Changing Paradigms in the Treatment of Acute Myeloid Leukemia in Older Patients

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Abstract: Standard therapy for acute myeloid leukemia (AML) has long consisted of intensive chemotherapy followed by allogeneic hematopoietic stem cell transplant. Older individuals (≥60 years), who constitute the majority of patients with AML, may not always benefit from such intensive approaches owing to increasing frailty, comorbidities, and a higher incidence of adverse-risk disease features. Recent years have seen major advances in the development of effective low-intensity therapies for AML. Low-intensity induction regimens based on hypomethylating agents, venetoclax, and nucleoside analogues are highly effective and safe. A greater emphasis is being placed on the importance of an accurate genetic classification of AML to identify patients who may benefit from novel targeted therapies, such as FLT3 and IDH inhibitors. Genomic classification also highlights a group of patients with high-risk disease (*TP53*-mutated), for whom improved treatments are urgently needed. Finally, given that relapse is the major cause of treatment failure in elderly patients with AML, innovative maintenance strategies incorporating targeted therapy are being investigated to delay or prevent relapse. In this article, we provide an updated review of the treatment of AML in older patients.

Introduction

Acute myeloid leukemia (AML) is an aggressive malignancy resulting from the acquisition of genetic defects within hematopoietic stem and progenitor cells.[1] AML is characterized by the accumulation of poorly differentiated and abnormally proliferative myeloid blasts in the blood and bone marrow.[2] Roughly 20,000 new cases of AML are diagnosed each year in the Unites States. The incidence of AML increases with advancing age; the median age of patients at diagnosis is 68 years.[3] Therefore, a large proportion of patients with AML are older persons, variably defined as 60 to 65 years of age and older.

In young and fit individuals, the standard treatment for AML consists of intensive chemotherapy (IC) combining cytarabine and an anthracycline, with or without consolidative allogeneic hematopoietic stem cell transplant (aHSCT).[2] Treating older patients with AML in this fashion is challenging and often not feasible for 2 reasons. First, although age alone is not a contraindication to IC,

Table 1. FDA-Approved Therapies for AML Pertinent to Older Patients

Drug	Mechanism of Action	FDA-Approved Indication
Azacitidine	HMA	AML with 20%-30% blasts
Decitabine	HMA	AML with 20%-30% blasts
Gemtuzumab ozogamicin	CD33-specific antibody-drug conjugate	Newly diagnosed or relapsed/refractory CD33-positive AML
CPX-351	Liposomal formulation of cytarabine and daunorubicin at a fixed 5:1 molar ratio	Newly diagnosed t-AML or AML-MRC
Venetoclax	BCL-2 inhibitor	Newly diagnosed AML patients older than 75 years or unfit for IC, in combination with HMA or LDAC
Midostaurin	Multitargeted kinase inhibitor (including FLT3)	Newly diagnosed *FLT3*-mutated AML, in combination with IC
Gilteritinib	FLT3 inhibitor	Relapsed/refractory *FLT3*-mutated AML
Ivosidenib	IDH1 inhibitor	Newly diagnosed *IDH1*-mutated AML patients older than 75 years or unfit for IC Relapsed/refractory *IDH1*-mutated AML
Enasidenib	IDH2 inhibitor	Relapsed/refractory *IDH2*-mutated AML
Glasdegib	Hedgehog inhibitor	Newly diagnosed AML patients older than 75 years or unfit for IC, in combination with LDAC
CC-486	Oral HMA	AML in first CR following IC, patients unable to complete intensive consolidation

AML, acute myeloid leukemia; AML-MRC, acute myeloid leukemia with myelodysplasia-related cytogenetic changes; CR, complete remission; FDA, US Food and Drug Administration; FLT3, FMS-like tyrosine kinase 3; HMA, hypomethylating agent; IC, intensive chemotherapy; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; LDAC, low-dose cytarabine; t-AML, therapy-related AML.

the incidence of frailty and/or medical comorbidities that increase the risk for morbidity and mortality with such treatments is increased in the elderly. Second, poor-risk disease features (eg, adverse cytogenetics, complex karyotypes, *TP53* mutations, therapy-related AML, and antecedent myelodysplastic syndrome [MDS]) are more common in the elderly. Owing to their biology, patients in these AML categories derive less benefit from intensive cytotoxic regimens, with high rates of primary refractory disease and relapse.[4,5] Therefore, IC poses an increasingly unfavorable risk-to-benefit ratio with advancing age.

The hypomethylating agents (HMAs) azacitidine (AZA) and decitabine (DAC) have long been considered the standard of care for older patients with AML who are unfit for IC (Table 1). In phase 3 studies evaluating elderly patients with newly diagnosed disease, median overall survival (OS) was longer with AZA than with conventional care regimens (CCRs) in both low (20%-30%) blast count AML (24.5 vs 16.0 months; *P*=.005) and high (>30%) blast count AML (10.4 vs 6.5 months; *P*=.1009).[6,7] Likewise, DAC has demonstrated efficacy in both low and high blast count AML in phase 3 studies.[8,9] HMA monotherapy is generally well tolerated in older patients, but the rates of complete remission (CR) are modest (~15%-20%). Patients

not achieving CR may still experience benefit in the form of disease stability and reduced transfusion requirements.

In recent years, an improved understanding of the biology and molecular heterogeneity of AML has led to the development of novel low-intensity and molecularly targeted therapies. These advances have bridged the gap between tolerability and efficacy and have revolutionized the treatment of AML in the elderly. This review provides a comprehensive overview of the treatment landscape in elderly patients with AML, with a focus on accurate disease classification at the genetic level.

Intensive Therapy

Although treatment strategies based on IC are generally less successful in elderly individuals than in younger ones, this approach may still be the best option for a subset of older patients.

Core-Binding Factor AML

AML cases harboring the cytogenetic alteration t(8;21), which results in formation of the fusion gene *RUNX1-RUNX1T1*, or inv(16)/t(16;16), which results in formation of the fusion gene *CBFB-MYH11*, express fusion proteins

that impair core-binding factor (CBF)–mediated transcription and result in a differentiation block.[10] These cases, referred to as CBF AML, demonstrate enhanced sensitivity to high-dose cytarabine and are associated with a favorable prognosis when treated with IC. Patients 60 years of age and younger with CBF AML have CR rates of 87% to 89% and a 5-year OS rate greater than 60% with cytarabine-based regimens.[11] CBF AML is rare in patients 60 years of age and older, accounting for fewer than 5% of cases.[12,13] In a retrospective study of 147 patients 60 years and older with CBF AML treated with induction chemotherapy followed by low-intensity (n=72) or intensive (n=56) consolidation, the CR rate was 88% and the 5-year OS rate was 31%. An intensive consolidation strategy was associated with significantly longer leukemia-free survival, driven mostly by benefit in the t(8;21) cohort.[13] Despite outcomes inferior to those of their younger counterparts, this finding suggests that fit older patients with CBF AML should be offered intensive cytarabine-based chemotherapy, as it represents an opportunity for cure.

The addition of the CD33-directed antibody-drug conjugate (ADC) gemtuzumab ozogamicin (GO; Mylotarg, Pfizer) to IC has been shown to improve OS in CBF AML. In an individual patient data meta-analysis of 5 randomized studies evaluating GO plus IC vs IC alone in newly diagnosed AML, the addition of GO was associated with an unchanged CR rate but a reduced risk for relapse. This translated to an absolute OS benefit of 20.7% at 6 years in patients with favorable cytogenetics—namely, t(8;21) and inv(16). Notably, the benefit of GO was not affected by age in this meta-analysis.[14] GO has been combined with daunorubicin/cytarabine (DA), daunorubicin/clofarabine, and fludarabine/cytarabine/granulocyte colony–stimulating factor (FLAG) regimens in older patients with AML, with an acceptable toxicity profile.[15,16] Age was not associated with worse relapse-free survival (RFS) or OS in these studies. Low-dose GO (3 mg/m^2 on day 1) or fractionated dosing (3 mg/m^2 on days 1, 4, and 7) regimens are preferable because they are associated with a lower rate of early mortality and equivalent efficacy in comparison with higher doses (6 mg/m^2).[14]

Non-CBF AML

For most older patients who do not have favorable cytogenetics, the benefits of intensive vs less-intensive therapy remain poorly defined owing to a lack of randomized data. In the AZA-AML-001 trial, patients were randomly assigned to AZA or a CCR, which in 1 arm consisted of standard IC. No survival differences were noted between the patients who received IC (n=44) and those preselected for IC as a CCR but then randomly assigned to AZA (n=43), with a median OS of 12.2 vs 13.3 months. However, the numbers of patients in this comparison were too few to draw significant conclusions.[7] A retrospective observational study of 671 older (≥65 years) patients with AML treated with either IC or HMA-based therapy revealed a significantly increased overall response rate (ORR; 47% vs 29%) and a trend toward increased 8-week mortality (18% vs 11%) with IC. Importantly, the improved ORR seen with IC did not translate to improved OS when IC was compared with HMA treatment (median OS, 6.7 months with IC vs 6.5 months with HMA; P=.413).[17] Similar retrospective studies evaluating older patients with high-risk therapy-related AML (t-AML), AML with an antecedent myeloid malignancy (secondary AML, or sAML), or AML with myelodysplasia-related cytogenetic changes (AML-MRC) did not observe a survival advantage of IC over HMA.[18,19] Median OS was uniformly poor in these studies irrespective of treatment intensity (5- to 8-month range), indicating the need for improved therapies beyond IC and HMA monotherapy in elderly patients with AML.

CPX-351 (Vyxeos, Jazz) is now approved for use in older patients with t-AML, sAML, or AML-MRC and is an important option for those who are fit for intensive chemotherapy. CPX-351 is a liposomal formulation of cytarabine and daunorubicin at a fixed 5:1 molar ratio to optimize synergy. This drug was shown to be superior to standard cytarabine/daunorubicin ("7 + 3") in a phase 3 randomized controlled trial (RCT), in terms of both CR rate (57% vs 40%; P=.04) and OS (median OS, 9.56 vs 5.95 months; P=.003). Median OS with CPX-351 was 9.63 months in the age 60 to 69 subgroup and 8.87 months in the age 70 to 75 subgroup.[20] It is unknown how CPX-351 would compare with lower-intensity therapies in this high-risk population. Attempts to reduce the dose of CPX-351 in less-fit patients with the goal of minimizing treatment-related mortality while preserving efficacy have been unsuccessful.[21]

Allogeneic Hematopoietic Stem Cell Transplant

A major hurdle in the treatment of older patients with AML is the lack of tolerable consolidation strategies. Consolidative aHSCT is one of the most effective treatments for preventing relapse in younger patients. With the development of reduced-intensity conditioning regimens, the availability of aHSCT has expanded to older patients. In older patients with AML who are medically fit and have a suitable donor, long-term disease control may be achieved with aHSCT. In a prospective phase 2 study, Devine and colleagues reported a disease-free survival rate of 42% and an OS rate of 48% at 2 years following reduced-intensity conditioning transplant in a select cohort of 114 older patients with AML in first CR (median age, 65 years; range, 60-74 years).[22] Other retrospective studies and meta-analyses also support the notion

that aHSCT can yield long-term disease control in fit older patients with AML.[23-25] In practice, however, fewer than 1 in 10 patients with AML aged 60 or older undergo aHSCT.[26] This highlights the need for alternative consolidation strategies in older individuals, including effective maintenance therapies and immune-based approaches.

Assessment of Fitness for Intensive Chemotherapy

The assessment of an elderly patient's fitness for IC is often subjective and left to the judgment of the treating physician. The hematopoietic stem cell transplant–specific comorbidity index (HCT-CI) has been validated to predict survival following IC in older patients with AML.[27,28] Sorror and colleagues recently published an AML composite model (AML-CM) to predict 1-year mortality after initial therapy for AML by augmenting the HCT-CI with hypoalbuminemia, thrombocytopenia, elevated lactate dehydrogenase, age, and cytogenetic/molecular risk.[29] This model incorporates both patient- and disease-specific characteristics and provides a more objective method for assigning patients to the appropriate treatment intensity. Geriatric assessment evaluates measures of functional status (including a battery of physical tests), comorbidities, cognitive function, socioeconomic status, and other factors to identify vulnerable older adults.[30] Geriatric assessment is a predictor of OS in intensively treated older patients with AML.[28] Prediction tools such as the AML-CM and geriatric assessment have yet to be widely adopted in clinical practice.

Low-Intensity Therapy

The poor tolerability of IC in the elderly, as well as its limited efficacy in non-CBF AML, have stimulated the development of low-intensity treatment regimens. Despite major advances in recent years, the treatment of elderly/unfit patients with AML continues to represent an unmet clinical need owing to their adverse disease biology and inferior survival in comparison with younger patients.

Venetoclax-Based Combinations

Venetoclax (Venclexta, AbbVie) is an oral small-molecule inhibitor of the anti-apoptotic protein BCL-2. Many hematologic malignancies, including AML, leverage BCL-2 to sequester pro-apoptotic proteins such as BIM and BAX. Venetoclax is capable of displacing these pro-apoptotic signals from BCL-2 in "primed" cells, thus promoting apoptosis.[31] As a single agent, venetoclax demonstrated modest activity in a cohort of 32 patients with relapsed/refractory (n=30) or untreated (n=2) AML, with a combined CR/CR with incomplete blood count recovery (CRi) rate of 19% and a median OS of 4.7 months.[32]

The efficacy of venetoclax is greatly enhanced within combination regimens. Notably, HMAs synergize with BCL-2 inhibitors by reducing the expression of MCL-1, a known promoter of resistance to venetoclax.[33,34] Following promising data from a phase 1b/2 study,[35] the phase 3 RCT VIALE-A randomly assigned patients with untreated AML ineligible for IC (owing to age ≥75 years or comorbidities) to receive either AZA plus venetoclax or AZA alone.[36] CR/CRi rates (66.4% vs 28.3%; *P*<.001) and median OS (14.7 vs 9.6 months; *P*<.001) were significantly better in the patients in the combination arm. Responses (CR/CRi) with AZA/venetoclax occurred rapidly (usually after cycle 1) and were durable (median, 17.5 months). The addition of venetoclax was associated with increased hematologic toxicity, especially thrombocytopenia, neutropenia, and febrile neutropenia. More than half of the patients in the combination arm required treatment delays and/or a reduction in the duration of venetoclax administration (ie, 21 of 28 days per cycle instead of 28 of 28 days) to allow count recovery. Despite the increased toxicity of venetoclax, VIALE-A established AZA plus venetoclax as the new standard of care for older/unfit patients with AML.

In parallel with VIALE-A, the phase 3 RCT VIALE-C randomly assigned patients with newly diagnosed AML who were unfit for IC to receive venetoclax plus low-dose cytarabine (LDAC) or LDAC alone.[37] The study did not meet its primary endpoint because the OS benefit in the combination arm did not reach statistical significance at the time of preplanned analysis at median follow-up of 12 months (median OS, 7.2 vs 4.1 months; *P*=.11). An additional unplanned analysis performed after an additional 6 months of follow-up demonstrated a significant advantage in median OS with venetoclax plus LDAC (8.4 vs 4.1 months; *P*=.04). CR/CRi rates were 48% and 13% for venetoclax plus LDAC and LDAC alone, respectively. It should be noted that 20% of the patients in VIALE-C had previously been exposed to HMAs for MDS before transformation to AML, a key patient population that was excluded from VIALE-A. These patients had a CR/CRi rate of 25% with venetoclax plus LDAC and a median OS of 5.5 months. This trial provided valuable outcome data for a venetoclax-based regimen in this clinically relevant and challenging population of elderly patients with AML.

Venetoclax is currently approved in combination with AZA, DAC, or LDAC for the treatment of newly diagnosed AML in patients who are 75 years of age and older or who are ineligible for IC. These venetoclax-based combinations appear particularly effective in patients with *IDH1*, *IDH2*, and *NPM1* mutations, who exhibit improved rates of response and prolonged remissions.[35-39] On the other hand, activating kinase mutations such as *FLT3*-ITD and *NRAS*/*KRAS* are associated with faster relapse and primary refractoriness.[39] This finding is par-

ticularly relevant given the availability of targeted FLT3 inhibitors (discussed later). Patients with *TP53* mutations and complex karyotypes do poorly when treated with venetoclax/AZA and venetoclax/LDAC, with lower response rates and short OS.[36,37,39] In addition, clinical and in vitro evidence suggests that AML with monocytic differentiation is more resistant to venetoclax-based therapy, possibly owing to a shift in reliance from BCL-2 to MCL-1.[40]

Double Nucleoside Analogue Regimens

Cladribine and clofarabine are purine nucleoside analogues that inhibit ribonucleotide reductase, leading to deoxynucleotide depletion and inhibition of DNA synthesis. Importantly, these drugs enhance the conversion of cytarabine to its active metabolite (ara-CTP), which then accumulates within leukemic blasts.[41,42] To exploit this synergy, cladribine or clofarabine has been combined with LDAC in double nucleoside analogue therapy (DNT) regimens.[42] These combinations represent alternative low-intensity chemotherapy backbones with high efficacy and low toxicity in the elderly.

In 2 single-arm phase 2 studies, cladribine or clofarabine was combined with LDAC in patients 60 years and older with newly diagnosed AML.[43,44] The DNT cycles were alternated with cycles of DAC for a total of up to 18 cycles. In an updated analysis of these 2 studies after a median follow-up of 60 months, cladribine/LDAC (n=129) and clofarabine/LDAC (n=119), both alternating with DAC, led to combined CR/CRi rates of 66% and 67%, respectively.[42] Responses were rapid, occurring after a median of 1 cycle. Toxicities were generally manageable, and the DNT regimens had low 4- and 8-week mortality rates (2% and 11%, respectively). Median OS was 13.8 months for cladribine/LDAC and 10.4 months for clofarabine/LDAC, values comparing favorably with OS in historical controls treated with HMA monotherapy. Higher composite CR (CRc) rates and longer median OS were observed in patients with *NPM1* (97%, 28.7 months), *FLT3*-ITD (95%, 15.2 months), *IDH2* (92%, 16.9 months), or *FLT3*-D835 (83%, 17 months) mutations. Interestingly, patients harboring *RUNX1* mutations, a factor generally associated with a poor prognosis in intensively treated patients,[45] had a 63% CR/CRi rate and a median OS of 17.6 months.[42] Unfortunately, similarly to what was observed in VIALE-A and VIALE-C, patients with *TP53* mutations and adverse karyotypes did poorly with the DNT regimen (CR/CRi rates of 44% and 56%, median OS 5.4 and 8.2 months, respectively).

An ongoing phase 2 study (NCT03586609) is exploring the addition of venetoclax to cladribine/LDAC alternating with AZA in older (age ≥60 years) or unfit patients with newly diagnosed AML (Table 2). Preliminary results

of this study (48 patients; median follow-up, 11 months) demonstrate an impressive CR/CRi rate of 94% and a 12-month OS rate of 70%.[46]

FLT3-Mutated AML

Mutations in the FMS-like tyrosine kinase 3 gene (*FLT3*) are common leukemic drivers in AML, occurring in approximately one-third of patients.[47,48] They are generally less common in the elderly.[49] These mutations, which can be internal tandem duplications (*FLT3*-ITD) or involve the tyrosine kinase domain (*FLT3*-TKD), result in constitutive activation and promote uncontrolled cellular proliferation/survival.[50] Therefore, small-molecule oral FLT3 inhibitors have been developed for the treatment of AML.

Two FLT3 inhibitors, midostaurin (Rydapt, Novartis) and gilteritinib (Xospata, Astellas), are currently approved by the FDA for the treatment of *FLT3*-mutated AML. RATIFY, a phase 3 RCT, demonstrated that the addition of midostaurin, a multitargeted kinase inhibitor, to standard IC improved OS in younger patients (aged 18-59 years) with newly diagnosed *FLT3*-mutated AML.[51] Although older patients were excluded from RATIFY, the FDA label for midostaurin has no upper age limit, and a phase 2 study has shown that patients aged 61 to 70 years benefit from improved event-free survival (EFS) with the addition of midostaurin to IC.[52] In the relapsed/refractory setting, the ADMIRAL study showed that gilteritinib, a more potent and specific FLT3 inhibitor, was superior to IC in terms of response rates and OS.[53] Ongoing research is exploring the addition of FLT3 inhibitors to low-intensity backbones for older patients with *FLT3*-mutated AML.

The multikinase inhibitor sorafenib (Nexavar, Bayer) was evaluated in combination with AZA in both relapsed/refractory and untreated *FLT3*-mutated AML in a series of phase 2 studies.[54,55] This combination led to CR/CRi rates of 43% and 70% in the relapsed and frontline settings, respectively. The median duration of remission was short in the patients with relapsed/refractory disease (2.3 months) but much longer in the untreated patients (14.5 months). Notably, the toxicity observed when sorafenib was combined with the low-intensity AZA backbone was considerably less than the toxicity previously observed when sorafenib was combined with IC.[56]

The phase 3 LACEWING trial compared the combination of gilteritinib and AZA vs AZA alone in the treatment of patients (aged ≥65 years and/or unfit) with newly diagnosed *FLT3*-mutated AML. Although the combination was associated with relatively high response rates (CRc of 67%), it failed to demonstrate improved OS at a planned interim analysis, and enrollment was terminated early.[57,58]

Other combinations currently being explored

include venetoclax plus gilteritinib for relapsed/refractory *FLT3*-mutated AML (NCT03625505), which has demonstrated high rates (86%) of modified composite CR (mCRc, consisting of CR + CRi + CR with incomplete platelet recovery + morphologic leukemia-free state).[59] In addition, triplet regimens such as AZA plus venetoclax plus gilteritinib (NCT04140487) and DAC plus venetoclax plus investigator's choice of FLT3 inhibitor (NCT03404193) are in the early phases of clinical evaluation. Early results from the DAC-based triplet study show high rates of CRc in the untreated (96%; n=12) and relapsed/refractory (62%; n=13) cohorts. Of note, this study allowed various FLT3 inhibitors (gilteritinib, sorafenib, and midostaurin), which complicates interpretation of the data.[60] Because prolonged myelosuppression has been observed with these combinations, further investigation is required to identify the optimal drug doses and administration schedules.

Overall, the optimal frontline treatment for elderly patients with *FLT3*-mutated AML remains unclear at the present time as FLT3 inhibitors combined with low-intensity backbones continue to be evaluated in clinical trials.

IDH1/2-Mutated AML

Recurrent isocitrate dehydrogenase 1 and 2 (*IDH1*, *IDH2*) gene mutations are identified in roughly 15% to 20% of cases of AML.[47,61,62] These mutated IDH enzymes generate the oncometabolite 2-hydroxyglutarate (2HG), which promotes DNA hypermethylation and impairs myeloid differentiation via inhibition of TET2. Critically, 2HG-induced leukemic transformation is reversible upon elimination of the abnormal metabolite.[63] These findings led to the development of the targeted agents ivosidenib (Tibsovo, Agios; an IDH1 inhibitor) and enasidenib (Idhifa, Celgene; an IDH2 inhibitor) for the treatment of AML with *IDH1* or *IDH2* mutations, respectively.

Ivosidenib first demonstrated encouraging activity in relapsed/refractory *IDH1*-mutated AML (CR plus CR with partial hematologic recovery [CRh] rate of 30.4%, lasting a median of 8.2 months).[64] Likewise, in patients with newly diagnosed disease who were ineligible for IC, ivosidenib monotherapy was associated with a CR/CRh rate of 42.4% (median duration of remission not reached).[65] These studies led to the FDA approval of ivosidenib for *IDH1*-mutated AML in both the relapsed/refractory and frontline (patients unfit or aged ≥75 years) settings. Ivosidenib was then combined with an AZA backbone in 23 patients with newly diagnosed *IDH1*-mutated disease to exploit synergy between these 2 agents in inducing differentiation. With the combination, the CR/CRh rate was 69.6%, and median OS had not been

reached after a median follow-up of 16 months.[66] This prompted the phase 3 RCT AGILE (NCT03173248), which compared ivosidenib plus AZA vs AZA alone in patients with newly diagnosed *IDH1*-mutated AML who were ineligible for IC. AGILE was recently announced to have met its primary endpoint of improved EFS as well as its secondary endpoints, including CR and OS.[67] A detailed analysis of these data is pending.

Likewise, the IDH2 inhibitor enasidenib has been shown to be effective as monotherapy for relapsed/refractory *IDH2*-mutated AML in a phase 1/2 study (CR/CRi, 26.1%; median OS, 9.3 months).[68] As a result, the FDA approved enasidenib in 2017 for this indication. In addition, enasidenib has demonstrated efficacy as monotherapy in the frontline setting (CR/CRi, 21%; median OS, 11.3 months) and in combination with AZA (CR, 53%; ORR, 71%; median OS, 22 months).[69,70]

IDH inhibitors are generally well-tolerated drugs in the elderly. By reducing 2HG levels, they promote the differentiation of myeloid blasts, and treatment results in progressive hematologic improvement without inducing aplasia.[64] A differentiation syndrome characterized by neutrophilic leukocytosis, fever, hypotension, edema, renal failure, and effusions occurred at rates ranging from 9.6% to 18% across the major IDH inhibitor trials.[64-66,68-70] Differentiation syndrome is managed with temporary IDH inhibitor discontinuation, glucocorticoids, diuresis, and cytoreduction with hydroxyurea.[64]

In summary, IDH inhibitors induce modest CR rates as single agents, but a larger proportion of patients may experience benefit in the form of stable disease. These drugs appear to be more effective when combined with an AZA backbone. Following VIALE-A and the establishment of AZA/venetoclax as the new standard of care in elderly and/or unfit patients with AML, ongoing and future research should focus on evaluating the benefits of adding an IDH inhibitor to an AZA/venetoclax backbone (triplet regimen) or sequentially adding one as long-term therapy after an initial response to AZA/venetoclax in patients with *IDH*-mutated AML. Early data for the AZA/venetoclax/ivosidenib triplet revealed very high response rates (ORR, 100%; CR/CRi, 85%; n=13).[71]

TP53-Mutated AML

Outcomes in patients who have AML with *TP53* mutations, which are often associated with adverse/complex karyotypes,[72] are consistently poor with current treatment modalities. In older patients with *TP53*-mutated AML, response rates are better with the addition of venetoclax to an HMA than with an HMA alone but remain lower than those in patients without *TP53* mutations. In addition, the responses are short-lived (3.4-5.6 months), and OS

Table 2. Selected Clinical Trials Exploring Novel Therapeutic Strategies Relevant in Elderly Patients With AML

NCT Identifier	Phase	Regimen	Population
NCT03586609	2	Cladribine + LDAC + venetoclax alternating with AZA + venetoclax	Newly diagnosed AML, older/unfit patients
NCT02752035	3	AZA + gilteritinib	Newly diagnosed *FLT3*-mutated AML, patients unfit for IC
NCT03625505	1b	Venetoclax + gilteritinib	Relapsed/refractory *FLT3*-mutated AML
NCT04140487	1/2	AZA + venetoclax + gilteritinib	Relapsed/refractory *FLT3*-mutated AML
NCT03404193	2	DAC + venetoclax + FLT3 inhibitor	Relapsed/refractory *FLT3*-mutated AML
NCT03173248	3	AZA + ivosidenib	Newly diagnosed *IDH1*-mutated AML, patients unfit for IC
NCT03471260	1b/2	AZA + venetoclax + ivosidenib	*IDH1*-mutated AML, patients unfit for IC
NCT03248479	1b	AZA + magrolimab	Newly diagnosed and relapsed/refractory AML
NCT04435691	1b/2	AZA + venetoclax + magrolimab	Newly diagnosed and relapsed/refractory AML
NCT03797261	1b	Venetoclax + AMG 176 (dual BH3 mimetic combination)	Relapsed/refractory AML
NCT03218683	1/1b/2a	Venetoclax + AZD5991 (dual BH3 mimetic combination)	Relapsed/refractory AML
NCT03672695	1b	Venetoclax + S64315 (dual BH3 mimetic combination)	Newly diagnosed unfit or relapsed/refractory AML
NCT04062266	2	AZA + venetoclax maintenance	AML in CR, patients ineligible for aHSCT
NCT05010772	1b	DAC + venetoclax or gilteritinib or ivosidenib or enasidenib maintenance based on molecular profile	AML in CR, patients ineligible for aHSCT

aHSCT, allogeneic hematopoietic stem cell transplant; AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; DAC, decitabine; FLT3, FMS-like tyrosine kinase 3; IC, intensive chemotherapy; IDH1, isocitrate dehydrogenase 1; LDAC, low-dose cytarabine; NCT, National Clinical Trial number.

is poor (5.2-7.2 months).[35,36,73,74] A higher *TP53*-mutant variant allele frequency also may have an adverse effect on prognosis. In patients treated with cytarabine-based regimens, a *TP53*-mutant variant allele frequency greater than 40% was associated with a significant reduction in OS (4.7 vs 7.3 months).[75] Given these findings, clinical trial enrollment, if possible, is often the best option for older patients with *TP53*-mutated AML. Several drugs focusing on *TP53*-mutated AML are currently undergoing development.

Eprenetapopt (APR-246), a small molecule reported to restore p53 function,[76] initially showed encouraging activity in *TP53*-mutated MDS and AML in phase 1/2 trials when combined with AZA, with reported ORRs of 52% to 71% (CRs ranged from 37% to 44%).[77,78] Unfortunately, the follow-up phase 3 RCT comparing the combination of eprenetapopt and AZA vs AZA alone in *TP53*-mutated MDS failed to meet its primary endpoint of CR rate.[79] APR-548, an orally bioavailable second-generation p53 reactivator, is undergoing phase 1 trials in MDS in combination with AZA (NCT04638309).

CD47 is a macrophage immune checkpoint that inhibits phagocytosis and is overexpressed on AML cells.[80] The anti-CD47 antibody magrolimab promotes the elimination of leukemic cells via phagocytosis. It also displays synergy with AZA, which promotes expression of pro-phagocytic signals on leukemic blasts.[81] The combination of magrolimab and AZA was evaluated in a phase 1b trial for the treatment of patients with newly diagnosed AML who were unfit for IC. The cohort (n=52) was enriched for poor-risk cytogenetics (64%) and *TP53* mutations (65%). The patients with *TP53*-mutated disease had a CR/CRi rate of 67%. The responses lasted a median of 9.9 months, and the median OS was 12.9 months. These results compared favorably with historical expectations for AZA/venetoclax in *TP53*-mutated AML.[82] Building on these results, investigators are currently evaluating a triplet regimen consisting of AZA, venetoclax, and magrolimab in a phase 1b/2 study (NCT04435691).

Laboratory and clinical data have shown that *TP53*-mutated AML clones are selected for and expand following venetoclax treatment.[39,83] This may be a consequence of lower levels of pro-apoptotic proteins such as BAX in p53-deficient cells, resulting in a higher apoptotic threshold. In vitro and in vivo data suggest that combined BH3-mimetic therapy, which can be achieved by combining venetoclax (a BCL-2 inhibitor) with an MCL-1 inhibitor, may overcome the resistance.[83,84] Several early-phase clinical trials are exploring this strategy in AML (NCT03797261, NCT03218683, and NCT03672695).[85]

Maintenance Therapy

High-dose cytarabine and aHSCT are 2 of the most powerful consolidation strategies in AML. Elderly patients are often ineligible for such therapies and thus have high rates of relapse. This problem has prompted investigation into maintenance therapy in AML. Maintenance consists of administering prolonged, easily tolerated treatments with the goal of delaying or preventing relapse in patients who have achieved remission.

The QUAZAR AML-001 study was a phase 3 RCT that randomized older aHSCT-ineligible patients with AML in first CR after IC to receive either CC-486 (Onureg, Bristol Myers Squibb; an oral formulation of AZA) or placebo. The treatment was continued until AML recurred or toxicity became unacceptable. The patients who received CC-486 experienced significantly longer OS in comparison with those who received placebo (median OS, 24.7 vs 14.8 months). Although associated with increased hematologic and gastrointestinal toxicities, CC-486 was generally well tolerated, and only 13% of the patients in the active treatment arm discontinued therapy owing to adverse events.[86] This study provided proof of concept that maintenance is a feasible strategy in older patients with AML who are unfit for intensive consolidation and led to the 2020 FDA approval of CC-486. A significant limitation of this study was that it did not include patients in CR following low-intensity induction regimens.

AZA plus venetoclax is highly active in AML in the frontline setting.[36] However, prolonged administration of this combination at full dose leads to significant myelosuppression. Therefore, a phase 2 trial has been designed to evaluate lower doses of AZA plus venetoclax as maintenance for aHSCT-ineligible patients with AML who have achieved remission after both high- and low-intensity induction regimens (NCT04062266). In addition, novel personalized maintenance strategies combining an oral low-dose HMA (DAC) with a targeted agent selected according to the individual patient's genetic profile (venetoclax, gilteritinib, ivosidenib, or enasidenib) are being investigated (NCT05010772).

Immunotherapy-based maintenance strategies have also been explored. The programmed death 1 inhibitor nivolumab (Opdivo, Bristol Myers Squibb) was evaluated in a phase 2 single-arm study in high-risk, aHSCT-ineligible patients with AML in remission (n=15). At a median follow-up of 30.4 months, median RFS was 8.48 months and median OS was not reached.[87] A phase 2 randomized trial of nivolumab vs observation as maintenance therapy in patients with AML in first CR is ongoing (NCT02275533). The immunomodulator lenalidomide (Revlimid, Celgene) has also been evaluated as maintenance therapy for high-risk aHSCT-ineligible patients. In a phase 2 study that included 28 patients, lenalidomide maintenance was associated with a median RFS of 23 months, and median OS was not reached. However, patients with sAML or t-AML did poorly, with a median RFS and median OS of 2.5 and 6.7 months, respectively.[88] At present, no immune-based maintenance therapy has been FDA-approved for AML.

Conclusion

Although intensive therapy may still be the best option for a subset of older patients with AML, such as those with CBF AML, lower-intensity approaches are increasingly being favored. These regimens are highly effective in inducing CR and have favorable toxicity profiles. Backbone regimens, such as AZA plus venetoclax and DNT regimens, are broadly active across multiple genetic AML categories. For patients with a targetable mutation (eg, *FLT3* or *IDH1/2*), the addition of a mutation-specific inhibitor to backbone regimens has shown promising results in clinical trials and will likely become the standard of care in the clinic within the coming years. Further research is required to delineate the optimal therapy in patients with *TP53*-mutated AML, in whom outcomes continue to be dismal with current approaches. Magrolimab and dual BH3-mimetic therapy are promising avenues in this patient group. Finally, all the previously mentioned low-intensity therapies are generally not considered curative, and rates of relapse continue to be high. Therefore, maintenance therapies that can be administered over prolonged periods to delay or prevent relapse should continue to be explored.

References

1. Warner JK, Wang JC, Takenaka K, et al. Direct evidence for cooperating genetic events in the leukemic transformation of normal human hematopoietic cells. *Leukemia*. 2005;19(10):1794-1805.

2. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373(12):1136-1152.

3. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2017. National Cancer Institute. https://seer.cancer.gov/csr/1975_2017/. Published April 15, 2020. Accessed November 10, 2021.

4. Kuykendall A, Duployez N, Boissel N, Lancet JE, Welch JS. Acute myeloid leukemia: the good, the bad, and the ugly. *Am Soc Clin Oncol Educ Book*. 2018;38:555-573.

5. Granfeldt Østgård LS, Medeiros BC, Sengeløv H, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. *J Clin Oncol*. 2015;33(31):3641-3649.

6. Fenaux P, Mufti GJ, Hellström-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol*. 2010;28(4):562-569.

7. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126(3):291-299.

8. Becker H, Suciu S, Rüter BH, et al. Decitabine versus best supportive care in older patients with refractory anemia with excess blasts in transformation (RAEBt) - results of a subgroup analysis of the randomized phase III study 06011 of the EORTC Leukemia Cooperative Group and German MDS Study Group (GMDSSG). *Ann Hematol*. 2015;94(12):2003-2013.

9. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2012;30(21):2670-2677.

10. Speck NA, Gilliland DG. Core-binding factors in haematopoiesis and leukaemia. *Nat Rev Cancer*. 2002;2(7):502-513.

11. Schlenk RF, Benner A, Krauter J, et al. Individual patient data-based meta-analysis of patients aged 16 to 60 years with core binding factor acute myeloid leukemia: a survey of the German Acute Myeloid Leukemia Intergroup. *J Clin Oncol*. 2004;22(18):3741-3750.

12. Grimwade D, Walker H, Harrison G, et al; Medical Research Council Adult Leukemia Working Party. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood*. 2001;98(5):1312-1320.

13. Prébet T, Boissel N, Reutenauer S, et al; Acute Leukemia French Association; Groupe Ouest-Est des leucémies et autres maladies du sang (GOELAMS); Core Binding Factor Acute Myeloid Leukemia (CBF AML) intergroup. Acute myeloid leukemia with translocation (8;21) or inversion (16) in elderly patients treated with conventional chemotherapy: a collaborative study of the French CBF-AML intergroup. *J Clin Oncol*. 2009;27(28):4747-4753.

14. Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol*. 2014;15(9):986-996.

15. Burnett AK, Russell NH, Hills RK, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. *J Clin Oncol*. 2012;30(32):3924-3931.

16. Borthakur G, Cortes JE, Estey EE, et al. Gemtuzumab ozogamicin with fludarabine, cytarabine, and granulocyte colony stimulating factor (FLAG-GO) as front-line regimen in patients with core binding factor acute myelogenous leukemia. *Am J Hematol*. 2014;89(10):964-968.

17. Quintás-Cardama A, Ravandi F, Liu-Dumlao T, et al. Epigenetic therapy is associated with similar survival compared with intensive chemotherapy in older patients with newly diagnosed acute myeloid leukemia. *Blood*. 2012;120(24):4840-4845.

18. Boddu PC, Kantarjian HM, Ravandi F, et al. Characteristics and outcomes of older patients with secondary acute myeloid leukemia according to treatment approach. *Cancer*. 2017;123(16):3050-3060.

19. Vachhani P, Al Yacoub R, Miller A, et al. Intensive chemotherapy vs. hypomethylating agents in older adults with newly diagnosed high-risk acute myeloid leukemia: A single center experience. *Leuk Res*. 2018;75:29-35.

20. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) Liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;36(26):2684-2692.

21. Walter RB, Othus M, Orlowski KF, et al. Unsatisfactory efficacy in randomized study of reduced-dose CPX-351 for medically less fit adults with newly diagnosed acute myeloid leukemia or other high-grade myeloid neoplasm. *Haematologica*. 2018;103(3):e106-e109.

22. Devine SM, Owzar K, Blum W, et al. Phase II study of allogeneic transplantation for older patients with acute myeloid leukemia in first complete remission using a reduced-intensity conditioning regimen: results from Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology)/Blood and Marrow Transplant Clinical Trial Network 0502. *J Clin Oncol*. 2015;33(35):4167-4175.

23. Solomon SR, Solh M, Jackson KC, et al. Real-world outcomes of unselected elderly acute myeloid leukemia patients referred to a leukemia/hematopoietic cell transplant program. *Bone Marrow Transplant*. 2020;55(1):189-198.

24. Modi D, Deol A, Kim S, et al. Age does not adversely influence outcomes among patients older than 60 years who undergo allogeneic hematopoietic stem cell transplant for AML and myelodysplastic syndrome. *Bone Marrow Transplant*. 2017;52(11):1530-1536.

25. Rashidi A, Ebadi M, Colditz GA, DiPersio JF. Outcomes of allogeneic stem cell transplantation in elderly patients with acute myeloid leukemia: a systematic review and meta-analysis. *Biol Blood Marrow Transplant*. 2016;22(4):651-657.

26. Vey N. Low-intensity regimens *versus* standard-intensity induction strategies in acute myeloid leukemia. *Ther Adv Hematol*. 2020;11:2040620720913010. doi:10.1177/2040620720913010.

27. Giles FJ, Borthakur G, Ravandi F, et al. The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol*. 2007;136(4):624-627.

28. Klepin HD, Geiger AM, Tooze JA, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood*. 2013;121(21):4287-4294.

29. Sorror ML, Storer BE, Fathi AT, et al. Development and validation of a novel acute myeloid leukemia-composite model to estimate risks of mortality. *JAMA Oncol*. 2017;3(12):1675-1682.

30. Klepin HD. Ready for prime time: role for geriatric assessment to improve quality of care in hematology practice. *Blood*. 2019;134(23):2005-2012.

31. Konopleva M, Letai A. BCL-2 inhibition in AML: an unexpected bonus? *Blood*. 2018;132(10):1007-1012.

32. Konopleva M, Pollyea DA, Potluri J, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. *Cancer Discov*. 2016;6(10):1106-1117.

33. Tsao T, Shi Y, Kornblau S, et al. Concomitant inhibition of DNA methyltransferase and BCL-2 protein function synergistically induce mitochondrial apoptosis in acute myelogenous leukemia cells. *Ann Hematol*. 2012;91(12):1861-1870.

34. Tahir SK, Smith ML, Hessler P, et al. Potential mechanisms of resistance to venetoclax and strategies to circumvent it. *BMC Cancer*. 2017;17(1):399.

35. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood*. 2019;133(1):7-17.

36. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.

37. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135(24):2137-2145.

38. Lachowiez CA, Loghavi S, Kadia TM, et al. Outcomes of older patients with NPM1-mutated AML: current treatments and the promise of venetoclax-based regimens. *Blood Adv*. 2020;4(7):1311-1320.

39. DiNardo CD, Tiong IS, Quaglieri A, et al. Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. *Blood*. 2020;135(11):791-803.

40. Pei S, Pollyea DA, Gustafson A, et al. Monocytic subclones confer resistance to venetoclax-based therapy in patients with acute myeloid leukemia. *Cancer Discov*. 2020;10(4):536-551.

41. Gandhi V, Estey E, Keating MJ, Chucrallah A, Plunkett W. Chlorodeoxyadenosine and arabinosylcytosine in patients with acute myelogenous leukemia: pharmacokinetic, pharmacodynamic, and molecular interactions. *Blood*. 1996;87(1):256-264.

42. Kadia TM, Ravandi F, Borthakur G, et al. Long-term results of low-intensity chemotherapy with clofarabine or cladribine combined with low-dose cytarabine alternating with decitabine in older patients with newly diagnosed acute myeloid leukemia. *Am J Hematol*. 2021;96(8):914-924.

43. Kadia TM, Faderl S, Ravandi F, et al. Final results of a phase 2 trial of clofarabine and low-dose cytarabine alternating with decitabine in older patients with newly diagnosed acute myeloid leukemia. *Cancer*. 2015;121(14):2375-2382.

44. Kadia TM, Cortes J, Ravandi F, et al. Cladribine and low-dose cytarabine alternating with decitabine as front-line therapy for elderly patients with acute myeloid leukaemia: a phase 2 single-arm trial. *Lancet Haematol*. 2018;5(9):e411-e421.

45. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.

46. Kadia TM, Borthakur G, Pemmaraju N, et al. Phase II study of venetoclax added to cladribine + low dose AraC (LDAC) alternating with 5-azacytidine demonstrates high rates of minimal residual disease (MRD) negative complete remissions (CR) and excellent tolerability in older patients with newly diagnosed acute myeloid leukemia (AML) [ASH abstract 25]. *Blood*. 2020;136(1)(suppl).

47. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.

48. Silva P, Neumann M, Schroeder MP, et al. Acute myeloid leukemia in the elderly is characterized by a distinct genetic and epigenetic landscape. *Leukemia*. 2017;31(7):1640-1644.

49. Schneider F, Hoster E, Schneider S, et al. Age-dependent frequencies of NPM1 mutations and FLT3-ITD in patients with normal karyotype AML (NK-AML). *Ann Hematol*. 2012;91(1):9-18.

50. Larrosa-Garcia M, Baer MR. FLT3 Inhibitors in acute myeloid leukemia: current status and future directions. *Mol Cancer Ther*. 2017;16(6):991-1001.

51. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-464.

52. Schlenk RF, Weber D, Fiedler W, et al; German-Austrian AML Study Group. Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with *FLT3*-ITD. *Blood*. 2019;133(8):840-851.

53. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory *FLT3*-mutated AML. *N Engl J Med*. 2019;381(18):1728-1740.

54. Ravandi F, Alattar ML, Grunwald MR, et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. *Blood*. 2013;121(23):4655-4662.

55. Ohanian M, Garcia-Manero G, Levis M, et al. Sorafenib combined with 5-azacytidine in older patients with untreated FLT3-ITD mutated acute myeloid leukemia. *Am J Hematol*. 2018;93(9):1136-1141.

56. Serve H, Krug U, Wagner R, et al. Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: results from a randomized, placebo-controlled trial. *J Clin Oncol*. 2013;31(25):3110-3118.

57. Wang E, Montesinos P, Minden M, et al. Phase 3, multicenter, open-label study of gilteritinib, gilteritinib plus azacitidine, or azacitidine alone in newly diagnosed FLT3 mutated (FLT3mut+) acute myeloid leukemia (AML) patients ineligible for intensive induction chemotherapy [ASH abstract 27]. *Blood*. 2020;136(1)(suppl).

58. Astellas Reports XOSPATA® (gilteritinib) in combination with azacitidine did not meet endpoint of overall survival in newly diagnosed FLT3 mutation-positive acute myeloid leukemia patients ineligible for intensive induction chemotherapy [press release]. https://www.astellas.com/us/news/5306. Published December 21, 2020. Accessed November 10, 2021.

59. Altman JK, Daver N, Maly J, et al. Efficacy and safety of venetoclax in combination with gilteritinib for relapsed/refractory FLT3-mutated acute myeloid leukemia: updated analyses of a phase 1B study [EHA abstract S135]. *HemaSphere*. 2021;5(suppl 1).

60. Maiti A, DiNardo CD, Daver NG, et al. Triplet therapy with venetoclax, FLT3 inhibitor and decitabine for FLT3-mutated acute myeloid leukemia. *Blood Cancer J*. 2021;11(2):25.

61. Ward PS, Patel J, Wise DR, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell*. 2010;17(3):225-234.

62. Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. *J Clin Oncol*. 2010;28(22):3636-3643.

63. Losman JA, Looper RE, Koivunen P, et al. (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. *Science*. 2013;339(6127):1621-1625.

64. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.

65. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*. 2020;135(7):463-471.

66. DiNardo CD, Stein AS, Stein EM, et al. Mutant isocitrate dehydrogenase 1 inhibitor ivosidenib in combination with azacitidine for newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2021;39(1):57-65.

67. Servier announces positive topline data from the global phase 3 study of TIBSOVO® (ivosidenib tablets) in combination with azacitidine in patients with previously untreated IDH1-mutated acute myeloid leukemia [press release]. https://www.servier.us/servier-announces-positive-topline-data-from-the-global-phase-3-study-of-tibsovo. Published August 2, 2021. Accessed November 10, 2021.

68. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722-731.

69. Pollyea DA, Tallman MS, de Botton S, et al. Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia. *Leukemia*. 2019;33(11):2575-2584.

70. Dinardo CD, Schuh AC, Stein EM, et al. Effect of enasidenib (ENA) plus azacitidine (AZA) on complete remission and overall response versus AZA monotherapy in mutant-IDH2 (mIDH2) newly diagnosed acute myeloid leukemia (ND-AML) [ASCO abstract 7501]. *J Clin Oncol*. 2020;38(15)(suppl).

71. Lachowiez CA, Borthakur G, Loghavi S, et al. A phase Ib/II study of ivosidenib with venetoclax +/- azacitidine in IDH1-mutated myeloid malignancies [ASCO abstract 7012]. *J Clin Oncol*. 2021;39(15)(suppl).

72. Schoch C, Kern W, Kohlmann A, Hiddemann W, Schnittger S, Haferlach T. Acute myeloid leukemia with a complex aberrant karyotype is a distinct biological entity characterized by genomic imbalances and a specific gene expression profile. *Genes Chromosomes Cancer*. 2005;43(3):227-238.

73. Kim K, Maiti A, Loghavi S, et al. Outcomes of TP53-mutant acute myeloid leukemia with decitabine and venetoclax. *Cancer*. 2021;127(20):3772-3781.

74. Venugopal S, Shoukier M, Konopleva M, et al. Outcomes in patients with newly diagnosed TP53-mutated acute myeloid leukemia with or without venetoclax-based therapy. *Cancer*. 2021;127(19):3541-3551.

75. Short NJ, Montalban-Bravo G, Hwang H, et al. Prognostic and therapeutic impacts of mutant TP53 variant allelic frequency in newly diagnosed acute myeloid leukemia. *Blood Adv*. 2020;4(22):5681-5689.

76. Zhang Q, Bykov VJN, Wiman KG, Zawacka-Pankau J. APR-246 reactivates mutant p53 by targeting cysteines 124 and 277. *Cell Death Dis*. 2018;9(5):439.

77. Sallman DA, DeZern AE, Garcia-Manero G, et al. Eprenetapopt (APR-246) and azacitidine in *TP53*-mutant myelodysplastic syndromes. *J Clin Oncol*. 2021;39(14):1584-1594.

78. Cluzeau T, Sebert M, Rahmé R, et al. Eprenetapopt plus azacitidine in *TP53*-mutated myelodysplastic syndromes and acute myeloid leukemia: a phase II study by the Groupe Francophone des Myélodysplasies (GFM). *J Clin Oncol*. 2021;39(14):1575-1583.

79. Aprea therapeutics announces results of primary endpoint from phase 3 trial of eprenetapopt in TP53 mutant myelodysplastic syndromes (MDS) [press release]. https://ir.aprea.com/news-releases/news-release-details/aprea-therapeutics-announces-results-primary-endpoint-phase-3. Published December 28, 2020. Accessed November 10, 2021.

80. Jaiswal S, Jamieson CH, Pang WW, et al. CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. *Cell*. 2009;138(2):271-285.

81. Feng D, Gip P, McKenna KM, et al. Combination treatment with 5F9 and azacitidine enhances phagocytic elimination of acute myeloid leukemia [ASH abstract 2729]. *Blood*. 2018;132(1)(suppl).

82. Sallman D, Asch A, Kambhampati S, et al. The first-in-class anti-CD47 antibody magrolimab combined with azacitidine is well-tolerated and effective in AML patients: phase 1b results. *Blood*. 2020;136(suppl 1):330.

83. Thijssen R, Diepstraten ST, Moujalled D, et al. Intact TP-53 function is essential for sustaining durable responses to BH3-mimetic drugs in leukemias. *Blood*. 2021;137(20):2721-2735.

84. Carter BZ, Mak PY, Kornblau SM, et al. TP53 deficient/mutant AMLs are resistant to individual BH3 mimetics: high efficacy of combined inhibition of Bcl-2 and Mcl-1 [ASH abstract 1271]. *Blood*. 2019;134(1)(suppl).

85. Parry N, Wheadon H, Copland M. The application of BH3 mimetics in myeloid leukemias. *Cell Death Dis*. 2021;12(2):222.

86. Wei AH, Döhner H, Pocock C, et al; QUAZAR AML-001 Trial Investigators. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383(26):2526-2537.

87. Reville PK, Kantarjian HM, Ravandi F, et al. Nivolumab maintenance in high-risk acute myeloid leukemia patients: a single-arm, open-label, phase II study. *Blood Cancer J*. 2021;11(3):60.

88. Abou Dalle I, Kantarjian HM, Ravandi F, et al. Phase 2 study of lenalidomide maintenance for patients with high-risk acute myeloid leukemia in remission. *Cancer*. 2021;127(11):1894-1900.