Curr. Treat. Options in Oncol. (2021) 22: 39
DOI 10.1007/s11864-021-00841-4

Leukemia (PH Wiernik, Section Editor)

New Treatment Options for Older Patients with Acute Myeloid Leukemia

Kapil Saxena[1]
Marina Konopleva[2,*]

Address
[1]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd Unit 463, Houston, TX, 77030, USA
[*,2]Department of Leukemia, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 428, Houston, TX, 77030, USA
Email: mkonople@mdanderson.org

Published online: 20 March 2021

This article is part of the Topical Collection on *Leukemia*

Keywords AML · Leukemia · Venetoclax · Hypomethylating agent

Opinion statement

The treatment of acute myeloid leukemia (AML) has evolved considerably over the past several years. Advances in the field have historically benefited younger patients; however, a growing understanding of the molecular basis of leukemogenesis has brought multiple targeted agents to the clinic for patients of all ages. These therapies have expanded the therapeutic landscape for elderly patients from more than best supportive care and low-intensity monotherapy. In general, we currently utilize a backbone regimen of a hypomethylating agent (HMA) or low-intensity chemotherapy with the BCL-2 inhibitor venetoclax for the majority of elderly patients with newly diagnosed AML. For patients with targetable mutations, we employ a doublet/triplet strategy of HMA + a targeted inhibitor +/– venetoclax, often in the context of a clinical trial. CPX-351 is reserved for patients with secondary or therapy-related AML. In this review, we will outline our approach to the treatment of elderly patients with AML, with particular emphasis on recently approved agents and emerging novel therapies.

Introduction

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy of myeloid precursor cells that is uniformly fatal without therapy. For the past several decades, therapy has typically been divided into intensive therapy with curative intent for "fit" patients and non-intensive therapy for patients not deemed fit for an

intensive approach. An intensive chemotherapy (IC) approach typically entails use of an anthracycline + cytosine arabinoside (AraC) backbone followed by consolidation with further chemotherapy or allogeneic stem cell transplantation (SCT) [1, 2]. Until recently, options for non-intensive therapy ranged from supportive care to single-agent hypomethylating agents (HMAs) [3–5]. Given that the median age at diagnosis of AML is 68 and peak incidence is between ages 75 and 85, a majority of patients are considered "elderly" and are treated with a non-intensive therapeutic approach [6, 5]. Unfortunately, outcomes for this group of patients have only slightly improved over the past 40 years, as improvements in the field have primarily benefited younger patients [7, 8]. This represents the core historical challenge in treating AML: a majority of clinical trials have not produced substantial benefits for the largest cohort of patients, the elderly. In this article, we will give a brief discussion of advances in intensive therapeutic approaches for elderly patients with AML followed by a more in-depth review of the major recent advancements in treating elderly patients with non-intensive therapies.

Defining fitness for intensive chemotherapy

When choosing a therapeutic approach for patients with AML, multiple disease-related and patient-related factors are incorporated. Knowledge of a patient's AML mutational status, cytogenetic abnormalities, and antecedent hematologic illnesses (preceding myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) or prior exposure to mutagenic therapy) helps risk-stratify patients into favorable, intermediate, and adverse prognostic categories [9]. Patients with favorable-risk AML can potentially be cured with IC alone, while patients with adverse-risk AML generally benefit from allogeneic SCT in CR1 [2, 10]. However, whether a patient should receive IC +/− SCT is highly dependent on an individual's risk for treatment-related morbidity and mortality from this intensive approach. Determining a patient's ability to tolerate IC +/− SCT is often paraphrased using the word "fitness," which is influenced by a patient's age, comorbidities, organ function, baseline functional status, and current level of illness [1, 11]. Of all these factors, age has classically exerted the most influence, not only as an absolute number but also because medical comorbidities tend to increase with age [1]. However, defining an elderly patient is quite variable in AML guidelines and elderly patients have historically been underrepresented in large AML trials [12, 13, 8]. Over time, it has become more appreciated that some elderly patients may be fit enough to tolerate IC. Thus, it is our approach to determine a patient's ability to tolerate IC +/− SCT based on the factors outlined above rather than age alone, and several groups have developed algorithms for assessing fitness for IC and SCT [14–16].

Despite our emphasis on using fitness rather than age alone to determine eligibility for an intensive therapeutic approach, elderly AML patients are much more likely to have several disease-related factors which make them less likely to benefit from current therapies, regardless of treatment intensity [17]. Older patients with AML have higher rates of adverse-risk mutations, unfavorable cytogenetics, an antecedent hematologic disorder, and therapy-related disease, all of which are associated

with inferior CR rates and poor overall survival (OS) [18, 7, 6, 19, 16]. Given these multiple factors, survival rates for patients with AML continue to stratify by age, with 5-year OS approaching 50% for patients < age 60 and ≤ 20% for patients ≥ 60 years old [6, 20].

Treatment of elderly patients eligible for intensive therapy

With regard to choice of IC for fit elderly patients, there is not extensive data characterizing which regimen is safest and most effective for de novo AML. However, a phase III randomized trial has compared the intensive regimen CPX-351 (liposomal daunorubicin + AraC) to the 7+3 regimen (continuous infusion AraC + daunorubicin) in patients aged 60–75 with secondary AML (sAML) [21]. The median age was nearly 68, and over 33% of patients were older than 70. With CPX-351, both CR rates and OS were improved compared to 7+3 (2-year OS 31.1% with CPX-351 vs 12.3% with 7+3), and 34% of patients treated with CPX-351 underwent SCT [21]. Early mortality was lower with CPX-351 (13.7% vs 21.2%), though this difference did not meet statistical significance [21]. The beneficial effects of CPX-351 compared to 7+3 in this trial persisted at the most recent analysis with median follow-up of 5 years [22].

Though data for effective IC regimens in elderly patients with de novo AML is relatively less impressive, a promising therapy was recently described, consisting of the 5+2 regimen + venetoclax. In the phase Ib dose-escalation study of 51 patients with a median age of 72, the CR/CRi rate was 97% for de novo AML with median OS of 31.3 months; inferior efficacy was observed for sAML (43% CR/CRi and 6.1 months median OS) [23•]. Thirty-day mortality with 5+2 + venetoclax was 6% in the total cohort [23•].

Older patients that may particularly benefit from IC are those with core-binding factor (CBF) AML [inv(16), t(16;16), or t(8;21)] because these patients can potentially be cured with IC alone. In younger patients, the intensive FLAG-Ida regimen (fludarabine, AraC, GCSF, and idarubicin) is particularly active in those with favorable-risk AML, such as CBF-AML [2]. However, the use of an anthracycline makes this regimen potentially toxic for older patients. The anti-CD33 antibody-drug conjugate gemtuzumab ozogamicin (GO) is active in patients with favorable-risk AML, and thus, the FLAG-GO regimen was developed to assess if substituting GO for idarubicin affects outcomes in CBF-AML [24]. In a non-randomized analysis of 162 patients with CBF-AML treated with FLAG-Ida or FLAG-GO, FLAG-GO was shown to be highly efficacious across a wide age range, including patients older than 65 [25]. At median follow-up of 6.5 years, FLAG-GO resulted in a 5-year relapse-free survival rate of 87% compared to 68% with FLAG-Ida, and thus this is our favored regimen for patients with CBF-AML who can tolerate IC [25].

Increased use of reduced-intensity conditioning (RIC) regimens, alternative graft sources (such as haploidentical donors), and improved prophylaxis against infection and graft-versus-host disease (GvHD) have all improved the safety of allogeneic SCT in older patients [26, 27]. Although rates of allogeneic SCT are steadily increasing in patients ≥ 65 years old (< 1% between 2000 and 2007), still only a small minority of elderly patients proceed to SCT based on more recent estimates (< 7%) [11, 28–30]. However, advances in non-intensive combination regimens have significantly increased CR rates, permitting more

elderly patients to proceed to SCT in CR1 [31••]. Though further discussion regarding the nuances of SCT in this population is outside the scope of this focused review, it is our overall approach that fit elderly patients with disease-specific indications for SCT should proceed to SCT if CR is attained with induction therapy.

Though SCT is the preferred approach for consolidation in fit patients with adverse-risk disease factors, many patients do not undergo SCT. Recently, a new therapeutic approach for these patients emerged with the use of oral azacitidine (CC-486) as post-remission maintenance therapy. In the international phase III QUAZAR AML-001 study, patients ≥ 55 years old with newly diagnosed AML who achieved CR/CRi with IC but did not proceed to SCT were randomized to placebo or CC-486 [32••]. Notably, patients were excluded if they achieved CR/CRi with an HMA. The study enrolled 472 patients (median age 68), a majority of whom had de novo AML (91%) and intermediate-risk cytogenetics (86%), and had received some type of chemotherapy consolidation prior to trial enrollment (80%) [32••]. At median follow-up of 41.2 months, OS was significantly improved with CC-486 compared to placebo (median OS 24.7 months vs 14.8 months; 2-year OS 50.6% vs 37.1%) [32••]. Furthermore, CC-486 was well-tolerated, with diarrhea as the most common grade 3 non-hematologic adverse event (AE) (5% vs 1%) [32••]. Based on these results, CC-486 received US Food and Drug Administration (FDA) approval in 2020 as maintenance therapy for patients with AML who were in CR/CRi after IC but were unable to proceed to SCT.

Evolution of non-intensive regimens for patients ineligible for IC

To describe how the combination of an HMA + the BCL-2 inhibitor venetoclax has become a standard-of-care non-intensive option for AML, we will provide a brief overview of the evolution of non-intensive regimens to provide historical context. Much of the early success in AML therapy arose from studies of AraC and anthracyclines between the 1960s and 1980s [33]. However, these early studies with IC also demonstrated that increasing age correlated with decreased response rates and increased toxicity [33–35]. Thus, for many years most older patients with AML were treated with a palliative approach of supportive care alone +/− hydroxyurea (HU) to control leukocytosis, with median survival typically ≤ 3 months [30, 8]. In one of the few randomized trials to assess the role of IC for elderly patients, patients > 65 years old were randomized to IC or supportive care [36]. Fifty-eight percent of patients treated with IC achieved CR and median OS was 21 weeks, compared to median OS of 11 weeks with supportive care +/− cytoreductive therapy (HU or subcutaneous AraC for leukocytosis) [36]. Although the intention was for the supportive care arm to receive outpatient management, both groups ultimately spent similar amounts of time in the hospital due to acute medical complications in the supportive care arm [36]. A follow-up randomized study compared subcutaneous low-dose AraC (LDAC) to IC in patients > 65 years old and demonstrated that IC produced higher CR rates than LDAC (52% vs 20%) [37]. However, LDAC resulted in fewer early deaths than IC (10% vs 31%), and thus OS was similar

between both arms, demonstrating that non-intensive therapy can be safer than IC for elderly patients with AML [37]. Subsequently, it was shown that LDAC improved CR rates and prolonged OS compared to supportive care, establishing LDAC as a suitable non-intensive therapy [38].

The next advancement in non-intensive therapies came in the 2010s with two randomized trials demonstrating that the HMAs azacitidine and decitabine prolonged survival compared to conventional care options (supportive care, LDAC, or IC) [4, 3]. Though HMAs became the standard-of-care for elderly patients, neither actually received FDA approval as monotherapy for AML. Meanwhile, a growing understanding of the molecular and cellular drivers of leukemogenesis was yielding novel targeted therapy options for AML. AML cells are highly dependent on the anti-apoptotic BCL-2 family of proteins for survival, and the small molecule ABT-199 (later known as venetoclax) is a specific and potent inhibitor of the anti-apoptotic protein BCL-2 [39]. In a phase II study of patients with relapsed/refractory (R/R) AML, venetoclax produced an overall response rate (ORR) of 19% and was fairly well-tolerated [40]. This led to a pivotal phase Ib study assessing the combination of an HMA (azacitidine or decitabine) + venetoclax in patients ≥ 65 years old and ineligible for IC. HMA + venetoclax (HMA/VEN) demonstrated promising efficacy, with a CR/CRi rate of 73% in the venetoclax 400 mg dosing cohort [41••]. The subsequent randomized phase III VIALE-A trial compared azacitidine (AZA) to azacitidine + venetoclax (AZA/VEN) in patients ineligible for IC [31]. Compared to AZA alone, AZA/VEN significantly prolonged OS from 9.6 months to 14.7 months and increased the CR/CRi rate from 28.3% to 66.4% [31]. AZA/VEN was generally well-tolerated, though there was increased myelosuppression and a higher incidence of febrile neutropenia (grade ≥ 3 febrile neutropenia AZA/VEN 42% vs AZA 19%) [31••]. Though rates of febrile neutropenia were higher in the AZA/VEN arm, serious AEs including pneumonia (16% vs 22%) and sepsis (6% vs 8%) had a similar incidence in the AZA arm, and 30-day mortality was similar in both arms (7% AZA/VEN vs 6% AZA) [31••]. Based on the results of the VIALE-A study, an HMA (azacitidine or decitabine) + venetoclax is our preferred backbone regimen for patients with AML not fit for IC and for a majority of our elderly patients.

Two additional regimens have been approved for AML: LDAC + venetoclax (LDAC/VEN) and LDAC + glasdegib. LDAC/VEN was compared to LDAC in the phase III randomized VIALE-C trial. The addition of venetoclax to LDAC improved the CR/CRi rate from 13% to 48%; however, the study did not meet its primary survival endpoint at the initial preplanned analysis [42•]. After an additional 6 months of follow-up, LDAC/VEN resulted in median OS of 8.4 months compared to 4.1 months with LDAC alone (p=0.04) [42•]. Around the same time, LDAC/glasdegib was compared to LDAC in a phase II randomized trial for patients with newly diagnosed, untreated AML or high-risk MDS [43]. Glasdegib is an oral inhibitor of the Hedgehog signaling pathway, which has been shown to play a role in maintaining the leukemia stem cell (LSC) compartment. Among the AML patients, the addition of glasdegib to LDAC improved median OS from 4.3 months to 8.3 months (p<0.01) and improved the ORR from 5.3% to 26.9% [43]. Both LDAC/VEN and LDAC/glasdegib are used less now compared to HMA/VEN and thus will not be further discussed in-depth in this review. However, both regimens remain possible alternative treatment options and have received FDA approval for use in elderly patients

with AML ineligible for IC [43, 42•]. It has not been assessed if either of these two regimens demonstrates efficacy post-HMA/VEN treatment, though it is unlikely; patients who progress/relapse after HMA/VEN currently have very poor outcomes [44].

Current and emerging non-intensive treatment approaches

It has been shown that awaiting molecular/cytogenetic results prior to starting induction therapy does not worsen outcomes in comparison to immediately starting therapy, and we use HU and/or AraC to control leukocytosis in the intervening period [45]. We will present our approach to treatment options for patients with AML ineligible for IC, summarized in Fig. 1. We will focus on both current FDA-approved treatment approaches and emerging therapies primarily studied in clinical trial settings.

IDH-mutated AML

Isocitrate dehydrogenase (IDH) is an enzyme that catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG) [46]. Recurrent mutations in two IDH isoforms, IDH1 (6–10%) and IDH2 (9–13%), have been identified in AML and are more often seen in elderly patients [47, 48]. IDH isoforms harboring specific pathogenic mutations cannot convert isocitrate to α-KG and instead

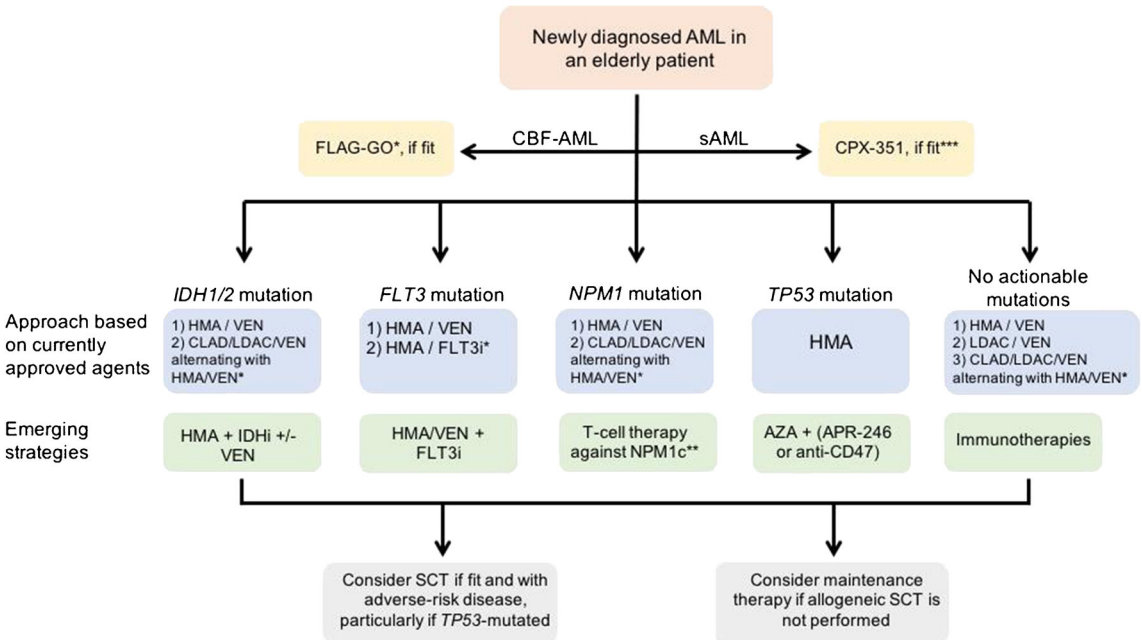

Fig. 1. Treatment approach to a newly diagnosed, elderly patient with AML. CBF, core-binding factor; FLAG-GO, fludarabine, cytarabine, GCSF, gemtuzumab ozogamicin; HMA, hypomethylating agent; VEN, venetoclax; AZA, azacitidine; CLAD, cladribine; LDAC, low-dose cytarabine; FLT3i, FLT3 inhibitor; IDHi, IDH inhibitor; SCT, allogeneic stem cell transplant. Green boxes contain regimens/agents that are not FDA-approved and are currently only in clinical trials or are still undergoing preclinical evaluation (indicated by **). *Use of this regimen includes approved agents, combination use is off-label. **Currently in preclinical models only. ***CPX-351 is approved for secondary AML; CPX-351+venetoclax is currently in clinical trials

catalyze the reaction of α-KG to the oncometabolite *R*-2-hydroxyglutarate (*R*-2-HG) [47, 49]. *R*-2-HG exerts a leukemogenic effect by inhibiting several α-KG-dependent enzymes involved in epigenetic modifications, thereby leading to abnormal cell differentiation [46]. The prognostic significance of *IDH* mutations in AML remains unclear, though a retrospective analysis of 826 patients with AML (20% *IDH*-mutated) found that patients with an *IDH*-mutation had similar ORR and OS as patients with wild-type *IDH* [47]. Notably, this study occurred before IDH-inhibitors (IDHi) or venetoclax were in use.

Historically, non-intensive treatment of *IDH*-mutated AML was HMA monotherapy. However, the treatment landscape has broadened following two pivotal early-phase clinical trials in R/R AML published in the past 4 years [48, 50]. Specific inhibitors for AML with an *IDH1*-mutation (ivosidenib) and *IDH2*-mutation (enasidenib) are now both FDA-approved for use in patients with R/R AML harboring these respective mutations. Furthermore, ivosidenib is also approved for frontline therapy based on efficacy in patients with newly diagnosed *IDH1*-mutated AML [51]. Among 33 evaluable patients in the single-arm study, 30.3% of patients achieved CR [51]. Duration of CR was not estimable, and median OS was 12.6 months [51]. Despite demonstrated efficacy of these inhibitors as monotherapy, we use HMA/VEN as frontline therapy for patients with *IDH*-mutated AML being treated outside of a clinical trial setting. This is due to (1) efficacy of this regimen in the VIALE-A study, (2) lack of randomized data for IDHi monotherapy in the frontline setting, (3) demonstrations both in vitro and in vivo that *IDH*-mutated AML cells are particularly sensitive to BCL-2 inhibition, even without an IDHi [52]. In VIALE-A, 75.4% of patients with *IDH*-mutated AML treated with AZA/VEN achieved CR, compared to 10.7% treated with AZA alone [31]. One-year OS was 66.8% with AZA/VEN compared to 35.7% with AZA [31]. Furthermore, in a pooled analysis of patients with an *IDH1/2* mutation treated in the initial phase Ib HMA/VEN study or in VIALE-A, median OS with AZA/VEN (n=79) was 24.5 months and 2-year OS 52.4%, compared to median OS of 6.2 months and 2-year OS 12.2% with AZA (n=28) [53].

Emerging strategies to improve outcomes for patients with *IDH*-mutated AML that are currently being studied in clinical trials include doublet/triplet combinations of an IDHi +/− AZA +/− VEN. The phase Ib results of ivosidenib + AZA for *IDH1*-mutated AML have recently been published and demonstrated both safety and efficacy of the combination regimen (NCT02677922) [54]. The ORR was 78.3%, including a CR rate of 60.9%, and the most common treatment-related grade ≥ 3 AEs were hematologic (22% neutropenia, 13% anemia and thrombocytopenia) [54]. With median follow-up of 16 months, 1-year OS is 82% [54]. Based on these results, the randomized, double-blind phase III AGILE trial comparing ivosidenib +/− AZA is currently evaluating patients with newly diagnosed *IDH1*-mutated AML ineligible for IC (NCT03173248). Similarly, an ongoing phase Ib/II study is also evaluating enasidenib +/− AZA in patients with newly diagnosed *IDH2*-mutated AML ineligible for IC. At interim analysis of 101 patients in the randomized phase II portion of the study, CR was achieved in 53% of patients treated with enasidenib + AZA versus 12% with AZA alone; median OS was 22 months in both arms (NCT02677922) [55]. Lastly, ivosidenib + VEN +/− AZA is being assessed as a triplet regimen in an ongoing phase Ib/II study of patients with *IDH1*-mutated AML or high-risk MDS (NCT03471260). At interim analysis of

18 evaluable patients with either newly diagnosed or R/R AML, ivosidenib + VEN +/− AZA produced a composite CR (CRc) rate of 78%, with 3 out of 18 patients proceeding to SCT [56].

FLT3-mutated AML

FLT3 encodes the receptor FMS-like tyrosine kinase 3. FLT3 signal transduction is involved in normal hematopoiesis and is expressed primarily by normal hematopoietic stem and early progenitor cells [57]. Overexpression of FLT3 is found in a high proportion of AML blasts, and activating mutations in *FLT3* are some of the most common mutations in AML [58, 59]. These mutations have been found in nearly one-third of patients and lead to constitutive kinase activation with resultant cellular proliferation through multiple downstream pathways [60]. Internal tandem duplication (ITD) mutations in the juxtamembrane domain are found in 20–25% of patients, and point mutations in the tyrosine kinase domain (TKD) are found in 5–10% of patients [60, 61]. *FLT3*-ITD mutations are associated with increased risk of relapse and decreased overall survival, while the prognostic impact of TKD mutations is less clear [62, 63]. The prognostic impact of a *FLT3*-ITD mutation is further influenced by the allelic ratio of the ITD mutation and the presence of co-occurring mutations, particularly in *NPM1* [64]. Given the prevalence and negative prognostic impact of *FLT3*-ITD mutations, treatment of patients with *FLT3* mutations with FLT3 inhibitors is a topic of great interest and has evolved significantly over the past 10 years.

FLT3 inhibitors (FLT3i) are divided into type 1 and type 2 inhibitors based on their ability to inhibit FLT3 with either an ITD or TKD mutation (type 1) or only an ITD mutation (type 2). First-generation FLT3i include the type 1 inhibitor midostaurin and the type 2 inhibitor sorafenib. Second-generation inhibitors include gilteritinib (type 1) and quizartinib (type 2). All of these inhibitors are multikinase inhibitors with off-target effects; however, second-generation inhibitors are more specific for FLT3 than first-generation inhibitors [60]. In the pivotal phase III RATIFY trial, the addition of midostaurin to the 7+3 IC regimen improved OS compared to 7+3 alone for patients with *FLT3*-mutated AML [13]. In addition, the ADMIRAL trial demonstrated that single-agent gilteritinib improved OS for patients with R/R FLT3-mutated AML compared to chemotherapy [65]. Despite these successes, no FLT3i has been FDA-approved yet for use in the frontline setting for patients ineligible for IC. In the VIALE-A study, patients with *FLT3* mutations had higher responses to AZA/VEN compared to AZA (CR rate 72.4% vs 36.4) [31]. In a pooled analysis of patients with a *FLT3* mutation (ITD or TKD) treated in the initial phase Ib HMA/VEN study or in VIALE-A, AZA/VEN appeared to be more effective compared to AZA alone, improving median OS from 8.6 months to 13.3 months [66]. However, subgroup analysis of the initial phase Ib/II trials of HMA/VEN and LDAC/VEN identified both ITD and TKD mutations as markers of resistance to venetoclax-based combination regimens compared to other molecular subgroups [67]. Thus, non-intensive regimens incorporating a FLT3i are being evaluated in clinical trials.

AZA + sorafenib has been evaluated in a single-arm phase II study of patients with *FLT3*-mutated AML ineligible for IC [68]. Twenty-seven previously untreated patients were included and the ORR was 78% (CR 26%) [68]. The

combination was well-tolerated; however, median OS was only 8.3 months [68]. The ongoing randomized phase III LACEWING trial (NCT02752035) is evaluating AZA +/− gilteritinib for patients with a *FLT3* mutation ineligible for IC [69]. Though the randomized cohort is still enrolling, the safety cohort of 15 patients treated with AZA/gilteritinib had a CRc rate of 66.7% [69]. Emerging non-intensive frontline treatment strategies for patients with *FLT3*-mutated AML include triplet combinations of HMA/VEN + FLT3i, based on demonstration of synergy between FLT3i and venetoclax in preclinical models [70, 71]. In a phase II trial of patients with AML treated with decitabine + venetoclax (DAC/VEN), patients with a *FLT3* mutation were allowed to take a FLT3i as well (gilteritinib, sorafenib, or midostaurin) [72]. In subgroup analysis of 16 treatment-naïve patients with a *FLT3* mutation, 11 received DAC/VEN + FLT3i. The CRc rate was 10/11, and 2-year OS was 90% [72]. Currently, the triplet combination of DAC/VEN + the FLT3i quizartinib is being studied in patients with newly diagnosed or R/R *FLT3*-mutated AML (NCT03661307) [73]. Though early, the data thus far demonstrate efficacy with a CRc rate of 9/10 and 6-month OS of 86% [73]. Lastly, the doublet regimen of gilteritinib + venetoclax is being evaluated in patients with *FLT3*-mutated R/R AML, the majority of whom have had prior FLT3i exposure (NCT03625505). In this heavily pretreated cohort, the modified CRc rate among 37 evaluable patients was 83.8% (CR/CRi 16.2%) [74]. Based on these studies, using currently approved non-intensive agents, HMA/VEN appears to have the most efficacy for *FLT3*-mutated AML. However, given the likelihood of relapse without incorporation of a FLT3i and preclinical evidence of synergy between FLT3i and BCL2-inhibition, venetoclax-based doublet/triplet regimens incorporating a FLT3i may provide potent options for these patients in the future.

NPM1-mutated AML

The gene *NPM1* encodes the protein NPM1 or nucleophosmin, a multifunctional phosphoprotein that shuttles between the nucleus and cytoplasm and most commonly localizes to nucleoli [75, 76]. It is involved in centrosome duplication, preventing nucleolar protein aggregation, and DNA repair [77, 76]. Mutated *NPM1* has been found in approximately 30% of AML cases, and the presence of an *NPM1* mutation significantly influences a patient's prognosis dependent on co-occurring mutations (*DNMT3A*, *FLT3*-ITD), cytogenetics, and age [78, 61, 79]. Pathogenic *NPM1* mutations result in an altered NPM1 structure which primarily localizes in the cytoplasm instead of nucleoli, and mutated NPM1 is typically referred to as NPM1c [75, 76]. In the absence of co-occurring *FLT3*-ITD mutations, NPM1c AML generally confers a favorable prognosis [75, 9].

Subsequent studies have demonstrated that the favorable prognostic impact of an *NPM1* mutation is highly age-dependent [79]. NPM1c AML patients treated with IC above the age of 65 have a worse OS compared to patients aged 55–65, even in the absence of a co-occurring *FLT3*-ITD mutation [80, 79]. In contrast, the use of HMA/VEN for elderly patients with NPM1c AML results in improved OS and higher CR rates compared to matched historical patients treated with IC or HMA alone [80]. In the randomized VIALE-A trial, AZA/VEN resulted in a CR rate of 66.7% compared to 23.5% with AZA alone for patients with NPM1c AML [31]. Furthermore, in a single-arm phase II trial of decitabine

for 10 days + venetoclax, newly diagnosed patients with NPM1c AML had a CR/CRi rate of 95% [81•]. Thus, we use HMA + venetoclax for newly diagnosed patients with *NPM1*-mutated AML without a co-occurring *FLT3*-ITD mutation who are over the age of 65, regardless of fitness. In general, these patients have been shown to respond well to venetoclax-containing regimens, whether paired with chemotherapy or an HMA [23•, 32••, 31••].

One final point to consider with NPM1c AML is that *NPM1* mutations are leukemic driver mutations [77]. The occurrence of an *NPM1* mutation appears to occur late in the process of a leukemogenesis, and the presence of an *NPM1* mutation correlates with active or emerging AML. Thus, patients with NPM1c AML who have achieved CR can be monitored with serial molecular testing for clearance and reappearance of their *NPM1* mutation. Achievement of undetectable levels of *NPM1*-mutations [molecular negativity for measurable residual disease (MRD)] highly correlates with improved OS, and molecular relapse predicts hematologic relapse [82]. Given these findings, an intriguing future possibility is the use of T cell-receptor-based cellular therapy targeting NPM1c peptides as a means to either eradicate residual disease in patients who have achieved an MRD-positive CR or as early intervention for patients with molecular relapse. Such strategies are currently being investigated in preclinical models [83].

TP53-mutated AML

TP53 encodes the tumor suppressor protein p53, the "guardian of the genome." The presence of intact p53-mediated pathways is integral to a cell's ability to respond to intracellular stressors such as DNA damage, oxidative stress, and oncogene activation [84, 85]. In response to these triggers, p53 can activate multiple transcriptional pathways involved in DNA repair, cell cycle control, and apoptosis [85]. Pathogenic mutations in *TP53* are most often missense mutations in the DNA-binding domain, reducing its ability to function as a transcription factor [86]. Though somatic *TP53* mutations are found in approximately 50% of solid tumor samples, they are relatively uncommon in AML (5–15%) [86, 84]. Furthermore, their occurrence is concentrated in patients with therapy-related AML and/or complex cytogenetics [61, 87].

TP53-mutated cells are typically less responsive to chemotherapy, likely due to their reduced ability to enter apoptosis following DNA damage [88, 89]. AML patients with *TP53* mutations have a decreased response to IC, shorter duration of CR, poor outcomes after allogeneic SCT, and reduced OS compared to patients without *TP53* mutations, particularly in those ≥ 60 years old [86, 85, 87, 90]. Thus, the presence of a *TP53* mutation alone is now classified as an adverse risk factor [9].

Unfortunately, treatment options for older patients with *TP53*-mutated AML are limited using currently approved agents. Historically, these patients were treated with HMA monotherapy. The combination of HMA + venetoclax has improved CR rates; however, OS remains poor. Among patients with a *TP53*-mutation in the VIALE-A study, AZA/VEN resulted in a CR rate of 55.3% compared to 0% in patients treated with AZA alone [31]. However, survival was not significantly improved: 34/38 patients passed away in the AZA/VEN group compared to 13/14 in the AZA group [31]. Similar results have been shown for patients with *TP53*-mutated AML treated frontline with DAC/VEN,

which resulted in a median OS of only 6.9 months despite a CR/CRi rate of 69% [81•]. Longer follow-up of the DAC/VEN *TP53*-mutated cohort revealed median OS of 5.2 months compared to 19.4 months for patients without a *TP53* mutation [91]. Notably, even in *TP53*-mutated patients who achieved CR/CRi with DAC/VEN, duration of remission was only 3.5 months, demonstrating that even responding patients quickly relapse [91].

Though current treatment options for *TP53*-mutated AML remain limited, two emerging therapies (APR-246 and magrolimab) have the potential to significantly improve outcomes for this population of patients in the near future. The first agent, APR-246, is a methylated form of the small molecule PRIMA-1. Upon entrance into a cell, APR-246 is degraded into its active compound MQ, which covalently modifies thiol groups in mutant p53, restoring wild-type function through conformational change [92]. Though this appears to be the primary mechanism of action of APR-246, it has shown growth-limiting activity in vitro against wild-type p53 cells also, suggesting an additional p53-independent mechanism [93]. This secondary mechanism may be through induction of reactive oxygen species, as APR-246 (through MQ) depletes intracellular stores of the antioxidant glutathione and inhibits the oxidoreductase enzyme TRXR1 [94, 95]. APR-246 was subsequently carried forward into clinical trials of *TP53*-mutated MDS and AML. In a phase II study of patients with *TP53*-mutated MDS or *TP53*-mutated oligoblastic AML, AZA + APR-246 has demonstrated promising efficacy with an ORR of 87% (53% CR) and median OS of 11.6 months (NCT03745716) [96]. The most common treatment-related AEs were nausea/vomiting (58%) and dizziness (31%) [96]. In a second phase II study for *TP53*-mutated MDS/AML conducted in Europe, 52 patients received AZA + APR-246 [97]. In this study, the ORR was 76% (53% CR/CRi) among 38 evaluable patients [97]. Given efficacy of AZA + APR-246, the combination of AZA/VEN + APR-246 is now being evaluated in a phase I trial for patients with *TP53*-mutated AML (NCT04214860).

The second agent that has shown promise for patients with *TP53*-mutated AML is the anti-CD47 monoclonal antibody (mAb) magrolimab, previously known as Hu5F9-G4. CD47 is a transmembrane protein expressed on several different types of cells [98]. Upon engagement of CD47 with its receptor SIRPα on phagocytic cells (such as macrophages and dendritic cells), phagocytosis is inhibited [98]. Thus, CD47 has been characterized as a "don't-eat-me" anti-phagocytic immune checkpoint. CD47 is overexpressed on AML cells compared to normal hematopoietic cells and may potentially be a LSC marker [99]. Treatment with an anti-CD47 mAb inhibits AML LSC engraftment in mice and increases AML cell phagocytosis [99]. This led to the development of the anti-CD47 mAb Hu5F9-G4, magrolimab [100]. Though non-leukemic cells also express CD47, phagocytosis through this pathway is triggered by both the presence of a pro-phagocytic "eat-me" signal and the absence of an anti-phagocytic "don't-eat-me" signal [98]. HMA therapy may increase AML cell expression of pro-phagocytic markers [98]. Clinically, AZA + magrolimab is being studied in a phase Ib trial of treatment-naïve patients with AML unfit for IC (NCT03248479). Among 34 patients evaluable at the most recent analysis, the CR/CRi rate in the overall population was 56% (44% CR) [101]. In the group of 21 evaluable patients with a *TP53*-mutation, the CR/CRi rate was 67% (48% CR) with median OS of 12.9 months. Notably, there were no immune-related AEs, and the most common treatment-related AE was anemia (31%)

[101]. It remains unclear why AZA + magrolimab is effective for patients with a *TP53* mutation, as its mechanism appears to be *TP53*-independent. It was recently shown that the presence of a *TP53* mutation in MDS and sAML correlates with an immunosuppressive bone marrow microenvironment, though CD47 expression was not specifically evaluated in the study [102]. It is also possible that anti-CD47-mediated cytotoxicity is not as dependent on an intact *TP53*-mediated apoptotic pathway as that of conventional chemotherapy. Magrolimab + AZA/VEN is now being studied in a phase Ib/II trial for patients with AML (NCT04435691), and additional anti-CD47 mAbs are being evaluated in early stage clinical trials.

Other treatment approaches

Several novel therapeutic approaches for AML are emerging from ongoing clinical trials, including combinations of multiple low-intensity agents as well immunotherapies. One efficacious combination approach is a regimen of cladribine/LDAC alternating with an HMA. Purine analogs, such as cladribine and fludarabine, have demonstrated efficacy in IC regimens, and thus, cladribine was added to LDAC/HMA to assess if synergy could be observed with these low-intensity agents [2, 103]. In a phase II trial of patients ineligible for IC or ≥ 60 years old with newly diagnosed AML or high-risk MDS, cladribine/LDAC alternating every 2 cycles with decitabine was evaluated [104]. Out of 118 patients, 44% were ≥ 70 years old, the CR/CRi rate was 68%, median OS was 13.8 months, and 1-year OS was 64% [104]. Given the efficacy of this regimen and the synergistic activity of venetoclax, cladribine/LDAC alternating with AZA is currently being examined in combination with venetoclax in a phase II study of newly diagnosed AML patients ≥ 60 years old or ineligible for IC (NCT03586609) [105]. Among 48 evaluable patients, the CR/CRi rate was 94% and 36 (75%) patients achieved MRD-negative CR/CRi as assessed by MFC. Four-week mortality was 0%, and 24% of responding patients proceeded to SCT [105].

Multiple different means of engaging or eliciting a T cell response against AML are also being investigated. These include immune checkpoint inhibitor (ICI) therapies, bispecific T cell engaging antibody-based molecules (BiTE® and DART®), and chimeric-antigen receptor T cells (CAR-T). The combination of AZA + nivolumab has shown efficacy in a single-arm phase II study of patients with R/R AML, resulting in a CR/CRi rate of 22% [106]. A separate single-arm phase II study of patients with R/R AML treated with AZA + pembrolizumab resulted in a CR/CRi rate of 14% [107]. Notably, AZA + pembrolizumab was also evaluated in patients ≥ 65 years old in the frontline setting. In this cohort, the CR/CRi rate was 47% among 17 evaluable patients, which is higher than the historical comparison of frontline AZA monotherapy (25–30%) [107, 4]. T cell engaging molecules which co-engage the CD3 receptor on T cells and a myeloid surface marker have also been studied in AML, currently in the relapsed/refractory setting. These include the CD3-CD123 DART® flotetuzumab and the CD3-CD33 BiTE® AMG 330. In a phase I/II study of flotetuzumab in patients with R/R AML, the ORR in 30 patients with early relapse or primary induction failure was 30% (NCT02152956) [108]. In the phase I study of AMG 330 for patients with R/R AML, 7 out of 42 (16.7%) patients achieved CR/CRi (NCT02520427) [109]. Lastly, early-phase clinical trials are currently assessing

the role of CAR-T cells against CD33 or CD123 in patients with R/R AML (NCT03971799, NCT04109482); results have not been published for either study yet. However, given that CD33 and CD123 are (1) present on non-malignant hematopoietic cells and (2) not expressed by all AML blasts, the risks of both on-target off-tumor toxicity (leading to severe cytokine-release syndrome and profound myelosuppression) and antigen escape (leading to early relapse) may limit their use as monotherapy [110]. Thus, these T cell–based therapies may ultimately be more useful as part of a combination regimen and/or as means to eradicate MRD after an initial response to induction therapy.

Conclusion

An elderly patient presenting with newly diagnosed AML continues to present a challenging clinical situation. In contrast to a younger population, elderly patients are more likely to present with adverse disease factors and have more medical comorbidities. However, considerable progress has occurred in the field compared to 5 years ago, when elderly patients were primarily treated with best supportive care, LDAC, or HMA monotherapy. There are now multiple new FDA-approved regimens for elderly patients with newly diagnosed AML, including HMA/VEN, LDAC/VEN, LDAC/glasdegib, and ivosidenib (for patients with an *IDH1*-mutation). Furthermore, numerous novel agents and combination regimens are emerging, which should further expand the therapeutic options for this historically difficult-to-treat population and are expected to provide improvements in both survival and quality-of-life.

Declarations

Conflict of Interest

Kapil Saxena declares that he has no conflict of interest.

Marina Konopleva has received research funding/clinical trial support from AbbVie, Genentech, F. Hoffmann-La Roche, Stemline Therapeutics, Forty Seven, Eli Lilly, Cellectis, Calithera, Ablynx, Agios, Ascentage, AstraZeneca, Rafael Pharmaceuticals, and Sanofi; has received compensation for service as a consultant from AbbVie, Genentech, F. Hoffman-La Roche, Stemline Therapeutics, Amgen, Forty Seven, and KisoJi Biotechnology; has received stock options/royalties related to a patent from Reata Pharmaceuticals; is listed as an inventor on a patent on CDDO-compounds and combination therapies issued and licensed to Reata Pharmaceuticals; is listed as an inventor on a patent on combination therapy with a mutant IDH1 inhibitor and a BCL-2 issued and licensed to Eli Lilly; and is a listed as an inventor on a pending patent on combination of a MCL-1 inhibitor and midostaurin, uses and pharmaceutical compositions thereof.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Ferrara F, Barosi G, Venditti A, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. Leukemia. 2013;27(5):997–9. https://doi.org/10.1038/leu.2012.303.
2. Burnett AK, Russell NH, Hills RK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. J Clin Oncol. 2013;31(27):3360–8. https://doi.org/10.1200/JCO.2012.47.4874.
3. 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):2670–7. https://doi.org/10.1200/JCO.2011.38.9429.
4. 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):291–9. https://doi.org/10.1182/blood-2015-01-621664.
5. Sekeres MA, Guyatt G, Abel G, et al. American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. Blood Adv. 2020;4(15):3528–49. https://doi.org/10.1182/bloodadvances.2020001920.
6. Juliusson G, Lazarevic V, Horstedt AS, et al. Acute myeloid leukemia in the real world: why population-based registries are needed. Blood. 2012;119(17):3890–9. https://doi.org/10.1182/blood-2011-12-379008.
7. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. Blood. 2006;107(9):3481–5. https://doi.org/10.1182/blood-2005-09-3724.
8. Hills RK, Burnett AK. Applicability of a "Pick a Winner" trial design to acute myeloid leukemia. Blood. 2011;118(9):2389–94. https://doi.org/10.1182/blood-2011-02-337261.
9. 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):424–47. https://doi.org/10.1182/blood-2016-08-733196.
10. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA. 2009;301(22):2349–61. https://doi.org/10.1001/jama.2009.813.
11. Ustun C, Lazarus HM, Weisdorf D. To transplant or not: a dilemma for treatment of elderly AML patients in the twenty-first century. Bone Marrow Transplant. 2013;48(12):1497–505. https://doi.org/10.1038/bmt.2013.67.
12. Mengis C, Aebi S, Tobler A, et al. Assessment of differences in patient populations selected for excluded from participation in clinical phase III acute myelogenous leukemia trials. J Clin Oncol. 2003;21(21):3933–9. https://doi.org/10.1200/JCO.2003.03.186.
13. 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):454–64. https://doi.org/10.1056/NEJMoa1614359.
14. Walter RB, Othus M, Borthakur G, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. J Clin Oncol. 2011;29(33):4417–23. https://doi.org/10.1200/JCO.2011.35.7525.
15. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912–9. https://doi.org/10.1182/blood-2005-05-2004.
16. Kantarjian H, Ravandi F, O'Brien S, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. Blood. 2010;116(22):4422–9. https://doi.org/10.1182/blood-2010-03-276485.
17. Frohling S, Schlenk RF, Kayser S, et al. Cytogenetics and age are major determinants of outcome in intensively treated acute myeloid leukemia patients older than 60 years: results from AMLSG trial AML HD98-B. Blood. 2006;108(10):3280–8. https://doi.org/10.1182/blood-2006-04-014324.
18. Herold T, Rothenberg-Thurley M, Grunwald VV, et al. Validation and refinement of the revised 2017 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. Leukemia. 2020. https://doi.org/10.1038/s41375-020-0806-0.
19. Tsai CH, Hou HA, Tang JL, et al. Genetic alterations and their clinical implications in older patients with acute myeloid leukemia. Leukemia. 2016;30(7):1485–92. https://doi.org/10.1038/leu.2016.65.
20. Kantarjian H. Acute myeloid leukemia–major progress over four decades and glimpses into the future. Am J Hematol. 2016;91(1):131–45. https://doi.org/10.1002/ajh.24246.
21. 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):2684–92. https://doi.org/10.1200/JCO.2017.77.6112.
22. Lancet JE, Uy GL, Newell LF, et al. Five-year final results of a phase 3 study of CPX-351 versus 7+3 in older adults with newly diagnosed high-risk/secondary acute myeloid leukemia (AML): outcomes by age subgroup and among responders. Abstract presented at the annual meeting of the American Society of Hematology. 2020. https://ash.confex.com/ash/2020/webprogram/Paper136874.html. Accessed 7 December 2020

23.• Chua CC, Roberts AW, Reynolds J, et al. Chemotherapy and Venetoclax in Elderly Acute Myeloid Leukemia Trial (CAVEAT): a phase Ib dose-escalation study of venetoclax combined with modified intensive chemotherapy. J Clin Oncol. 2020;38(30):3506–17. https://doi.org/10.1200/JCO.20.00572
Demonstation of safety and efficacy of intensive chemotherapy (5+2) with venetoclax in elderly patients.
24. Borthakur G, Cortes JE, Estey EE, et al. Gemtuzumab ozogamicin with fludarabine, cytarabine, and granulocyte colony stimulating factor (FLAG-GO) as frontline regimen in patients with core binding factor acute myelogenous leukemia. Am J Hematol. 2014;89(10):964–8. https://doi.org/10.1002/ajh.23795.
25. Borthakur GM, Cortes JE, Ravandi F, et al. Fludarabine, cytarabine, G-CSF and gemtuzumab ozogamicin (FLAG-GO) regimen results in better molecular response and relapse-free survival in core binding factor acute myeloid leukemia than FLAG and Idarubicin (FLAG-Ida). Blood. 2019;134:290.
26. Ciurea SO, Kongtim P, Varma A, et al. Is there an optimal conditioning for older patients with AML receiving allogeneic hematopoietic cell transplantation? Blood. 2020;135(6):449–52. https://doi.org/10.1182/blood.2019003662.
27. Lipof JJ, Loh KP, O'Dwyer K, et al. Allogeneic hematopoietic cell transplantation for older adults with acute myeloid leukemia. Cancers (Basel). 2018;10(6):179. https://doi.org/10.3390/cancers10060179.
28. D'Souza A, Fretham C, Lee SJ, et al. Current use of and trends in hematopoietic cell transplantation in the United States. Biol Blood Marrow Transplant. 2020;26(8):e177–e82. https://doi.org/10.1016/j.bbmt.2020.04.013.
29. Muffly L, Pasquini MC, Martens M, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. Blood. 2017;130(9):1156–64. https://doi.org/10.1182/blood-2017-03-772368.
30. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. Haematologica. 2012;97(12):1916–24. https://doi.org/10.3324/haematol.2012.066100.
31.•• Di Nardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617–29. https://doi.org/10.1056/NEJMoa2012971
Randomized trial demonstrating survival benefit to azacitidine/venetoclax compared to azacitidine as frontline non-intensive therapy for AML.
32.•• Wei AH, Dohner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. N Engl J Med. 2020;383(26):2526–37. https://doi.org/10.1056/NEJMoa2004444
Phase III placebo-controlled randomized trial demonstrating benefit to oral azacitidine maintenance therapy in patients ineligible for SCT.
33. Lichtman MA. A historical perspective on the development of the cytarabine (7days) and daunorubicin (3days) treatment regimen for acute myelogenous leukemia: 2013 the 40th anniversary of 7+3. Blood Cells Mol Dis. 2013;50(2):119–30. https://doi.org/10.1016/j.bcmd.2012.10.005.
34. Yates J, Glidewell O, Wiernik P, et al. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study. Blood. 1982;60(2):454–62.
35. Kahn SB, Begg CB, Mazza JJ, et al. Full dose versus attenuated dose daunorubicin, cytosine arabinoside, and 6-thioguanine in the treatment of acute nonlymphocytic leukemia in the elderly. J Clin Oncol. 1984;2(8):865–70. https://doi.org/10.1200/JCO.1984.2.8.865.
36. Lowenberg B, Zittoun R, Kerkhofs H, et al. On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group. J Clin Oncol. 1989;7(9):1268–74. https://doi.org/10.1200/JCO.1989.7.9.1268.
37. Tilly H, Castaigne S, Bordessoule D, et al. Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly. J Clin Oncol. 1990;8(2):272–9. https://doi.org/10.1200/JCO.1990.8.2.272.
38. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer. 2007;109(6):1114–24. https://doi.org/10.1002/cncr.22496.
39. Pan R, Hogdal LJ, Benito JM, et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. Cancer Discov. 2014;4(3):362–75. https://doi.org/10.1158/2159-8290.CD-13-0609.
40. 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):1106–17. https://doi.org/10.1158/2159-8290.CD-16-0313.
41.•• Di Nardo 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. https://doi.org/10.1182/blood-2018-08-868752
Pivotal phase Ib study of HMA/venetoclax demonstrating high CR/CRi rates.
42.• 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):2137–45. https://doi.org/10.1182/blood.2020004856
Phase III randomized trial comparing low-dose cytarabine with venetoclax compared to low-dose cytarabine.
43. Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2019;33(2):379–89. https://doi.org/10.1038/s41375-018-0312-9.
44. Maiti A, Rausch CR, Cortes JE, et al. Outcomes of relapsed or refractory acute myeloid leukemia after frontline hypomethylating agent and venetoclax regimens. Haematologica. 2020. https://doi.org/10.3324/haematol.2020.252569.
45. Rollig C, Kramer M, Schliemann C, et al. Does time from diagnosis to treatment affect the prognosis of patients with newly diagnosed acute myeloid leukemia? Blood. 2020;136(7):823–30. https://doi.org/10.1182/blood.2019004583.
46. Liu X, Gong Y. Isocitrate dehydrogenase inhibitors in acute myeloid leukemia. Biomark Res. 2019;7:22. https://doi.org/10.1186/s40364-019-0173-z.
47. DiNardo CD, Ravandi F, Agresta S, et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. Am J Hematol. 2015;90(8):732–6. https://doi.org/10.1002/ajh.24072.
48. 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):2386–98. https://doi.org/10.1056/NEJMoa1716984.
49. 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):225–34. https://doi.org/10.1016/j.ccr.2010.01.020.
50. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood. 2017;130(6):722–31. https://doi.org/10.1182/blood-2017-04-779405.
51. 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):463–71. https://doi.org/10.1182/blood.2019002140.
52. Chan SM, Thomas D, Corces-Zimmerman MR, et al. Isocitrate dehydrogenase 1 and 2 mutations induce BCL-2 dependence in acute myeloid leukemia. Nat Med. 2015;21(2):178–84. https://doi.org/10.1038/nm.3788.
53. Pollyea DA, DiNardo CD, Arellano ML, et al. Results of venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with IDH 1/2 mutations. Blood. 2020;136:5–7.
54. 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. 2020;39(1):57–65.
JCO2001632. https://doi.org/10.1200/JCO.20.01632.
55. 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). J Clin Oncol. 2020;38(15_suppl):7501. https://doi.org/10.1200/JCO.2020.38.15_suppl.7501.
56. DiNardo C, Lachowiez C, Borthakur G, et al. Phase IB/II study of the IDH1-mutant inhibitor ivosidenib with the BCL2 inhibitor venetoclax +/- azacitidine in IDH1-mutated hematologic malignancies. EHA Library. 2020;294963:S143.
57. Kindler T, Lipka DB, Fischer T. FLT3 as a therapeutic target in AML: still challenging after all these years. Blood. 2010;116(24):5089–102. https://doi.org/10.1182/blood-2010-04-261867.
58. Carow CE, Levenstein M, Kaufmann SH, et al. Expression of the hematopoietic growth factor receptor FLT3 (STK-1/Flk2) in human leukemias. Blood. 1996;87(3):1089–96.
59. Nakao M, Yokota S, Iwai T, et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia. 1996;10(12):1911–8.
60. Daver N, Schlenk RF, Russell NH, et al. Targeting FLT3 mutations in AML: review of current knowledge and evidence. Leukemia. 2019;33(2):299–312. https://doi.org/10.1038/s41375-018-0357-9.
61. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374(23):2209–21. https://doi.org/10.1056/NEJMoa1516192.
62. Bacher U, Haferlach C, Kern W, et al. Prognostic relevance of FLT3-TKD mutations in AML: the combination matters–an analysis of 3082 patients. Blood. 2008;111(5):2527–37. https://doi.org/10.1182/blood-2007-05-091215.
63. Kottaridis PD, Gale RE, Frew ME, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood. 2001;98(6):1752–9. https://doi.org/10.1182/blood.v98.6.1752.
64. Dohner K, Thiede C, Jahn N, et al. Impact of NPM1/FLT3-ITD genotypes defined by the 2017 European LeukemiaNet in patients with acute myeloid leukemia. Blood. 2020;135(5):371–80. https://doi.org/10.1182/blood.2019002697.

65. 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):1728–40. https://doi.org/10.1056/NEJMoa1902688.
66. Konopleva M, Thirman M, Pratz KW, et al. Results of venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with FLT3 mutations. Blood. 2020;136:8–10.
67. 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. https://doi.org/10.1182/blood.2019003988.
68. 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):1136–41. https://doi.org/10.1002/ajh.25198.
69. Wang ES, 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. Abstract presented at the annual meeting of the American Society of Hematology. 5 December 2020. https://ash.confex.com/ash/2020/webprogram/Paper137708.html. Accessed 5 December
70. Ma J, Zhao S, Qiao X, et al. Inhibition of Bcl-2 synergistically enhances the antileukemic activity of midostaurin and gilteritinib in preclinical models of FLT3-mutated acute myeloid leukemia. Clin Cancer Res. 2019;25(22):6815–26. https://doi.org/10.1158/1078-0432.CCR-19-0832.
71. Mali RS, Zhang Q, DeFilippis R, et al. Venetoclax combines synergistically with FLT3 inhibition to effectively target leukemic cells in FLT3-ITD+ acute myeloid leukemia models. Haematologica. 2020. https://doi.org/10.3324/haematol.2019.244020.
72. Maiti A, DiNardo CD, Ravandi F, et al. Venetoclax, FLT3 inhibitor and decitabine in FLT3mut acute myeloid leukemia: subgroup analysis of a phase II trial. Blood. 2020;136:53–5.
73. Yilmaz M, Kantarjian H, Muftuoglu M, et al. Quizartinib with decitabine +/- venetoclax is highly active in patients (Pts) with FLT3-ITD mutated (mut) acute myeloid leukemia (AML): clinical report and signaling Cytof profiling from a phase IB/II trial. Blood. 2020;136:19–20.
74. Daver N, Altman JK, Maly J, et al. Efficacy and safety of venetoclax in combination with gilteritinib for relapsed/refractory FLT3-mutated acute myeloid leukemia in the expansion cohort of a phase 1b study. Blood. 2020;136:20–2.
75. Falini B, Mecucci C, Tiacci E, et al. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. N Engl J Med. 2005;352(3):254–66. https://doi.org/10.1056/NEJMoa041974.
76. Heath EM, Chan SM, Minden MD, et al. Biological and clinical consequences of NPM1 mutations in AML. Leukemia. 2017;31(4):798–807. https://doi.org/10.1038/leu.2017.30.
77. Falini B, Brunetti L, Sportoletti P, et al. NPM1-mutated acute myeloid leukemia: from bench to bedside. Blood. 2020;136(15):1707–21. https://doi.org/10.1182/blood.2019004226.
78. Angenendt L, Rollig C, Montesinos P, et al. Chromosomal abnormalities and prognosis in NPM1-mutated acute myeloid leukemia: a pooled analysis of individual patient data from nine international cohorts. J Clin Oncol. 2019;37(29):2632–42. https://doi.org/10.1200/JCO.19.00416.
79. Ostronoff F, Othus M, Lazenby M, et al. Prognostic significance of NPM1 mutations in the absence of FLT3-internal tandem duplication in older patients with acute myeloid leukemia: a SWOG and UK National Cancer Research Institute/Medical Research Council report. J Clin Oncol. 2015;33(10):1157–64. https://doi.org/10.1200/JCO.2014.58.0571.
80. 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):1311–20. https://doi.org/10.1182/bloodadvances.2019001267.
81.• Di Nardo CD, Maiti A, Rausch CR, et al. 10-day decitabine with venetoclax for newly diagnosed intensive chemotherapy ineligible, and relapsed or refractory acute myeloid leukaemia: a single-centre, phase 2 trial. Lancet Haematol. 2020;7(10):e724–e36. https://doi.org/10.1016/S2352-3026(20)30210-6
Phase II study demonstrating potent efficacy of decitabine/venetoclax as non-intensive therapy.
82. Ivey A, Hills RK, Simpson MA, et al. Assessment of minimal residual disease in standard-risk AML. N Engl J Med. 2016;374(5):422–33. https://doi.org/10.1056/NEJMoa1507471.
83. van der Lee DI, Reijmers RM, Honders MW, et al. Mutated nucleophosmin 1 as immunotherapy target in acute myeloid leukemia. J Clin Invest. 2019;129(2):774–85. https://doi.org/10.1172/JCI97482.
84. Pant V, Quintas-Cardama A, Lozano G. The p53 pathway in hematopoiesis: lessons from mouse models, implications for humans. Blood. 2012;120(26):5118–27. https://doi.org/10.1182/blood-2012-05-356014.
85. Hunter AM, Sallman DA. Current status and new treatment approaches in TP53 mutated AML. Best Pract Res Clin Haematol. 2019;32(2):134–44. https://doi.org/10.1016/j.beha.2019.05.004.
86. Dutta S, Pregartner G, Rucker FG, et al. Functional classification of TP53 mutations in acute myeloid leukemia. Cancers (Basel). 2020;12(3):637. https://doi.org/10.3390/cancers12030637.
87. Nakano Y, Naoe T, Kiyoi H, et al. Prognostic value of p53 gene mutations and the product expression in de novo acute myeloid leukemia. Eur J Haematol.

2000;65(1):23–31. https://doi.org/10.1034/j.1600-0609.2000.90138.x.
88. Bykov VJ, Issaeva N, Shilov A, et al. Restoration of the tumor suppressor function to mutant p53 by a low-molecular-weight compound. Nat Med. 2002;8(3):282–8. https://doi.org/10.1038/nm0302-282.
89. O'Connor PM, Jackman J, Bae I, et al. Characterization of the p53 tumor suppressor pathway in cell lines of the National Cancer Institute anticancer drug screen and correlations with the growth-inhibitory potency of 123 anticancer agents. Cancer Res. 1997;57(19):4285–300.
90. Kadia TM, Jain P, Ravandi F, et al. TP53 mutations in newly diagnosed acute myeloid leukemia: clinicomolecular characteristics, response to therapy, and outcomes. Cancer. 2016;122(22):3484–91. https://doi.org/10.1002/cncr.30203.
91. Kim K, Maiti A, Kadia TM, et al. Outcomes of TP53-mutant acute myeloid leukemia with venetoclax and decitabine. Blood. 2020;136:33–6.
92. Lambert JM, Gorzov P, Veprintsev DB, et al. PRIMA-1 reactivates mutant p53 by covalent binding to the core domain. Cancer Cell. 2009;15(5):376–88. https://doi.org/10.1016/j.ccr.2009.03.003.
93. Ali D, Jonsson-Videsater K, Deneberg S, et al. APR-246 exhibits anti-leukemic activity and synergism with conventional chemotherapeutic drugs in acute myeloid leukemia cells. Eur J Haematol. 2011;86(3):206–15. https://doi.org/10.1111/j.1600-0609.2010.01557.x.
94. Ali D, Mohammad DK, Mujahed H, et al. Anti-leukaemic effects induced by APR-246 are dependent on induction of oxidative stress and the NFE2L2/HMOX1 axis that can be targeted by PI3K and mTOR inhibitors in acute myeloid leukaemia cells. Br J Haematol. 2016;174(1):117–26. https://doi.org/10.1111/bjh.14036.
95. Bykov VJN, Eriksson SE, Bianchi J, et al. Targeting mutant p53 for efficient cancer therapy. Nat Rev Cancer. 2018;18(2):89–102. https://doi.org/10.1038/nrc.2017.109.
96. Sallman DA, De Zern AE, Garcia-Manero G, Steensma DP, Roboz GJ, Sekeres MA, et al. Phase 2 results of APR-246 and azacitidine (AZA) in patients with *TP53* mutant myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia (AML). Blood. 2019;134:676.
97. Cluzeau T, Sebert M, Rahme R, et al. APR-246 combined with azacitidine in TP53 mutated myelodysplastic syndromes (MDS) and acute myeloid leukemia. A phase 2 study by the Groupe Francophone des Myélodysplasies (GFM). EHA Library. Blood. 2020;134(Supplement_1):677.
98. Chao MP, Takimoto CH, Feng DD, et al. Therapeutic targeting of the macrophage immune checkpoint CD47 in myeloid malignancies. Front Oncol. 2019;9:1380. https://doi.org/10.3389/fonc.2019.01380.
99. Majeti R, Chao MP, Alizadeh AA, et al. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell. 2009;138(2):286–99. https://doi.org/10.1016/j.cell.2009.05.045.
100. Liu J, Wang L, Zhao F, et al. Pre-clinical development of a humanized anti-CD47 antibody with anti-cancer therapeutic potential. PLoS One. 2015;10(9):e0137345. https://doi.org/10.1371/journal.pone.0137345.
101. Sallman DA, Asch AS, 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;15:7507.
102. Sallman DA, McLemore AF, Aldrich AL, et al. TP53 mutations in myelodysplastic syndromes and secondary AML confer an immunosuppressive phenotype. Blood. 2020. https://doi.org/10.1182/blood.2020006158.
103. Holowiecki J, Grosicki S, Giebel S, et al. Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized phase III study. J Clin Oncol. 2012;30(20):2441–8. https://doi.org/10.1200/JCO.2011.37.1286.
104. 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–e21. https://doi.org/10.1016/S2352-3026(18)30132-7.
105. 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). Blood. 2020;136:17–9.
106. Daver N, Garcia-Manero G, Basu S, et al. Efficacy, safety, and biomarkers of response to azacitidine and nivolumab in relapsed/refractory acute myeloid leukemia: a nonrandomized, open-label, phase II study. Cancer Discov. 2019;9(3):370–83. https://doi.org/10.1158/2159-8290.CD-18-0774.
107. Gojo I, Stuart RK, Webster J, et al. Multi-center phase 2 study of pembroluzimab (Pembro) and azacitidine (AZA) in patients with relapsed/refractory acute myeloid leukemia (AML) and in newly diagnosed (≥65 Years) AML patients. Blood. 2019;134(134):832.
108. Uy GL, Aldoss I, Foster MC, et al. Flotetuzumab as salvage immunotherapy for refractory acute myeloid leukemia. Blood. 2020. https://doi.org/10.1182/blood.2020007732.

109. Ravandi F, Walter RB, Subklewe M, et al. Updated results from phase I dose-escalation study of AMG 330, a bispecific T-cell engager molecule, in patients with relapsed/refractory acute myeloid leukemia (R/R AML). J Clin Oncol. 2020;38:7508.
110. Perna F, Berman SH, Soni RK, et al. Integrating proteomics and transcriptomics for systematic combinatorial chimeric antigen receptor therapy of AML. Cancer Cell. 2017;32(4):506–1.
e5. https://doi.org/10.1016/j.ccell.2017.09.004.

Publisher's note