinations with CRc rates ranging from 25% to 81.4%. Based on these encouraging results, phase 3 trials in patients with newly diagnosed *NPM1*-mutated and *KMT2A*-rearranged AML have started (NCT06652438; NCT06852222) or will begin soon (Komet-017-NIC).

Fully oral regimens

Recent developments in the treatment of elderly and unfit AML patients have also focused on entirely oral regimens. These emerging therapeutic strategies aim to provide effective disease control while significantly improving patient convenience, quality of life, and outpatient treatment feasibility. Oral HMAs combined with targeted agents such as VEN are transforming the landscape of AML therapy by potentially reducing hospital visits and enhancing treatment adherence.

Decitabine/Cedazuridine + Venetoclax. A phase 2 trial investigated this all-oral combination of DEC–*C* + VEN in elderly AML patients with both frontline and R/R AML. In the frontline cohort, the study reported an ORR of approximately 64%, with a CRc rate near 50%. Median OS exceeded 15 months, demonstrating durable clinical benefit. The regimen was generally well tolerated, with manageable grade ≥3 neutropenia and febrile neutropenia (~18%), and low treatment-related mortality.[113]

This work served as the basis for a recent multicenter phase 1/2 trial (ASCERTAIN-V; NCT04657081) evaluating the all-oral DEC–*C* + VEN regimen in patients with newly diagnosed AML aged ≥75 years or with significant comorbidities. In the pivotal phase 2b cohort ($n = 101$, median age 78 years), the CRc rate was 63.4%, with a mOS of 15.5 months. The most common Grade ≥3 adverse events were febrile neutropenia (49.5%) and neutropenia (35.6%), with no new safety signals being observed.[114,115] Based on these results, the FDA has recently accepted the supplemental new drug application (sNDA) for this all-oral combination of VEN + DEC–C in newly diagnosed AML patients ineligible for intensive chemotherapy.

Molecular Targeted Agents + Venetoclax + Decitabine/Cedazuridine. For patients with *IDH1/2*-mutated AML, a recent phase 1/2 trial is currently evaluating the combination of DEC–*C* + VEN + IVO or ENA. In the *IDH1*-mutated cohort, interim 2023 update results showed a CRc rate of 90% among ND-AML patients ($n = 14$), with a 50% CRc in the R/R setting.[116] Updated pooled analysis in frontline *IDH1/2*-mutated AML ($n = 60$, median age 71), including 38 patients with *IDH1* mutations treated with HMA (57% DEC–C, 43% AZA) + VEN + IVO, further reinforces these findings.[117]

Building on the sensitivity of *IDH2*-mutated AML to AZA + VEN, the same ongoing phase 1b/2 trial included 23 patients with *IDH2* mutations who received DEC–C (days 1-5), VEN (days 1-14), and ENA (starting day 8) in 28-day cycles. In this subgroup, the CRc rate was 100%, with a mOS of 35.2 months and a 2-year relapse rate of 24%. Notably, 50% of relapses lacked detectable *IDH2*-

Table 6
Summary of Investigational Menin Inhibitor-Based Triplet Regimens in Elderly, Unfit AML Patients.

Menin inhibitor	Target population	Trial phase/ID	Regimen	Key efficacy	Safety / Key adverse events	Trial status / Notes
Revumenib	ND-AML ≥60y with *NPM1*m or *KMT2A*r	Phase 1b dose-escalation and explansion (NCT03013998) [111]	REV + AZA + VEN	cCR 81.4%, all MRD evaluable MRD-negative	DS 19% (grade 3 in 5%); QTc prolongation 12%	Excellent tolerability, high clinical activity
	ND-AML ≥18y with *NPM1*m or *KMT2A*r, ineligible for IC	EVOLVE-2 (AMLSG 35-24 / HOVON 177); Phase 3 RCT (NCT06652438)	AZA + VEN + REV vs AZA + VEN + placebo	Ongoing trial	-	Currently enrolling
Bleximenib	R/R AML with NPM1m or KMT2Ar, ineligible for IC (Cohort A3)	ALE1002 Phase 1b dose-escalation (NCT05453903)[132]	BLEX + AZA + VEN	ORR 79%; cCR (CR/CRh/CRi) 41% ($n = 34$, ≥50 mg BID); ORR 65%, cCR (CR/CRh/Cri) 29% in prior VEN-exposed	DS 3% (2 pts: grade 3 and grade 5/DLT); no QTc prolongation; no TLS	Dose escalation ongoing; (Arm B: ND-AML)
	ND-AML ≥18y with *NPM1*m or *KMT2A*r, ineligible for IC	cAMeLot–2; Phase 3 RCT (NCT06852222)	AZA + VEN + BLEX vs AZA + VEN + placebo	Ongoing trial	-	Currently enrolling
Ziftomenib	R/R AML with *NPM1*m or *KMT2A*r, ineligible for IC	KOMET–007 Phase 1a (NCT05735184)[112]	ZIFTO + AZA + VEN	ORR 50%; cCR (CR/CRh) 25%; *NPM1*m: cCR 50%	DS 8% (all G2–3; manageable), no QTc prolongation or DLTs; common Grade 3+ AEs: cytopenias, febrile neutropenia	Phase 1b expansion ongoing; Phase 3 (KOMET–017-NIC) planned in 2025

This table summarizes clinical trials evaluating menin inhibitors (combined with hypomethylating agents and venetoclax in elderly or unfit patients with AML harboring NPM1 mutations or KMT2A rearrangements. Abbreviations: AML = acute myeloid leukemia; AZA = azacitidine; BLEX = bleximenib; CRc = composite complete remission; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; DLT = dose-limiting toxicity; DS = differentiation syndrome; IC = intensive chemotherapy; KMT2Ar = KMT2A rearrangement; MRD = measurable residual disease; ND = newly diagnosed; NPM1m = NPM1 mutation; ORR = overall response rate; R/*R* = relapsed/refractory; REV = revumenib; TLS = tumor lysis syndrome; VEN = venetoclax; ZIFTO = ziftomenib.

mutant clones. The regimen was well tolerated, with lower rates of IDH-inhibitor-related toxicity, including differentiation syndrome, compared to ENA monotherapy - possibly due to the cytoreductive effect of HMA + VEN.

These results support the VEN + DEC–*C* + IDHi triplets as a highly promising frontline strategy in elderly patients with *IDH1/2*-mutated AML, with durable responses and a manageable safety profile. Prospective randomized studies are warranted to compare these triplets against standard VEN + HMA doublets.

For patients with *NPM1*-mutated or *KMT2A*-rearranged AML, the SAVE study (NCT05360160) investigated the triplet combination of DEC–*C* + VEN + REV.[118] Among 19 patients, CRc was 84% overall and 89% in the ND cohort. MRD negativity was seen in 81% of evaluable responders. Median OS was not reached in ND and was 9.3 months in R/R patients.

In the maintenance setting, a similar strategy is being evaluated in a phase 1b trial (NCT05010772, Cohort 2), investigating DEC–*C* + VEN combined with targeted agents (Gilteritinib, Enasidenib, or Ivosidenib) in AML patients in CR following LDAC- or HMA-based therapy who are ineligible for transplant.[119] Preliminary results indicate good tolerability and promising early RFS. The study is ongoing, and a longer follow-up is needed to assess the durability of the benefit.

Conclusions

In recent years, the therapeutic landscape of AML has been transformed, moving from decades of stagnation to better genetic risk stratification for intensive and less-intensive treatment and a broad portfolio of targeted agents. Significant advances came particularly from research over the past 15 years, where systems biology approaches have identified the complement of driver mutations in AML. These discoveries have prompted the development of novel drugs targeting these mutations, such as mutated FLT3. Building on this progress, the field is now also advancing toward therapies that exploit subtype-specific epigenetic vulnerabilities, as seen with menin inhibitors, moving beyond strategies that rely solely on direct mutation targeting.

Many of the novel drugs discussed in this review are being assessed in ongoing randomized trials in both combination with intensive chemotherapy, as well as chemotherapy-free, multi-agent regimens designed for less intensive treatment. Already at late stages of clinical development, results from some of these trials are expected soon and will likely reshape AML care profoundly. While these developments will provide more effective therapeutic options for specific AML subtypes, clinicians will face the challenge to balance the benefits of intensified targeted approaches against the promise of multi-agent, chemotherapy-free regimens that may achieve durable remissions but carry new toxicity profiles. Thoughtfully designed future clinical trials comparing these novel intensive and less-intensive strategies will therefore be instrumental in guiding clinician choices and ushering in a new era of precision medicine in AML.

Author contributions

Discussion and analysis of published data: CS, AG, HD, MWMK. Editing of the manuscript: CS, AG, HD, MWMK. Writing of the manuscript: CS, AG, HD, MWMK. Creating the Figure: CS.

Declaration of competing interest

CS and AG declare no conflicts of interest related to this work. HD: Consultancy: AbbVie, Otsuka, Pfizer, Servier, Syndax; clinical research funding to institution: AbbVie, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, Servier; travel, accommodation: Abbvie, Servier. MWMK receives is a consultant for Pfizer, Kura Oncology, Jazz Pharmaceuticals, Bristol-Myers Squibb/Celgene Abbvie, Servier, Johnson & Johnson, and Blueprint; is on the speaker's bureau of Gilead, received travel support from Abbvie, Servier, Johnson & Johnson, Bristol-Myers Squibb/Celgene, and Daiichi Sankyo, and research funding from Kura-Oncology and Syndax.

CRediT authorship contribution statement

Carolin Seeling: Conceptualization, Data curation, Investigation, Methodology, Validation, Visualization, Writing – original draft. **Arnold Ganser:** Conceptualization, Data curation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Hartmut Döhner:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Michael W.M. Kühn:** Conceptualization, Data curation, Formal analysis, Investigation, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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