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Hypomethylating agent-based therapies in older adults with acute myeloid leukemia – A joint review by the Young International Society of Geriatric Oncology and European Society for Blood and Marrow Transplantation Trainee Committee

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Abstract

Acute myeloid leukemia (AML) is associated with poor outcomes in older adults. A major goal of treatment is to balance quality of life and functional independence with disease control. With the approval of new, more tolerable regimens, more older adults are able to receive AML-directed therapy. Among these options are hypomethylating agents (HMAs), specifically azacitidine and decitabine. HMAs have become an integral part of AML therapy over the last two decades. These agents are used either as monotherapy or nowadays more commonly in combination with other agents such as the Bcl-2 inhibitor venetoclax. Biological AML characteristics, such as molecular and cytogenetic risk factors, play crucial roles in guiding treatment decisions. In patients with high-risk AML, HMAs are increasingly used rather than intensive chemotherapy, although further trials based on a risk-adapted approach using patient-and disease-related factors are needed. Here, we review trials and evidence for the use of HMA monotherapy and combination therapy in the management of older adults with AML. Furthermore, we discuss the use of HMAs and HMA combination therapies in AML, mechanisms of action, their incorporation into hematopoietic stem cell transplantation strategies, and their use in patients with comorbidities and reduced organ function.

Keywords

Hypomethylating agents; azacitidine; decitabine; guadecitabine; older adults; acute myeloid leukemia

Introduction

The incidence of acute myeloid leukemia (AML) increases with age; the incidence is 17.6 per 100,000 in those aged ≥65 years compared to 1.8/100,000 in those aged <65 years in the US [1]. Despite improvements in recent years, overall survival (OS) in older adults remains poor; median OS (mOS) is 6–11 months in studies up to 2021 [2–5]. Therefore, consideration of patient preferences is essential when choosing treatments, as older patients may prioritize functional independence and quality of life (QoL) over survival duration [6, 7].

Hypomethylating agents (HMAs) such as azacitidine (AZA) and decitabine (DEC) are lower intensity treatments and have been used increasingly for the treatment of AML in the last two decades. With the approval of the Bcl-2 inhibitor venetoclax (VEN), its combination with HMAs has become the standard of care for many older adults with AML, especially those who are unfit for intensive chemotherapy (IC). As a result, outcomes in older adults

have likely improved, although the disease is still largely incurable. For the purpose of this review, “older” is defined as ≥60 years, although it is important to acknowledge that physiologic age is more important than chronological age.

In this narrative review, we provide an overview of HMAs and discuss their use alone and in combination therapies in AML, their mechanisms of action, and their incorporation in hematopoietic stem cell transplantation (HSCT) strategies. We also review the use of HMAs in patients with impaired kidney function.

Mechanism of action of HMAs

HMAs are pan-DNA methyltransferase (DNMT) inhibitors. AZA is a ribonucleoside and DEC, a deoxyribonucleoside [8]. HMAs interfere with cancer cell survival by reactivating transcriptionally silenced tumor suppressor genes, reversing the acquired DNA methylation of cancer cells, and targeting specific gain-of-function mutations in epigenetic enzymes [9]. In addition to the demethylating effects, incorporation of AZA, but not DEC, in RNA blocks transfer RNA methylation [10] and decreases protein synthesis [11] which promotes apoptosis (Figure 1). Furthermore, HMAs reactivate endogenous retroviral elements, thereby inducing an anti-tumor immune response via interferons [12]. HMAs also increase the expression of tumor-associated antigens which potentially triggers anti-tumoral T-cell-mediated immune responses [13]. In a small series of patients with myelodysplastic neoplasia (MDN), HMA treatment is associated with demethylation and up-regulation of the oncogene *SALL4* which is associated with an inferior survival [14], although the clinical implication of this finding requires further study.

AZA and DEC are administered intravenously (AZA and DEC) or via subcutaneous (AZA) injection. AZA is also available orally (CC-486), but oral AZA is not bioequivalent to the injectable form [15] and therefore should not be substituted for injectable versions. When taken continuously, oral AZA prolongs drug exposure and correlates with the extent of hypomethylation [15]. Oral AZA is approved for use in the maintenance setting for AML. DEC is available as a fixed oral combination with cedazuridine, a cytidine deaminase inhibitor that increases the oral bioavailability of DEC. DEC/cedazuridine is approved in the US for use in MDN and chronic myelomonocytic leukemia (CMML), but not in AML [16]. A newer HMA, guadecitabine, a prodrug of DEC, is resistant to deamination by cytidine deaminases, resulting in a prolonged half-life of the active metabolite [17]. As guadecitabine failed its primary endpoint in the ASTRAL study [18], its use is not further explored in clinical trials. Although AZA and DEC are generally seen as equivalent, no randomized trials have compared AZA with DEC. Two large meta-analyses included published clinical trials that had tested either AZA and DEC [19, 20]. One found no difference in all outcomes [20], and the second suggested that mortality may be lower with AZA compared to DEC, although with low certainty [19]. There were no differences in treatment-related toxicities [19]. These results were supported by the ASTRAL-1 study that compared guadecitabine with AZA/DEC/low-dose cytarabine (LDAC) as first-line treatment for older adults with AML. In a separate post-hoc analysis of the standard-of-care arm, no differences between AZA and DEC in mOS or in common treatment-related toxicities were observed [21].

Pharmacokinetics of HMAs under specific considerations: Impaired renal function—Chronic kidney disease (CKD) is common in older adults [22, 23]. AZA and DEC are metabolized via hydrolysis and deamination by cytidine deaminase, which is primarily located in the liver. Metabolism is independent of cytochrome p450 enzymes. AZA and DEC are primarily eliminated in the urine [8]. Because patients with a glomerular filtration rate (GFR) of <40–60ml/min were excluded from many trials, data on HMA use in this population are scarce. A pharmacokinetic study in patients with GFR<30 ml/min demonstrated higher mean concentrations after AZA without drug accumulation [24] that would justify dose adjustment. In a case series of 28 patients with MDN and a GFR of 30–60 ml/min, no increased toxicity was demonstrated compared to individuals with normal kidney function [25]. Another single center study reported similar findings, but patients with GFR<30 ml/min did experience higher rates of toxicities [26]. An additional single center observational study using DEC [27] included 48 patients with GFR<60 ml/min and 63 patients with GRF>60 ml/min; those patients with GFR <60 ml/min demonstrated an increased incidence of grade ≥3 respiratory toxicities measured using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (40% vs. 14%; p=0.0037). All patients who developed grade ≥3 heart failure, myocardial infarction, and new-onset of atrial fibrillation had impaired kidney function [27]. Patients with impaired kidney function in this study were older (73 vs. 68 years; p<0.001), and the presence of CKD in itself is a risk factor for cardiac events. Recently, two case reports suggested that AZA use in patients undergoing hemodialysis is safe [28, 29]. Because AZA is removed during hemodialysis [29], it should be administered after treatment. In summary, severe renal impairment does not preclude HMA therapy. However, patients with a GFR<30 ml/min require close monitoring for side effects [8].

HMA monotherapy

Several clinical trials have investigated HMA monotherapy in the frontline setting of older adults with AML. Pivotal studies are summarized below and in Table 1:

AZA-AML-001—The AZA-AML-001 trial demonstrated the efficacy of AZA in comparison to conventional care regimens (CCR) in adults aged ≥65 years with AML and led to the approval of AZA as monotherapy for adults with AML deemed unfit for intensive chemotherapy (IC) approaches [30]. In this randomized phase III trial, patients were preselected for a defined treatment intensity [(IC, LDAC, or best supportive care (BSC)] before they were randomized to AZA versus CCR. Median OS was in favor of patients who received AZA, although this difference was not statistically significant (Table 1). In a post-hoc multivariate analysis, AZA reduced the risk of death by 31% [hazard ratio (HR), 0.69; 95% confidence interval (CI), 0.54–0.88; p=0.0027)] in comparison to CCR. Interestingly, patients who were preselected for BSC and randomized to receive AZA demonstrated a mOS of 5.8 vs. 3.7 months (p=0.0288) in comparison to those who received BSC.

DACO-016 trial—Based on the DACO-016 trial that demonstrated the efficacy of DEC as monotherapy in comparison to BSC/LDAC in adults aged ≥65 years with AML, DEC was approved for treatment of AML in this population. Similar to the AZA-AML-001

trial, DEC given as a five-day regimen was compared with BSC/LDAC regimens in the randomized phase III DACO-016 trial [31]. Median OS was similar in both groups (DEC: 7.7 months; 95% CI, 6.2–9.2 months; BSC/LDAC: 5.0 months; 95% CI, 4.3–6.3 months) with significantly higher response rates in patients randomized to DEC (17.8% vs. 7.8%; p=0.001) [31].

FLUGAZA Trial—The FLUGAZA trial supported the efficacy of AZA as monotherapy in comparison to an induction chemotherapy with moderate intensity in adults ≥65 years with AML. In this randomized phase III trial, AZA monotherapy was compared with FLUGA, a moderately intensive induction therapy regimen consisting of cytarabine (75mg/m^2 subcutaneously/intravenously, day 2–6), fludarabine (25 mg/m^2 intravenously/40 mg/m^2 orally, days 2–6), and G-CSF priming (filgrastim 5μg/kg, days 1–3). Treatment was continued until patients achieved measurable residual disease (MRD) negativity. Although early remission rates were significantly higher in the FLUGA arm with similar early mortality rates, mOS was superior in the AZA arm (9.8 vs. 4.1 months, p=0.005)[32].

Registry-based data—Several registry analyses support the findings from randomized trials demonstrating efficacy of HMAs as monotherapies in real-world settings. An analysis of the Austrian Azacitidine Registry compared patients treated in the real-world setting (n=95) who met the inclusion criteria of the AZA-AML-001 trial and demonstrated similar OS (Table 1) [33]. Pooled European registry data including >3000 patients aged ≥70 years treated with IC or HMAs from 2007 to 2018 [4] demonstrated no significant difference in mOS between the treatment groups, but patients who received IC had higher rates of response (Table 1). A time-dependent effect of the treatments on OS was demonstrated: HMAs were associated with a lower risk for death within the first 1.5 months of treatment, whereas IC was associated with a significantly improved OS after four months of treatment [4].

Benefits of HMA beyond remission—A meta-analysis of 26 trials (20 of which involved HMAs) [34] that included patients with newly diagnosed AML demonstrated a significant correlation between complete remission (CR)/CR with incomplete count recovery (CRi) and mOS. However, failure to achieve a CR does not mean that patients fail to benefit from treatment. In the AZA-AML-001 study, patients in the AZA group had an increased OS compared with CCR even among those patients who failed to achieve a CR (6.9 vs. 4.2 months, respectively; HR, 0.77; 95% CI, 0.62–0.95; p=0.017) [30]. In the DACO-016 study, OS improved in patients who achieved transfusion independence, even among those who did not achieve CR [35]. In a single center study of 56 patients aged 59–91 years with newly diagnosed AML treated with an HMA, stable disease for ≥6 cycles led to an OS benefit (18 vs. 4 months; p=0.0002) [36]. In an analysis of 302 patients from the Austrian Azacitidine Registry, disease stabilization and/or a hematological response resulted in a clinically relevant OS benefit (mOS among those with stable disease: 8.1 months; mOS among those with hematological response: 9.7 months; and mOS among those who achieved both: 18.9 months; mOS (without stable disease/hematological response): 3.2 months] [37]. Other possible benefits included reduction in transfusion frequency and improved QoL [30, 35, 38].

HMA combination therapies: Approved options

Given the benefits of HMA monotherapies, several HMA combination therapies have been investigated and approved. Some of these combinations specifically target potential mechanisms of treatment resistance [39]. In this section, we summarize the key studies.

HMA and venetoclax—Preclinical data demonstrated that HMAs plus VEN provides synergies in inducing apoptosis through several mechanisms (e.g., AZA upregulates NOXA, a key player within the mitochondrial apoptosis pathway, thereby increasing the sensitivity of leukemic blasts to the BCL-2 inhibition by VEN [40].) Based on the results of the VIALE-A study that compared AZA/VEN with AZA monotherapy in adults ≥75 years or with comorbidities precluding IC, AZA/VEN was approved for this patient population and has become the standard of care for many older adults with AML.

After the successful Phase Ib study of HMA/VEN [41], the subsequent phase III VIALE-A study on AZA/VEN versus AZA alone included patients ineligible for IC based on their age (≥75 years) and/or coexisting conditions. Approximately 60% of patients were ≥75 years. The study demonstrated improved mOS in the combined arm (14.7 vs. 9.6 months; HR, 0.66; $p<0.0001$), and serious AE rates were similar (83% in the AZA/VEN vs. 73% in the AZA arms) [42]. In a subgroup analysis by age, the OS benefit extended to patients ≥75 years (HR, 0.54; 95% CI, 0.39–0.73). In addition, more patients achieved transfusion independence for PRBCs and platelets in the AZA/VEN arm. The median time to first response was 1.0 month (range: 0.6–14.3) in the AZA/VEN arm compared to 2.6 months in the AZA alone arm (range: 0.8–13.2). Although the percentage of patients who discontinued treatment due to AEs and early mortality was similar in both groups, several AEs were more frequent in the AZA/VEN arm [e.g., neutropenia (AZA/VEN: 19%; AZA: 10%), febrile neutropenia (AZA/VEN: 20%; AZA: 4%)] [42].

Response rates for HMA/VEN in patients with *NPM1*- and *IDH1/2*-mutated AML were >65% [42–44], which corresponded to reasonable median durations of response (*IDH1/2*: 29.5 months, *NPM1*: not reached; Table 3) [45]. These results will likely encourage the comparison of HMA/VEN and IC in fit older adults with *NPM1*- and *IDH1/2*-mutated AML. The high CR and OS rates in patients with *IDH1/2*-mutated AML are due to the strong dependence of these subtypes on *BCL-2* due to the oncometabolite (R)-2-hydroxyglutarate. This oncometabolite inhibits the activity of cytochrome c oxidase (COX) in the mitochondrial electron transport chain. Reduced COX activity lowers the mitochondrial threshold to trigger apoptosis during *BCL-2* inhibition [46]. In contrast, the ORR in patients with *TP53* mutations was ~53–55% [45, 47] with a median duration of response of 6.5 months [45]. Although these response rates were superior to those reported in many different trials in patients treated with IC, the OS was not different from that achieved with AZA alone [48], and the OS in patients with *TP53* mutations remained inferior compared to other molecular subtypes (Table 3), as *TP53* mutations contribute to primary and acquired AZA/VEN resistance [49].

Most clinical trials on HMA/VEN have excluded patients with core binding factor (CBF-) leukemia [30, 31, 41, 42] based on its sensitivity to high-dose cytarabine. Although CBF leukemia occurs less frequently in older than in younger patients with AML, older patients

are often less likely to be able to receive IC with high-dose cytarabine. One multicenter retrospective case series demonstrated a response rate of 80% in patients with newly diagnosed or relapsed/refractory (R/R) CBF leukemia who received HMA/VEN. Of those, 70% were >65 years old [50]. Further data on the efficacy of HMA/VEN-based treatments in CBF leukemia are required before its standard use can be recommended.

HMA and ivosidenib, an isocitrate dehydrogenase (IDH) 1 inhibitor—The *IDH1* inhibitor ivosidenib (IVO) is approved by the US Food and Drug Administration (FDA) for R/R AML with *IDH1* mutation. Although IVO has shown an ORR of ~40% as monotherapy in R/R AML, the duration of response was limited [51, 52]. *IDH1/2* inhibition induces a differentiation of leukemic blasts rather than eradication [53]. This fact underlines the need for combination therapy that synergizes with *IDH* inhibitors to promote apoptosis. Based on the results of the AGILE trial [54] that compared AZA/IVO with AZA monotherapy, the FDA recently approved this combination for adults with newly diagnosed, *IDH1*-mutated AML who are unfit for IC.

The phase III AGILE trial compared AZA/IVO with AZA/placebo and included patients with newly diagnosed, *IDH1*-mutated AML ineligible for IC due to age ≥75 years and/or a coexisting condition (severe cardiac or pulmonary disorder, renal impairment, or elevated bilirubin). The median age was ~76 years. The study demonstrated a mOS benefit for AZA/IVO of 24.0 vs. 7.9 months (HR for death, 0.44; 95% CI, 0.27–0.73; p=0.001) [54]. Median time to CR was not significantly different between arms. Transfusion independence was higher with AZA/IVO (46% vs. 18%; p=0.006) [54].

In summary, assessment of patient-related (through geriatric assessment) and disease-related factors (Table 3) as well as patient preferences is essential when choosing treatments for older adults with newly diagnosed AML. Information on GA domains and tools for their evaluation have been previously described [55, 56]. A proposed approach is shown in Figure 2. In addition to disease responses, important patient-centered outcomes such as time spent at home and quality of life should be considered. For example, time spent at home following HMA treatments is longer than that following IC (205 vs. 187 days), with similar times for AZA/VEN and AZA monotherapy [57, 58].

In the authors' opinion, if patients are deemed unfit to receive IC, HMA/VEN should be the first-line treatment. For patients with *IDH1*-mutated AML, HMA/IVO can also be considered. The median time-to-response (CR/CRi) was 1.3 months (range, 0.6 to 9.9) for AZA/VEN [59] and 4.0 months (range, 1.7–8.6) for AZA/IVO [54]. AZA/VEN may be considered for patients with highly proliferative disease and for those in urgent need of achievement of response. Among patients who are frail but who wish to pursue treatment, monotherapy with HMAs or *IDH* inhibitors (the latter for among those with IDH-1 mutated AML) can be considered.

HMA combination therapies: Experimental combinations

Several HMA combinations are currently being explored in clinical trials. We summarize synergistic mechanisms and provide an overview of the preliminary results below and in Table 2. Studies generally included heterogenous groups of patients of all ages with

newly diagnosed AML and relapsed/refractory (R/R) AML. When available, patient ages are included in Table 2.

HMA and fms-like tyrosine kinase 3 (FLT3) inhibitors—Synergistic anti-leukemia activity in *FLT3*-mutated AML was demonstrated in preclinical models for HMA/*FLT3*-inhibitor combinations compared with either agent alone [9, 60]. These combinations were subsequently studied clinically in *FLT3*-mutated AML using gilteritinib [61, 62] and in both *FLT3*-mutated and *FLT3*-WT AML using quizartinib [63]. Overall response rates (ORR) varied from 67% in the AZA/gilteritinib study to 87% in the AZA/quizartinib study (Table 2) [62–64]. Recently, the combination of DEC as a 10-day regimen plus VEN plus a *FLT3*-inhibitor of choice (sorafenib, gilteritinib, or midostaurin) showed a promising ORR of 92% with MRD negativity in 56% of newly diagnosed AML patients aged ≥ 60 years (N=12) [65]. The randomized phase III trial (LACEWING) that compared AZA monotherapy with AZA and gilteritinib in patients ineligible for IC was prematurely closed, as interim analysis failed the boundary for futility and the OS did not differ between arms, although the composite CR rate of the combination was superior [61]. Whether the combination of HMA with a *FLT3* inhibitor provides added benefits needs to be further evaluated, possibly in the context of triplet therapies with VEN.

HMA and enasidenib, an IDH2 inhibitor—*IDH2* inhibition has the same mechanistic rationale as *IDH1* inhibition. The *IDH2* inhibitor enasidenib is approved by the FDA for R/R AML with *IDH2* mutation with an ORR of ~40% [51]. Early phase studies combining HMA and enasidenib demonstrated promising CR rates of 54% in older adults with newly diagnosed AML [66, 67]. Further randomized trials of this combination are pending.

HMA and checkpoint inhibitors—In the last decade, immune checkpoint inhibitors have revolutionized the treatment of several solid cancers. The rationale for their use in AML was the expression of PD-L1 on leukemic blasts, especially in *TP53*-mutated disease [68]. Early single-arm trials with the combination of HMAs and checkpoint inhibitors in R/R AML patients of all ages provided some encouraging evidence. The results are summarized in Tables 2 and 3. However, the Intergroup LEAP (Less Intense AML Therapy Platform) trial (S1612, NCT03092674), a randomized phase II/III study comparing AZA plus nivolumab with AZA as monotherapy in adults ≥ 60 years with newly diagnosed AML or high-risk MDN deemed unfit for IC [69] was prematurely closed due to an increased rate of therapy-related mortality in the combination arm [70].

HMA and magrolimab—Magrolimab is an anti-CD47 antibody that disrupts the major macrophage immune checkpoint (“do not eat me signal”), thereby enabling a robust anti-leukemic immune response [71]. In preclinical studies, upregulation of CD47 by AZA and synergistic activity of AZA plus magrolimab was demonstrated [72]. A phase Ib trial of AZA/magrolimab demonstrated that the treatment was well tolerated in unfit patients with AML or high-risk MDN who had not received treatment [73]. Remarkably, among participants with *TP53*-mutated AML, mOS was 12.9 months with 10/21 patients (48%) achieving a CR and 4/21 (19%) a CRi [74]. Thus, the combination of AZA/magrolimab could potentially fill the gap for patients with *TP53*-mutated AML unfit for IC,

although additional studies are needed. The ENHANCE-2 trial, a phase III trial comparing AZA/VEN/magrolimab with AZA/VEN/placebo, is currently ongoing for patients with AML unfit for IC.

Other HMA combinations—Other HMA combinations are currently being tested in clinical trials. Among these are the histone deacetylase inhibitors romidepsin [75] and vorinostat [76], the exportin-1 inhibitor selinexor [77], the CD33-antibody-drug conjugate vadastuximab talirine [78], the inhibitor of neural precursor cell expressed, developmentally downregulated 8 (NEDD8) activating enzyme (NAE) pevonedistat [79, 80], the CD33 antibody-drug conjugate gemtuzumab ozogamicin [81], the proteasome inhibitor bortezomib [82], and the *TP53* reactivator eprenetapopt (APR-246) [83].

Future directions in the upfront setting

Many questions remain about the use of HMA-based therapies in the upfront setting. First, should AZA/VEN or AZA/IVO be used in patients with newly diagnosed *IDH1*-mutated AML. Second, because HMA/VEN is associated with prolonged neutropenia, studies to guide its dose adjustment are needed. AZA/VEN is given continuously. Whether it can be stopped or interrupted after achieving MRD negativity is unclear. Drug interruption could lead to better QoL. Third, sequential therapies are attractive areas of investigation to improve treatment tolerability (e.g., switch from AZA/VEN to AZA/IVO after achieving a CR to potentially avoid prolonged neutropenia; switch from HMA monotherapy to HMA/VEN due to concern over the use of combination therapies in the upfront setting; switch from HMA/VEN to HMA monotherapy due to adverse events). Finally, triplet therapies may have the potential to overcome therapy resistance by targeting molecular vulnerabilities of the respective AML subtypes.

HMAs as maintenance therapy

Oral AZA (CC-486) is approved for maintenance therapy following IC in older adults with AML who are not candidates for HSCT or choose not to move forward to HSCT based on the results of the QUAZAR AML-001 study [84]. Other HMAs are being studied for maintenance therapy as summarized below but are not approved for this indication.

QUAZAR AML-001 confirmed an OS benefit for oral AZA (CC-486; 300 mg daily, d1–14, q4 wks) versus placebo after IC. A total of 472 patients aged ≥55 years with AML in CR/CRi ineligible for HSCT were included. Patients randomized to receive CC-486 AZA had improved mOS (24.7 vs. 14.8 months; $p<0.01$) and relapse-free survival (RFS) (10.2 vs. 4.8 months; $p<0.01$) [84]. Neutropenia was more common than in the AZA arm (41% vs, 25%). Patients received a median of 12 cycles (range: 1–90). Common AEs included low-grade gastrointestinal events such as nausea which lasted a median of 10 days and grade 3–4 hematologic events which rarely required dose modifications. Only 13% of AEs resulted in permanent discontinuation of the drug [84]. CC-486 did not worsen patient-reported fatigue and QoL [85]. Treatment-related cytopenias typically resolved by cycle 6. Among patients who relapsed, blood counts generally decreased after approximately 9 cycles [86]. CC-486 resulted in a higher rate of conversion to MRD negativity in comparison to placebo (37% vs. 19%). Conversion was also associated with a better OS and PFS [87].

The randomized phase II ECOG-ACRIN E2906 trial was the first HMA maintenance trial performed in older patients with AML after IC and consolidation therapy (N=120; median age 69 years; range 60–85; 74% had intermediate cytogenetic risk). Patients were randomized 1:1 to receive maintenance DEC (20 mg/m^2, d1–3, q4 wks) or observation alone. At a median follow up of 49.8 months and a median of 6 cycles of DEC, disease-free survival (DFS) (15.3 vs. 9.2 months; HR, 0.77; 95% CI, 0.50–1.19; p=0.12) and OS (25.8 vs. 19.5 months; HR, 0.69; 95% CI, 0.43–1.09; p=0.06) showed non-significant trends in favor of DEC [88].

The randomized phase III HOVON97 study demonstrated that AZA (50 mg/m^2 subcutaneous injection, d1–5, q4 wks) administered until relapse for a maximum of 12 cycles as post-remission treatment after at least 2 cycles of IC and achievement of CR/CRi resulted in a significantly better DFS compared to observation (N=60) in adults ≥60 years (DFS: 64% vs 42% at 12 months; p=0.04) [89]. The benefit remained significant even after adjustment for poor-risk features (HR, 0.62; 95% CI, 0.41–0.95; p=0.026), but no OS benefit was demonstrated (84% vs. 70% at 12 months; p=0.69) [89].

Based on data from case series, HMAs appear to be effective maintenance therapies in patients with CBF AML who were MRD-positive after completion of IC [90, 91]. These results are not specific to older adults and need to be confirmed in randomized trials before HMA maintenance can be recommended in patients with CBF leukemia.

In summary, based on the QUAZAR AML-001 study, maintenance therapy with CC-486 is recommended in older adults after IC who achieved first CR and chose not to receive HSCT.

HMAs and HSCT

HSCT is a curative treatment approach for patients with intermediate- or high-risk AML. Although HSCT is generally reserved for people who are fit (and usually those aged ≤70–80 years), the percentage of patients >70 years who receive HSCT is steadily increasing [92]. Few randomized trials exist in the HSCT setting, especially among older adults. This paucity of results needs to be taken into account when considering data on HMA use in the HSCT setting.

Bridging to HSCT—HMAs have been used successfully as a bridge to HSCT. In the R/R setting, a retrospective study of 655 patients who received HMAs as salvage therapy found that 6% (mean age=56 years) underwent HSCT [93]. Median OS after HSCT was fifteen months. When HMA/VEN was used as salvage treatment in a case series, six out of nine patients were able to undergo HSCT, although only one was aged >60 years [94]. In another retrospective study of 33 patients (median age=62 years) with R/R AML treated with DEC/VEN, only three patients underwent HSCT [95]. A post-hoc analysis of 31 patients (median age 69 years; 10% of the trial population) who received HSCT after upfront treatment with HMA/VEN or LDAC/VEN in two pivotal clinical trials (NCT02287233 and NCT02203773) found a one-year post-HSCT OS of 68%, and 55% of patients remained in remission for at least one year post-HSCT [96]. Similar survival rates after HSCT following treatment with HMA/VEN in either the front-line or R/R setting have been demonstrated in several observational studies [97–102].

HMA as part of conditioning for HSCT—A few small studies (N=23–65) have investigated the addition of HMAs to the conditioning regimen prior to HSCT, although this is not routinely done in clinical practice [103–105]. A phase I study (N=23) combined high-dose DEC with busulfan and cyclophosphamide conditioning and found a high response rate (40% DFS, median= 3.3 years) without increased treatment-related toxicities in the early phase after HSCT [103]. However, given the myeloablative intensity of the regimen, only patients aged <55 years of age were included in the study. The combination of a non-myeloablative conditioning regimen (fludarabine/2 Gy total-body irradiation) with DEC was tested in a prospective Dutch study of 30 patients (median age=59 years) who underwent HSCT for myeloid malignancies (seventeen patients had AML) [104]. The addition of DEC was found to enhance the induction of a tumor-associated antigens-reactive CD8+ T cell response in vivo, and the authors suggested that DEC may contribute to disease control post-HSCT. A third retrospective study reported outcomes after combining DEC with standard myeloablative regimens in 65 patients with R/R AML (median age=37 years) and found a higher OS at three years when compared with a historical cohort (50% vs. 18.5%; $p<0.05$) [105]. Whether integration of HMAs into conditioning regimens might provide acceptable tolerability and effectiveness needs to be determined in future clinical trials.

Maintenance after HSCT—Several clinical trials have investigated the use of HMAs as post-HSCT maintenance therapy [106]. A meta-analysis of ten studies found two-year OS and RFS estimates of 66% and 62%, respectively [107]. A randomized, open-label phase II study of granulocyte colony-stimulating factor (G-CSF) combined with DEC prophylaxis vs. control in patients with high-risk MRD-negative AML after HSCT (all aged ≤62 years) found that patients in the intervention arm had decreased relapse rates and improved OS at two years (86% vs. 70% in the control arm; $p=0.01$) [108]. In contrast, a randomized, open-label phase III trial of AZA maintenance post-HSCT vs. control in patients with AML or MDS (median age=57 years) had inconclusive results for OS (HR for OS, 0.84; $p=0.43$) [109].

Relapse after HSCT—HMAs have also been investigated for pre-emptive or salvage treatment of relapse post-HSCT [110]. Pre-emptive use, often in conjunction with donor lymphocyte infusion (DLI) in the case of decreasing chimerism and/or molecular relapse is promising [110]. The RELAZA trial evaluated the efficacy of AZA monotherapy in the case of decreasing donor chimerism (as a surrogate for an imminent molecular relapse) after HSCT and demonstrated a stabilization or increase in chimerism in 80% of patients [111]. The median age was 58 years. No randomized or prospective observational studies for the use of HMA with DLIs are currently available, but the efficacy of this combination was shown in several case series (summarized in [112]). The immunological rationales for this strategy comprise the upregulation of cancer antigens and/or endogenous retroviruses together with changes in cell-mediated immune responses. For example, AZA was shown to increase the number of CD4+CD25+FOXP3+CD127–regulatory T-cells after HSCT, thereby promoting a graft-versus-leukemia effect without increasing the risk for graft-versus-host disease [110]. Despite these results, treatment schedules (sequence of AZA/DLIs, duration, and dosages) for this approach are not standardized.

In summary, HMAs could facilitate bridging to HSCT, especially in the R/R setting. Their pre-emptive application in the case of a molecular relapse after HSCT is widely employed, particularly in combination with DLIs. Post-HSCT HMA maintenance is not generally used due to mixed results, and further studies are needed to identify which patients might benefit the most from such an approach.

HMAs for relapsed disease—Relapsed AML has a dismal prognosis and no standardized treatment approach. Although studies, primarily retrospective, have demonstrated that HMA monotherapy or combination therapies may improve outcomes, no prospective randomized trials comparing HMA with IC salvage have been conducted. Therefore, the choice of therapy must be individualized. Early clinical trials and retrospective data are summarized in Table 4. Weak evidence has been reported for HMA/VEN effectiveness, even in patients who had been treated with or progressed during HMA monotherapy [113, 114].

Conclusion

HMA combination therapies are effective in older adults with AML and reasonably tolerated in selected patients. Nonetheless, prognosis remains poor in this population. Further research is needed to improve outcomes, especially among those with adverse risk factors such as high-risk cytogenetics and *TP53* mutations.

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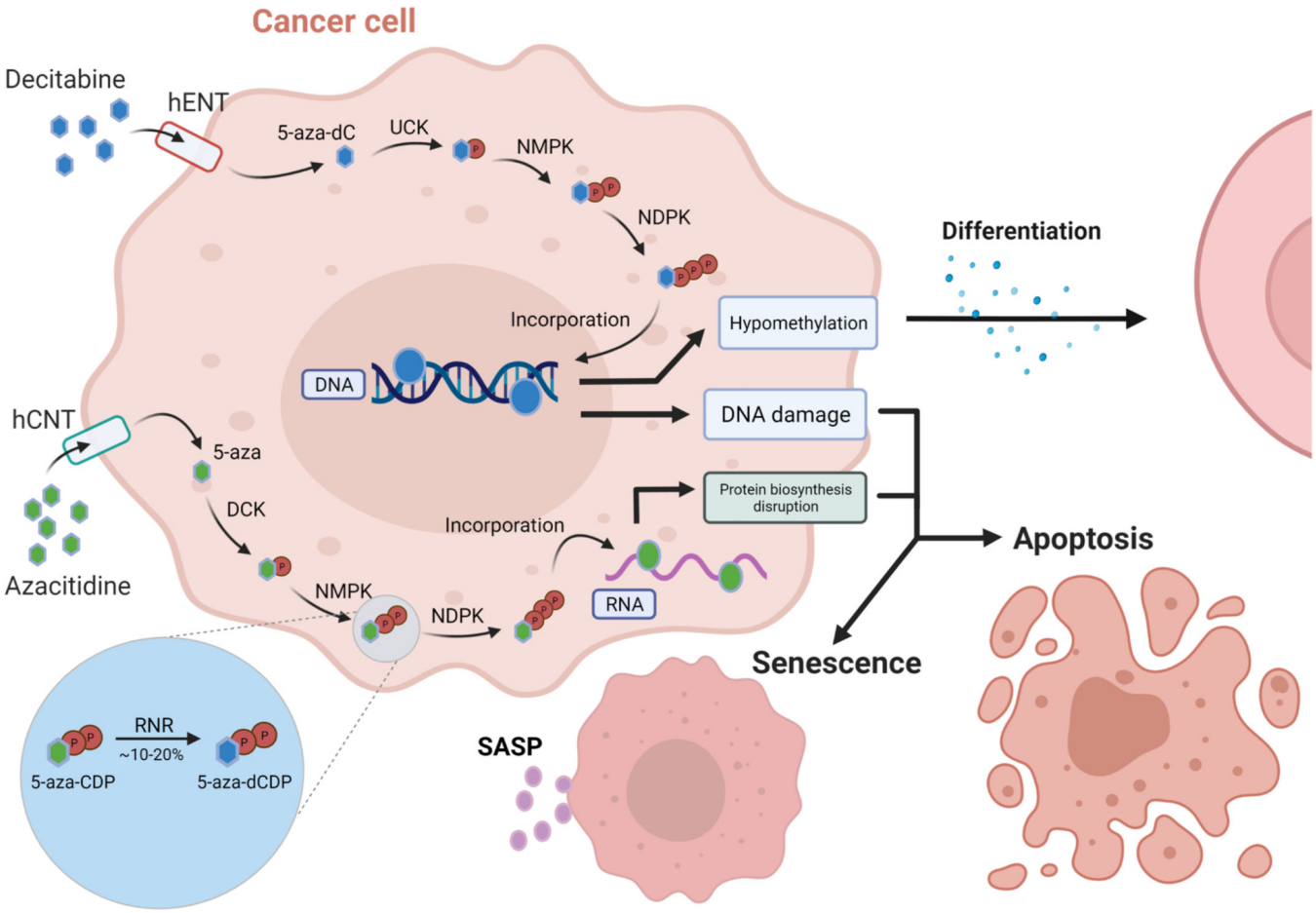

Figure 1: Mechanisms of action of hypomethylating agents

Hypomethylating agents are unstable in plasma after absorption due to spontaneous hydrolysis and deamination by cytidine deaminase (CDA) [115]. The cellular uptake is mediated by different nucleoside transporters (hCNT for AZA and hENT for DEC). The enzymes catalyzing the first limiting phosphorylation step are uridine-cytidine kinase (UCK) for AZA and deoxycytidine kinase (DCK) for DEC, respectively. Following their cellular uptake, which is dependent on nucleoside transporters, they are three times successively phosphorylated by intracellular kinases. The active tri-phosphorylated metabolite of 5-aza-dCTP (DEC) is directly incorporated into DNA during cell cycle. For AZA, only 10–20% of AZA follows the DNA incorporation during replication; the majority of 5-aza-CTP is incorporated in RNA. DAC incorporated into DNA binds DNMT1 and leads to its degradation, promoting a progressive DNA hypomethylation after several rounds of replication [17]. This has been postulated to lead to an activation of repressed tumor suppressor genes [116], inducing senescence and apoptosis. The figure was created with BioRender.com.

Abbreviations: AZA, azacitidine; DEC, decitabine; hCNT human concentrative nucleoside transporter; hENT, human equilibrative nucleoside transporter; NDPK, nucleoside diphosphate kinase; NMPK, nucleoside monophosphate kinase; RNR, ribonucleotide reductase; SASP, Senescence-associated secretory phenotype.

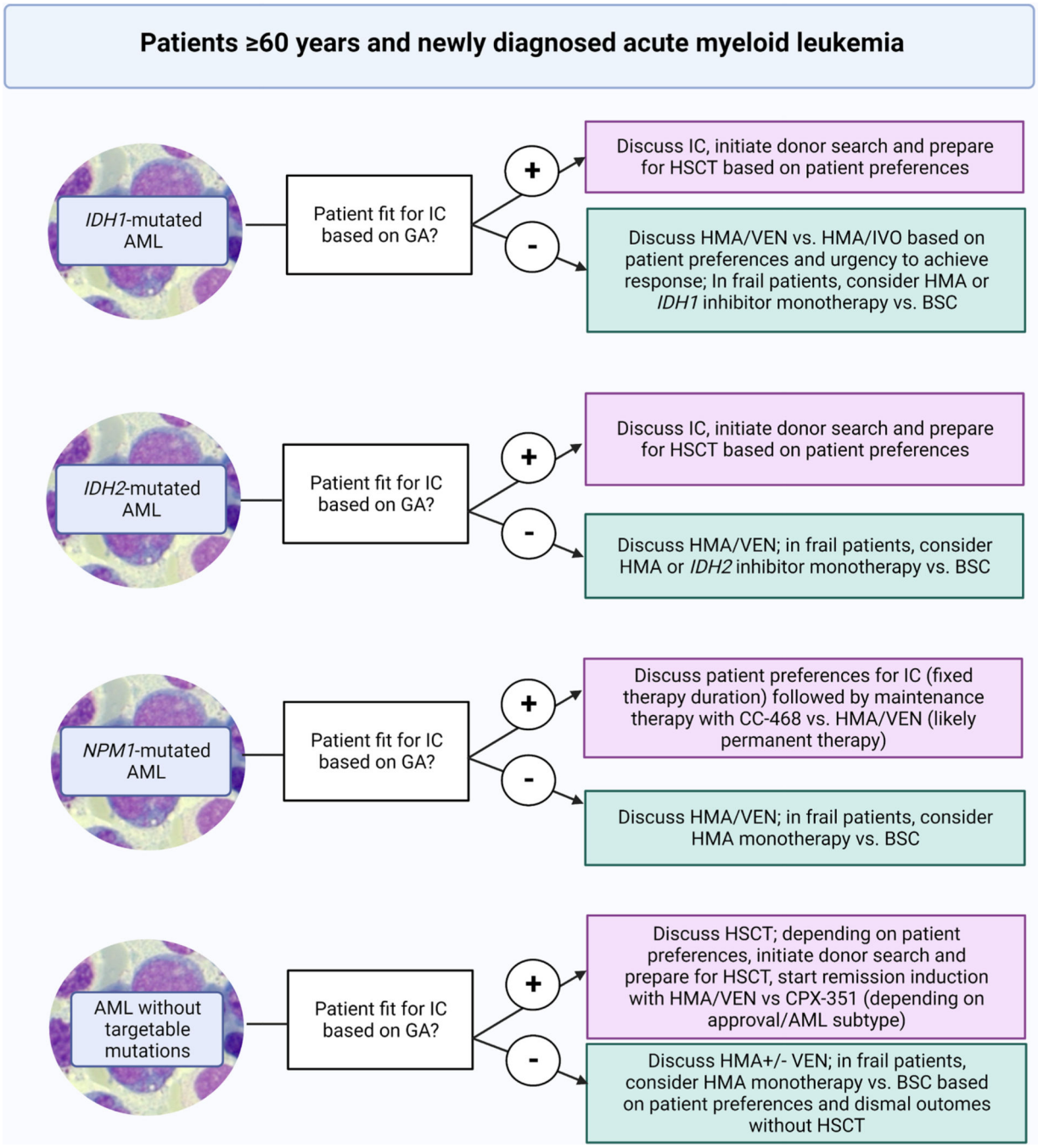

Figure 2: How to guide therapy-decisions in older adults with AML

Future therapy-decision making in older adults with AML will most likely be guided by an integrative approach of GA- und biology-driven factors. This figure depicts possible pathways in decision making that are not based on solid evidence due to lack of data but rather biological rationales and practise-guided concepts. GA impairments predictive of worse outcomes with IC are short physical performance battery (SPPB) sum score <9 and/or mini mental state examination (MMSE) <24 [117]. Among comorbidities that preclude from intensive chemotherapy are symptomatic heart failure, advanced chronic kidney failure,

and/or other life-threatening comorbidities. For evaluation of patient priorities, possible factors for discussion are the time spend at home, chance of cure or long-term control versus palliative options, treatment-related side-effects, transfusion requirements, and quality of life.

Abbreviations: IC, intensive chemotherapy, comprises “7+3”-like therapies +/− Gemtuzumab ozogamizin and Midostaurin.

Table 1:

Summary of data on HMAs as monotherapy in AML

Study	Design and setting	Trial arms	N and age (years)	Key findings
Phase III trials				
AZA-AML-001 (NCT01074047) [30]	Phase III Newly diagnosed AML>30% blasts	AZA 75 mg/m^2 d1–8, q4 wks vs. CCRs (18.2% BSC, 64% LDAC, and 17.8% IC)	N=488; median age: 75 y (range: 64–91 y)	mOS: AZA 10.4 m (95% CI, 8.0–12.7 m) vs. CCRs 6.5 m (95% CI, 5.0–8.6 m), p=0.1009
DAC0–016 [31]	Phase III Newly diagnosed AML	DEC 20 mg/m^2 d1–5, q4 wks vs. TC (BSC/LDAC)	N=485; median age: 73 y (range: 64–91 y)	mOS: DEC 7.7 m (95% CI, 6.2–9.2 m) vs. TC 5.0 m (95% CI, 4.3–6.3 m), p=0.108 CR/CRp: DEC 17.8% vs. TC 7.8%
ASTRAL-1 (NCT02920008) [18]	Phase III Newly diagnosed AML	GUA 60 mg/m^2, d1–5, q4 wks vs. TC (AZA, DEC, LDAC)	N=815; median age: 76 y (range: 56–94 y); PA75: ~62%	mOS: GUA 7.1 m vs. TC 8.47 m, p=0.73 mOS (if received ≥4 cycles): GUA 15.6 m vs. TC 13.6 m, p=0.02 mOS (if received ≥6 cycles): GUA 19.5 m vs. TC 14.0 m, p=0.002
FLUGAZA (NCT02319135) [32]	Phase III Newly diagnosed AML	FLUGA q4 wks (fludarabine 25 mg/m^2, d2–6, cytarabine 75 mg/m^2, d2–6, and filgrastim 5μg/kg, d1–3) vs. AZA 75 mg/m^2, d1–7, q4 wks	N= 283; median age: 75 y (range: 65–90 y)	mOS: FLUGA 4.1 m (95% CI, 2.7–5.5 m) vs. AZA 9.8 m (95% CI, 5.6–14 m), p=0.005) CR after 3 cycles: FLUGA 18% vs. AZA 9%, p=0.04 CR/CRi after 9 m: FLUGA 33% vs. AZA 29%, p=0.41
Phase II trials				
NCT01786343 [118]	Phase II Newly diagnosed AML	DEC-5 q4 wks (DEC 20 mg/m^2, d1–5,) vs. DEC-10 q4 wks (DEC 20 mg/m^2, d1–10)	N=78; median age: 77 y	1y-OS: 25% in both arms; no differences in CR, CRi, OS
Retrospective data				
Austrian Azacitidine Registry (NCT01595295) [37]	Newly diagnosed AML (46%)	AZA monotherapy (various regimens)	N=302; median age: 73 y (range: 30–93 y); PA60: n.f.s.; PA75: 43%.	mOS: 9.6 m (95 % CI, 8.53–10.7m)
[4]	Pooled European registry data Newly diagnosed AML ≥70 y	HMAs (various monotherapy regimens) vs. IC (various regimens)	N=3,700 (HMAs: N=1,073; IC: N=1,199); median age: 75 y (range: 72.5–79 y)	mOS: IC 10.9 m (95% CI, 9.7–11.6 m) vs. HMA 9.2 m (95% CI, 8.3–10.2 m) CR/CRi: IC 56.1% vs. HMA 19.7%, p <0.0001
[119]	Pooled European registry data	AZA monotherapy	N=710; median age: 75 y (range: 60–93 y)	mOS: 9.0 m (95% CI, 8.8–11 m)
[120]	Retrospective data (three centers) Newly diagnosed AML and MDS	AZA, standard regimen in 69%, 5-day regimen in 31%	N=115; N (AML)=63; N (MDS)=53; median age: 82 y (range: 80–92 y)	mOS (AML): 9.7 m
[121]	Retrospective data (Apulian Hematological Network) Newly diagnosed AML and R/R AML	DEC 20 mg/m^2, d1–5, q4 wks	N=199; newly diagnosed AML: N=94; median age: 75.4 y (range: 61–91 y)	mOS: 8.7 m (95% CI, 7.4–10.3 m)
[122]	Single center retrospective data (Moffitt Cancer Center). Newly diagnosed AML	HMAs vs. IC (cytarabine/ anthracycli ne or equivalent)	N=980 (HMA: N=255, IC: N=360); mean age (HMA): 76.5 y (range: 70.1–95.2 y), median age (IC): 73.9 y (range: 70.5–90.4 y)	mOS: HMA 14.4 m vs. IC 10.8 m (HR, 1.35; 95% CI, 1.10–1.65, p=0.004)

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; BSC, best supportive care; CCRs, conventional care regimens; CI, confidence interval; CMML, chronic myelomonocytic leukemia; CR, complete response; CRi, complete response with incomplete count recovery; DED,

decitabine; GUA, guadecitabine; HMA, hypomethylating agent; HR, hazard ratio; IC, intensive chemotherapy; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; m, months; n.f.s., not further specified; ORR, overall response rate; OS, overall survival; mOS, median overall survival; PA60, percentage above 60 years; PA75, percentage above 75 years; R/R, relapsed or refractory; TC, treatment of choice; y, years

Table 2:

Summary of data from combination trials of treatment for AML

Study	Design and setting	Trial arms	N and age (years)	Key findings
HMA plus venetoclax				
NCT02203773 [41]	Phase Ib Newly diagnosed AML	VEN 400, 800, or 1200 mg/d in combination with either DEC 20 mg/m^2, d1–5, or AZA 75 mg/m^2, d1–7	N=145; median age: 74 y (range: 65–86 y); PA75: 36%	CR/CRi: 67% Patients ≥75y: CR/CRi: 65%. CR/CRi median duration: 11.3 m mOS: 17.5 m Median duration of response, EFS, and OS (AZA/VEN; CR/CRi with MRD− vs MRD+): not reached [96]
VIALE-A NCT02993523 [42]	Phase III Newly diagnosed AML	AZA 75 mg/m^2 subQ or IV, d1-7, q4 wks/VEN (400mg PO, d1–28) vs. AZA 75 mg/m^2, d1–7/placebo, q4 wks	N=431; median age: 76 y (range: 49–91 y); PA60: n.f.s.; PA75: 61%	mOS: AZA/VEN 14.7m vs. AZA/placebo 9.6 m (HR for death, 0.66, p<0.001) Composite CR: AZA/VEN 66.4% vs. AZA/placebo 28.3%, p<0.001
NCT03404193 [123]	Phase II, single-center Newly diagnosed and R/R AML	Induction: DEC 20 mg/m^2 d1-10/VEN 400mg PO, d1–28; consolidation: DEC 20 mg/m^2, d1–5/VEN 400 mg PO, d1–28	N=70 (newly diagnosed AML); median age: 72 y (range: 70–78 y)	mOS: 18.1 m (95% CI, 10.0 m–not reached) ORR: 89%
HMA plus sorafenib				
NCT02196857 and NCT01254890 [124]	Phase I/II Newly diagnosed AML	AZA 75 mg/m^2, d1–7 sorafenib 400 mg BID, d1–28; q4 wks	N=27; median age: 74 y (range: 61–86 y)	mOS: 8.3 m CR: 26%
HMA plus FLT3 inhibitor				
NCT01892371 [63]	Phase I/II Newly diagnosed and R/R AML or high-risk MDS	Arm 1: AZA 75 mg/m^2, d1-7/ quizartinib 600 mg/d PO Arm 2: LDAC 20 mg BID, d1-10/ quizartinib 600mg PO, d1-28, q4 wks	N=74; median age: 72 y (range: 58–82 y); median age (frontline AZA/quizartinib) : 75 y (range: 64–82 y); PA60: n.f.s.; PA75: n.f.s.	Frontline setting * mOS: AZA/quizartinib 12.8 m vs. LDAC/quizartinib 4 m ORR: AZA/quizartinib 87% vs. LDAC/quizartinib 74%
LACEWING [62]	Phase III Newly diagnosed AML, FLT3+	AZA 75 mg/m^2, d1–7/GIL 120 mg/d PO, d1–28, q4 wks	N=74 (AZA/GIL), N=49 (AZA); median age: 78 y (AZA/GIL), 75 y (AZA); range: 59–75	mOS: AZA/GIL 9.82 m vs. AZA 8.87 m (HR 0.916, p=0.753) CR: AZA/GIL 16.2 vs. AZA 14.3 %, p=0.762
HMA plus *IDH1*–2 inhibitors				
NCT02677922 [66]	Phase Ib/II Newly diagnosed AML	AZA 75 mg/m^2, d1–7/ENA 100 mg/d, d1–28, q4 wks	Phase Ib: N=6; median age: 68 y (range: n.f.s.) Phase II: N=101; median age: 75 y (range: n.f.s.); PA60: n.f.s.	mOS: AZA/ENA 22 m vs. AZA alone 22.3 m (HR, 0.99, p=0.97) CR: AZA/ENA 54% vs. AZA only 12%, p<0.0001
NCT02677922 [67]	Phase Ib Newly diagnosed AML Phase III Newly diagnosed *IDH1*-mutated AML	AZA 75 mg/m^2, d1–7/IVO 500 mg/d, d1–28, q4 wks	N=23; median age: 76 y (range: 61–88 y); PA75: 52.2%	CR: 60.9% CRi/CRp: 8.7%
AGILE (NCT03173248) [54]		AZA 75 mg/m^2, d1–7/IVO 500 mg/d, d1–28, q4 wks vs. AZA 75 mg/m^2, d1-7/placebo, q4 wks	N=146; median age (AZA/IVO): 76.0 y (range: 58–84 y); median age (AZA/placebo): 75.5 y (range: 45–94 y); PA60: n.f.s.; PA75: n.f.s.	mOS: AZA/IVO 24.0 m vs. AZA/placebo 7.9 m (HR for death, 0.44; 95% CI, 0.27–0.73, p=0.001) CR: AZA/IVO 47% (95% CI, 35–59) vs. AZA/placebo 15% (95% CI, 8–25, p<0.001)
HMA plus pevonedistat				
NCT01814826 [79]	Phase Ib Treatment-unrelated AML	AZA 75 mg/m^2, d1–5, d8, d9/ pevonedistat 20 or 30 mg/m^2, d1, d3, d5, q4 wks	N=64; median age: 75 y (range: 61–89 y); PA75: n.f.s.	mOS: 7 m CR: 31.3%

Study	Design and setting	Trial arms	N and age (years)	Key findings
NCT02610777 [80]	Phase II LB-AML and higher risk MDS/CMML	AZA 75 mg/m^2, d1-7/ pevonedistat 20 mg/m^2, d1, d3, d5, q4 wks vs. AZA 75 mg/m^2, d1–7, q4 wks alone	N=120; median age: 72 y (range: n.f.s.); PA75: 35%	mOS: AZA/pevonedist at 21.8 m vs. AZA alone 19 m ** Median EFS: AZA/ pevonedist at 21 m vs. AZA alone 16.6 m
HMA plus checkpoint inhibitor				
NCT02397720 [125]	Phase II R/R AML	AZA 75mg/m^2, d1–7, Nivolumab 3mg/kg, d1, d14, q4–6 wks	N=77; median age: 70 y (range: 22–90 y); PA60 (AZA/Nivoluma b): 80%	mOS: 6.3 m CR/CRi: 22%
NCT02996474 [126]	Feasibility trial R/R AML	DEC 20mg/m^2, d8–12, d15–19/ pembrolizum ab 200 mg/m^2, d1 q3 wks	N=10; median age: 62 y (range: 30–81 y); PB60: n.f.s.	stable disease (or better): 6/10 patients
NCT03390296 [127]	Phase Ib/II R/R AML	AZA 75 mg/m^2, d1–7/avelumab 3 mg/kg to the first 7 patients enrolled and 10 mg/kg for the remaining 12 patients	N=19; median age: 66 y (range: 22–83 y); PA60: 74%	mOS: 4.8 m ORR: 10.5%
HMA plus magrolimab				
NCT03248479 Abstract only [73]	Phase Ib Newly diagnosed and R/R high-risk MDS and unfit AML	AZA 75mg/m^2, d1–7/ Magrolimab 1–30 mg/kg dose escalation, d1, d4, d8, d15; q4 wks	N (total cohort)=68; N (AML)=29; median age: 72 y (range: n.f.s.); PA60: n.f.s.	CR AML patients only: 40% CRi AML patients only: 4% Transfusion independence AML patients only: 64% 6m OS AML patients only: 91%
HMA plus ibrutinib				
NL5751 (NTR6017) [128]	Phase II Unfit AML or high-risk MDS	DEC 20 mg/m^2, d1–5/ibrutinib 560 mg PO d1–28 vs. decitabine 20 mg/m^2, d1–5 alone	N=144; median age: 75 y (range: 66–89 y); PA75: n.f.s.	CR/CRi: DEC/ibrutinib 40% vs. DEC alone 31% mOS: DEC/ibrutinib 11.4 m vs. DEC alone 11 m

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; BSC, best supportive care; CMML, chronic myelomonocytic leukemia; CR, complete response;; CRi, complete response with incomplete count recovery; CRp, complete response with incomplete platelet recovery; d, days; DED, decitabine; EFS, event free survival; ENA, enasidenib; GIL, gilteritinib; HMA, hypomethylating agent; HR, hazard ratio; IVO, Ivosidinib; LB-AML, low-blast AML; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; mOS, median overall survival; m, months; MRD, measurable residual disease; n.f.s., not further specified; ORR, overall response rate; OS, overall survival; PA60, percentage above 60 years; PA75, percentage above 75 years; R/R, relapsed or refractory; VEN, venetoclax; wks, weeks; y, years

* Results include patients with AML and MDS

** Results include patients with AML, MDS, and CMML

Table 3.

Composite remission rates according to molecular aberrations

Study	Therapy regimen	*NPM1* mut	*IDH1/2* mut	*FLT3-ITD*	*TP53*mut	Cytogenetics	Comment
NCT02993523 [42]	AZA/VEN vs. AZA	HMA/VEN 66.7% (95% CI, 46.0–83.5) vs. HMA 23.5% (95% CI, 6.8–49.9), p=0.012	HMA/VEN 75.4% (95% CI, 62.7–85.5) vs. HMA 10.7% (95% CI, 2.3–28.2), p<0.001	HMA/VEN 72.4% (95% CI, 52.8–87.3) vs. HMA 36.4% (95% CI, 17.2–59.3), p=0.02	HMA/VEN 55.3% (95% CI, 38.3–71.4) vs. HMA 0%, p<0.001		Only small subgroups
NCT02993523+ NCT02203773 [138]	AZA/V EN vs. AZA			HMA/V EN 67% vs. HMA 36%			Pooled data, post-hoc analysis
NCT02993523+ NCT02203773 [43]	AZA/V EN vs. AZA		HMA/V EN 79% vs. HMA 11%				Pooled data, post-hoc analysis
NCT03404193 [139]	DEC-10/VEN					Intermedi ate CGR 89% vs. adverse CGR 66%	Treatment-naïve patients
NCT03404193 [140]	DEC10-VEN				Mut 66% vs. wt 89%, p=0.002		Post-hoc analysis, small numbers in subgroups
Retrospective single-center data [44]		HMA/V EN 96%, HMA 36%, IC 89%; age>65 y: HMA + VEN 88%, HMA 28%, IC 56%; HMA/VEN vs. HMA, p<0.001; HMA/V EN vs. IC, p=0.01					Retrospective single-center data, small numbers

Abbreviations: AZA, azacitidine; CI, confidence interval; CGR, cytogenetic risk (acc. To ELN classification); DEC, decitabine; DEC-10, decitabine regimen for 10 days; HMA, hypomethylating agent; IC, intensive chemotherapy; mut, mutated; VEN, venetoclax; wt, wild-type.

Table 4:

Summary of data from trials on HMA/HMA combinations for treatment of R/R AML

Study	Design and setting	Trial arms	N and age (years)	Key findings
HMA monotherapy				
NCT01261312 [129]	Phase II dose-expansion R/R AML	GUA-5 60/90 mg/m^2, d1–5, q4 wks vs. GUA-10 60 mg/m^2, d1–10, q4 wks	N=103; median age: 60 y (range: 22–82 y); PA60: n.f.s.	1-y OS: 28% ORR: 23.3% (95% CI, 15.5%–32.7%) Median time to CR: GUA-5 236 d (range: 64987 d) vs. GUA-10 77 d (range: 38–172 d, p ≤0.04)
NCT02197676 [130]	Phase II R/R AML (low-blast count) and high-risk MDS after prior AZA exposure	GUA 60mg/m^2, d1–5, q4 wks	N=56; median age: 75 y (range: 70–79 y)	mOS: 7.1 m mOS (responders): 17.9 m (OS>2y in 3 patients) ORR: 14.3% no response in *TP53*-mutated AML
[131]	Retrospective data, 9 centers R/R AML, 20% post-HSCT	AZA/DEC monotherap y (various regimens; +DLI post-HSCT)	N=100; median age: 64.3 y (range: 25–82 y); PA60: n.f.s.	mOS: 6.5 m mOS (SD) 10.6 m mOS (ORR): 13 m mOS (no response): 3.3 m ORR: 24% SD: 26%
[132]	Retrospective data, international multicenter R/R AML	AZA/DEC monotherap y (various regimens, incl. DEC-10, and combination therapies used in 22.4%)	N=655; median age: 65 y (range: 16–92 y); PA60: n.f.s.	CR/CRi:16.5 % mOS: 6.7 m (95% CI, 6.1–7.3 m) mOS (CR/CRi): 21m
HMA plus venetoclax				
[133]	Retrospective data R/R AML prior HMA monotherapy included	AZA/VEN (various regimens)	N=77; median age: 64 y (range: 22–85 y); PA60: n.f.s.	mOS: 13.1 m (95% CI, 9.2–15.1 m) PFS: 12 m (95% CI, 8.2 –15.4 m) median duration of response: 8.9 m (95% CI, 5.7–13.9 m) ORR: 78%
NCT03404193 [123]	Phase II Newly diagnosed AML and R/R AML	Induction: DEC 20 mg/m^2, d1–10/VEN 400 mg/d, d1–28 consolidatio n: DEC 2 0mg/m^2, d1–5/VEN 400 mg, d1–28	N (R/R)=55; median age: 62 y (53–73 y); PA60: n.f.s.	mOS: 7.8 m (95% CI, 5.4–13.3 m) ORR: 62% (95% CI, 49–74)
[134]	Retrospective data R/R AML	DEC/VEN (various regimens	N=22; median age: 47.5 y (range: 12–84 y); PA60: n.f.s.	mOS: 6 m (95% CI, 1–9 m) 1-y OS rate: 31.8% 1-y OS (responders) 59.1% 1-y OS (no responders): 10.4% CR rate after cycle 1: 40.9%
[135]	Retrospective analysis R/R AML 23% post-HSCT	HMA/VEN (72%, various regimens), LDAC/VEN (28%, various regimens)	N=47; N (≥ 60 y)=42% (20/47); N (≥70 y)=10% (5/47); median age: 56 y (range: 33–74 y); PA60: 48%	mOS: 10.7 m DFS (CR+): 10.6 m ORR: 55% MRD negativity: 16/47 patients
[114]	Retrospective data R/R AML after/during HMA	HMA/VEN (various regimens; LDAC/VEN, N=3)	N=23; median age: 76 y (range: 41–92 y); PA60: n.f.s.	mOS (CR/CRi+): 10.8 m CR/CRi: 43%
[136]	Retrospective data R/R AML	DEC-10/VEN (N=65) vs. IC (various regimens, N=130)	N=195; median age (HMA/VEN): 64 y; median age (IC): 58 y; PA60 (HMA/VEN): 60%; PA60 (IC): 53%	mOS: HMA/VEN 6.8 m vs. IC 4.7 m (HR, 0.56; 95% CI, 0.37–0.86 m, p=0.008)
[137]	Retrospective data 40% with prior HMA therapy	AZA or DEC/VEN (various regimens)	N=42; median age: 64.5 y (range: 18–79 y); PA60: 90.9%	mOS: 5 m (95% CI, 3–9 m) mOS (CR/CRi+): 15 m (95% CI, 5-not reached) CR/CRi: 14 (33.3%) 60-d mortality rate: 33.3% CR/CRi after prior HMA: AZA 75% vs. DEC 34.3%
HMA plus checkpoint inhibitor				
NCT02397720 [125]	Phase II R/R AML	AZA 75mg/m^2, d1–7, Nivolumab 3mg/kg, d1, d14, q4–6	N=77; median age: 70 y (range: 22–90 y); PA60 (AZA/Nivoluma b): 80%	mOS: 6.3 m CR/CRi: 22%

Study	Design and setting	Trial arms	N and age (years)	Key findings
NCT03390296 [127]	Phase Ib/II R/R AML	AZA 75 mg/m^2, d1–7/ avelumab 3 mg/kg to the first 7 patients enrolled and 10 mg/kg for the remaining 12 patients	N=19; median age: 66 y (range: 22–83 y); PA60: 74%	mOS: 4.8 m ORR: 10.5%

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; CR, complete response; CRc, composite response; CRi, complete response with incomplete count recovery; CRp, complete response with incomplete platelet recovery; d, days; DEC, decitabine; DEC-5, DEC as a 5 days regimen; DEC-10, DEC as a 10 days regimen; DLI, donor lymphocyte infusion; EFS, event free survival; GUA, guadecitabine; GUA-5, GUA as a 5 days regimen; GUA-10, GUA as a 10 days regimen; HMA, hypomethylating agent; HR, hazard ratio; HSCT, hematopoietic stem-cell transplantation; mOS, overall survival; MDS, myelodysplastic syndrome; mOS, median overall survival; m, months; n.f.s., not further specified; ORR, overall response rate; OS, overall survival; PA60, percentage above 60 years; PFS, progression-free survival; R/R, relapsed or refractory, SD, stable disease; wks, weeks; y, years.