Review Article

Acute Myeloid Leukemia: Treatment and Research Outlook for 2021 and the MD Anderson Approach

Hagop M. Kantarjian, MD ; Tapan M. Kadia, MD ; Courtney D. DiNardo, MD ; Mary Alma Welch, MMSC; and Farhad Ravandi, MD

The unraveling of the pathophysiology of acute myeloid leukemia (AML) has resulted in rapid translation of the information into clinical practice. After more than 40 years of slow progress in AML research, the US Food and Drug Administration has approved nine agents for different AML treatment indications since 2017. In this review, we detail the progress that has been made in the research and treatment of AML, citing key publications related to AML research and therapy in the English literature since 2000. The notable subsets of AML include acute promyelocytic leukemia (APL), core-binding factor AML (CBF-AML), AML in younger patients fit for intensive chemotherapy, and AML in older/unfit patients (usually at the age cutoff of 60-70 years). We also consider within each subset whether the AML is primary or secondary (therapy-related, evolving from untreated or treated myelodysplastic syndrome or myeloproliferative neoplasm). In APL, therapy with all-trans retinoic acid and arsenic trioxide results in estimated 10-year survival rates of ≥80%. Treatment of CBF-AML with fludarabine, high-dose cytarabine, and gemtuzumab ozogamicin (GO) results in estimated 10-year survival rates of ≥75%. In younger/fit patients, the "3+7" regimen (3 days of daunorubicin + 7 days of cytarabine) produces less favorable results (estimated 5-year survival rates of 35%; worse in real-world experience); regimens that incorporate high-dose cytarabine, adenosine nucleoside analogs, and GO are producing better results. Adding venetoclax, FLT3, and IDH inhibitors into these regimens has resulted in encouraging preliminary data. In older/unfit patients, low-intensity therapy with hypomethylating agents (HMAs) and venetoclax is now the new standard of care. Better low-intensity regimens incorporating cladribine, low-dose cytarabine, and other targeted therapies (FLT3 and IDH inhibitors) are emerging. Maintenance therapy now has a definite role in the treatment of AML, and oral HMAs with potential treatment benefits are also available. In conclusion, AML therapy is evolving rapidly and treatment results are improving in all AML subsets as novel agents and strategies are incorporated into traditional AML chemotherapy. ***Cancer* 2021;127:1186-1207**. © *2021 American Cancer Society*.

LAY SUMMARY:

- Ongoing research in acute myeloid leukemia (AML) is progressing rapidly.
- Since 2017, the US Food and Drug Administration has approved 10 drugs for different AML indications.
- This review updates the research and treatment pathways for AML.

KEYWORDS: acute myelogenous leukemia, new drugs, progress, research, therapy.

INTRODUCTION

Understanding of the biology and pathophysiology of acute myeloid leukemia (AML) has accelerated translational discoveries and is contributing to a steady improvement in the outlook and prognosis of AML.[1-4] Recent important transitions into clinical practice include small molecule–targeted therapies such as the fms-like tyrosine kinase 3 (FLT3) and isocitrate dehydrogenase (IDH) inhibitors and the BCL2 inhibitor venetoclax. The "3+7" regimen (3 days of daunorubicin + 7 days of cytarabine) developed in the late 1970s is an accepted standard of care, producing estimated 5-year survivals of 30% to 35% in younger patients (age <60 years)[5] and 10%-15% in older patients (age ≥60 years).[6] This intensive chemotherapy regimen, investigated in cooperative group trials that include highly selected patients, may translate into even worse outcomes in community oncology practices, which see patients who are older as well as those with secondary AML and multiple comorbidities (ie, hypertension, diabetes, cardiac and other organ dysfunctions). Figure 1 shows the MD Anderson Cancer Center outcomes in AML in younger and older patients between 1970 and 2020.

AML is not a single entity, but rather an umbrella diagnosis that comprises multiple subtypes with different prognostic and predictive features and can be treated effectively with selective and targeted therapies, which are still being optimized. For example, the chemotherapy-free regimen of all-trans retinoic acid (ATRA) and arsenic trioxide produces estimated cure rates of >80% in acute promyelocytic leukemia (APL).[7-10] The addition of gemtuzumab ozogamicin (GO [CD33-targeted monoclonal antibody conjugated to calicheamicin]) to high-dose cytarabine-based chemotherapy in core binding factor (CBF) AML has increased the estimated long-term survival rate from 50% to 75%.[11-15]

Corresponding Author: Hagop M. Kantarjian, MD, Department of Leukemia, MD Anderson Cancer Center, 1400 Holcombe Boulevard, Unit 428, Houston, TX 77030 (hkantarjian@mdanderson.org).

Department of Leukemia, MD Anderson Cancer Center, Houston, Texas

DOI: 10.1002/cncr.33477, **Received:** November 20, 2020; **Revised:** December 31, 2020; **Accepted:** January 11, 2021, **Published online** March 18, 2021 in Wiley Online Library (wileyonlinelibrary.com)

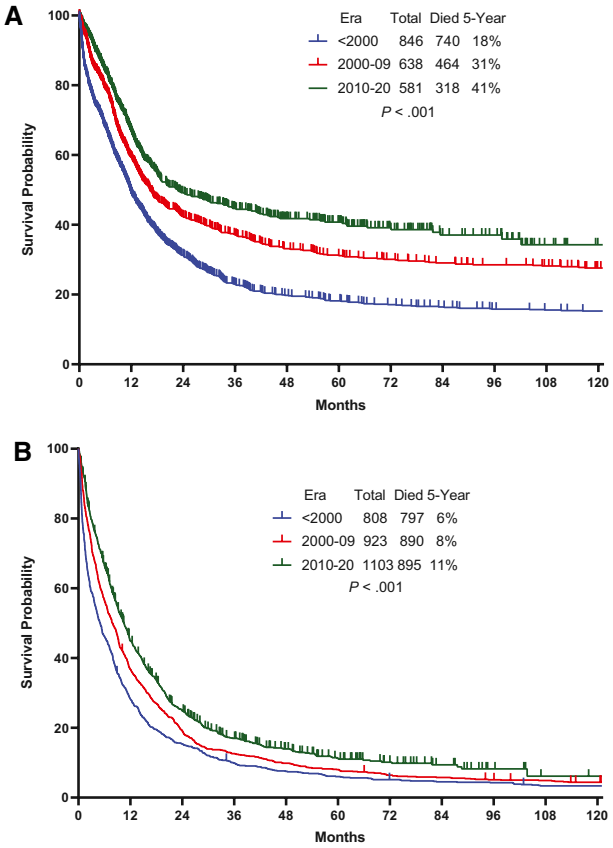

Figure 1. Survival of (A) younger patients and (B) older patients with de novo acute myeloid leukemia treated at MD Anderson over 5 decades.

Ongoing research now focuses on multiple AML subsets and treatment combinations. These include 1) novel intensive chemotherapy regimens for younger patients (and fit older patients) adding high-dose cytarabine, nucleoside analogs (eg, fludarabine and cladribine), and targeted agents (FLT3 or IDH inhibitors, venetoclax) during induction and consolidations; 2) lower-intensity regimens for older/unfit patients utilizing hypomethylating agents (HMAs [eg, azacitidine or decitabine, parenteral or oral formulations]) and/or low doses of cladribine/cytarabine rotating with HMAs, to which venetoclax or other targeted inhibitors are added as indicated; and 3) novel therapies targeting *TP53*-mutated AML (eg, APR246, a TP53 modulator; magrolimab, an anti-CD47 monoclonal antibody that enhances macrophage-mediated phagocytosis) and mixed-lineage leukemia (*MLL1*)-rearranged disease (menin inhibitors). Combinations of small molecule–targeted therapies, with or without standard chemotherapy, may improve survival further in AML subsets (as was done in APL) and may improve the cure rates in previously incurable AMLs. In addition, the notion that maintenance therapy has no role in AML has been put to rest by the results of a recent randomized trial demonstrating a survival benefit with oral azacitidine maintenance after intensive chemotherapy (discussed later under "Maintenance Therapy").

While many AML experts continue to adhere to the 3+7 regimen as the standard of care, others do not. In fact, the somewhat defeatist mood that prevailed until 2015 has evolved into a highly optimistic vision, as the previously meager therapeutic armamentarium for AML has been enriched by several important anti-AML agents that have been approved by the US Food and Drug Administration (FDA). In this review, we discuss the progress that has been made in AML research, outline the approaches that will be taken by the MD Anderson Cancer Center in 2021, and explore investigational strategies for the coming years.

RELEVANCE OF THE CYTOGENETIC AND MOLECULAR ABNORMALITIES, AND OF MEASURABLE RESIDUAL DISEASE, IN AML IN REMISSION

Cytogenetic Abnormalities

A modification of the National Comprehensive Cancer Network (NCCN) cytogenetic/molecular classification of AML is shown in Table 1. The important cytogenetic subsets include: 1) "favorable" karyotypes, including APL, which is characterized by the translocation between chromosomes 15 and 17 [t(15;17)(q22,q21)], and CBF-AML, which includes the cytogenetic/molecular subsets of inversion 16 [inv16(p13;q22)] or t(16;16)(p13;q22)] and t(8;21)(q22;q22); 2) "intermediate" karyotypes, which essentially comprise diploid (ie, normal) karyotypes (~40%-50% of patients); 3) "unfavorable" karyotypes, which comprise complex karyotypes (≥3 chromosomal abnormalities) and most MLL translocations (translocations involving 11q23); and 4) other karyotypes. In addition, patients with translocations involving chromosome 3q26.2 (*EVI1*), the location of the MECOM (MDS1 and EVI1 complex locus) gene, have an extremely poor outcome.[16] Some studies include particular cytogenetic abnormalities [eg, single trisomy 8 or single translocation (9;11)] in the intermediate karyotypes (Table 1).[17,18] The prognostic significance of a single translocation (9;11)(p22;q23)/*KMT2A-MLLT3* has been debated[19,20] but may be intermediate in a small subset of younger patients with de novo AML (not therapy-related or secondary).[21]

TABLE 1. NCCN Cytogenetic/Molecular Classification of Acute Myeloid Leukemia

NCCN Classification	Cytogenetics	Molecular Abnormalities
Better risk	inv(16) or t(16;16); t(8;21); t(15;17)	Normal cytogenetics; *NPM1* mutation in the absence of *FLT3*-ITD or isolated biallelic CEBPα mutation
Intermediate risk	Normal cytogenetics; +8 alone; t(9;11)[a]; other undefined	t(8;21), inv(16), t(16;16) with *c-KIT* mutation[a]; *NPM1*-mutated and *FLT3*-ITD–mutated (high allelic ratio[b]); *NPM1*-wild type and *FLT3*-ITD wild type; *NPM1*-wild type and *FLT3*-ITD–mutated (low allelic ratio[c])
Poor risk	Complex (≥3 clonal chromosomal abnormalities); monosomal karyotype −5, 5q−, 7, 7q−, 11q23–non-t(9;11); inv(3), t(3;3), t(6;9), or t(9;22)	TP53 mutation; RUNX1 mutation; ASXL1 mutation; NPM1-wild type and *FLT3*-ITD–mutated (high allelic ratio[b])

Abbreviations: ELN, European LeukemiaNet; inv, inversion; NCCN, National Comprehensive Cancer Network; t, translocation.
Adapted from the National Comprehensive Cancer Network.[18]
[a]The NCCN Classification applies generally to younger patients. In older patients, its validation is ongoing, but older patients may have significantly worse outcomes within the same ELN/NCCN risk categories. For example, t(9;11) was shown to be intermediate only in de novo or younger AML, but not in older or therapy-related AML. At MD Anderson, we consider any t(−;11q23) to be adverse. We do not consider *c-KIT* mutation to be adverse in CBF-AML. Also, although we considered any *FLT3*-ITD AML to be unfavorable regardless of allelic ratio, this is changing rapidly with the incorporation of FLT3 inhibitors into frontline chemotherapy and into post–stem cell transplantation maintenance.
[b]High allelic ratio is ≥0.5.
[c]Low allelic ratio is <0.5.

Mutations

Next-generation sequencing identifies 1 or more somatic mutations in more than 90% of patients with AML.[22,23] Frequently mutated genes (>5%) include *FLT3*, *NPM1*, *DNMT3A*, *IDH1*, *IDH2*, *TET2*, *RUNX1*, *TP53*, *NRAS*, *CEBPα*, and *WT1*. Based on functional analysis and known biologic pathways, they are categorized into subsets: myeloid transcription factor fusions or mutations, *NPM1* mutations, tumor suppressor gene mutations, epigenome-modifying gene mutations, activated signaling pathway gene mutations, cohesin complex gene mutations, and spliceosome complex gene mutations. These mutations exhibit patterns of co-occurrence or mutual exclusivity that help to identify AML pathways of clonal dominance and shifts that may guide targeting therapies.

Mutations may have prognostic and/or predictive values, which may be altered with the introduction of targeted therapies (eg, adding FLT3 inhibitors to frontline chemotherapy). The prognostic-predictive significance of mutations is more important in normal karyotype AML.[24,25] Among the favorable and unfavorable karyotype subsets, prognosis is largely defined by the cytogenetic abnormalities.

In normal-karyotype AML, mutations of either a biallelic *CEBPα* (≤2%) or nucleophosmin-1 (*NPM1*; 50%) in the absence of an *FLT3* internal tandem duplication (*FLT3*-ITD) mutation confer more favorable prognoses.[4] In contrast, a *FLT3* mutation, particularly the *FLT3*-ITD variant, defines a poorer prognosis, particularly with a high *FLT3* allelic ratio (>50%) and no cooccurring *NPM1* mutation. In normal-karyotype *NPM1*-mutated AML, the presence of a *FLT3* mutation (~50% of patients with a diploid karyotype and *NPM1* mutation) predicts a worse outcome historically (before the incorporation of FLT3 inhibitors into frontline AML therapy).

Generally, the burden of a pathogenic mutation is reported as the variant allelic frequency, which is the percentage of the mutated gene over the total (ie, wild type + mutated gene). The exception is the *FLT3* mutation, reported as allelic ratio (which creates some confusion). The *FLT3*-ITD allelic ratio is defined as the ratio of the area under the curve of *FLT3*-ITD divided by the area under the curve of FLT3 wild type using a semiquantitative DNA fragment analysis.[26] The allelic ratio strongly influenced outcome in several studies of newly diagnosed patients with *FLT3*-mutated AML who were treated with chemotherapy regimens that did not include FLT3 inhibitors.[27-29] This may change with the incorporation of FLT3 inhibitors into chemotherapy and into postallogeneic stem cell transplantation (SCT) maintenance. A higher *FLT3*-ITD allelic ratio (generally defined as ≥0.5) is associated with worse survival, likely reflecting dominance of the *FLT3* clone. At MD Anderson, we add a FLT3 inhibitor to frontline chemotherapy for any level of positivity (even an allelic ratio <0.1) to prevent relapse with an expanded *FLT3*-mutated clone.

Other mutations (*ASXL1*, *RUNX1*, *TP53* and others) and co-occurrence of multiple mutations may also predict for worse outcomes.[30-36] Mutations and/or deletions of the tumor suppressor gene *TP53* (located on the short arm of chromosome 17) occur in 2%-20% of patients, and are associated with older age, complex karyotype, and therapy-related disease.[31-33]

Several mutations are potentially targetable or respond to specific therapies. The normal-karyotype *NPM1*-mutated AML is highly responsive to cytarabine-based regimens and to regimens containing HMAs and

venetoclax. The *FLT3* mutations (30% of AML), including *FLT3*-ITD and *FLT3*- tyrosine kinase domain (TKD) mutations (D835 most common), can be targeted with FLT3 inhibitors (midostaurin, gilteritinib, sorafenib, quizartinib). Mutations in the IDH1/2 proteins (20% of patients with AML) can be effectively treated with combinations that contain the IDH inhibitors: ivosidenib for *IDH1* and enasidenib for *IDH2*. In addition, the *IDH* mutations engender strong BCL-2 dependence for survival, rendering them particularly sensitive to venetoclax-based therapy.[37] Most patients with *TP53* mutations do not seem to benefit from intensive chemotherapy and may have similar or improved outcomes, and less toxicity, with lower-intensity approaches.[32,33,38] They may also benefit from investigational therapies such as APR246 and magrolimab (discussed later). The cytogenetic-molecular subset of "mixed-lineage leukemia" (translocations involving 11q23; *MLL1* rearrangement, now referred to as *KMT2A*) may respond to novel menin inhibitors (SNDX-5613, KO-539, others).[39] In CBF-AML, *c-KIT* mutations may be associated with worse outcome.[40,41] This may be treatment-dependent, since we did not find them to be adverse in patients treated with fludarabine-cytarabine-GO–based regimens.[11,12] Potent *c-KIT* inhibitors (avapritinib, dasatinib) added to chemotherapy may be beneficial.[42,43]

The prognostic/predictive value of mutations can be age dependent and modified by new therapies. For instance, the predictive value of a mutation may be stronger in younger patients (cure rate with intensive chemotherapy/allogeneic stem cell transplantation 40%-60%) than in older patients (estimated 2-year survival historically less than 20%). Also, the addition of a targeted therapy (eg FLT3 inhibitors or venetoclax) to chemotherapy regimens may alter the prognostic significance of the mutation.

Measurable Residual Disease in Remission

Measuring residual disease in AML in complete remission (CR) is currently the standard of care.[44-50] Detectable measurable residual disease (MRD) at the time of morphologic CR is associated with a higher relapse rate and worse survival. It has been measured with 2 commonly used methodologies: multicolor flow cytometry and molecular quantification.[44-49]

Polymerase chain reaction (PCR) is used to monitor certain AML translocations and mutations quantitatively (eg, in APL, CBF, and *NPM1*-mutated AML) and is expanding to other molecular subsets (*IDH1/2* and *FLT3*). In APL, monitoring with PCR quantification of promyelocytic leukemia-retinoic receptor alpha (*PML-RARα*) detects early relapse.[51] The same applies for CBF-AML. Inv16 and t(16;16) result in the CBF beta/myosin heavy chain 11 (*CBFB/MYH11*) fusion gene. The t(8;21) produces the fusion gene of runt-related transcription factor 1 (*RUNX1/RUNX1T1*). Measurable detection of molecular fusion genes by quantitative PCR in CBF-AML, particularly in inv16, predicts for relapse.[52,53] Patients with the t(8;21) subtype may have persistent MRD levels below 0.1% but remain in durable CR and may possibly be cured (literature case reports; unpublished data). Among other subsets of AML, monitoring MRD by next-generation sequencing is informative, as in patients who have *NPM1* mutations.[54,55] Better outcomes are reported in *FLT3*- and *IDH*-mutated AML with molecular clearance. In contrast, the persistence of other mutations by next-generation sequencing may not be as informative. For example, the persistence of mutations in *DNMT3A*, *TET2*, and *ASXL1* (DTA mutations, of the "DTA molecular triad") does not predict for relapse. Combining multicolor flow cytometry and PCR modalities may improve the capability of MRD studies to predict for relapse.[44]

Measurable residual disease in CR may warrant consideration of therapeutic interventions. In APL, therapy at the time of molecular relapse prevented overt hematologic relapse.[51] Allogeneic SCT for persistent MRD in CR in CBF-AML improved survival compared with continuation of standard therapy.[52,53] Interventions that could eradicate MRD in CR may include allogeneic SCT; more intensified chemotherapy regimens; HMAs (parenteral or newly approved oral formulations) plus venetoclax; targeted therapy combinations when indicated for particular molecular abnormalities (FLT3 or IDH inhibitors); antibody therapies (eg, CD123 or CD33 monoclonal or bispecific antibodies); or immune therapies (eg, checkpoint inhibitors).

TRANSLATION OF BIOLOGIC INFORMATION INTO CLINICAL PRACTICE AND RESEARCH

As heterogeneous entities, the AML subsets necessarily require different selective therapies, depending on disease biology (cytogenetics, mutations, and pathophysiologic pathways), patient age and comorbidities, and patient wishes and goals. Next, we discuss the treatment of AML subsets using FDA-approved agents, as well as approaches with investigational agents.

ACUTE PROMYELOCYTIC LEUKEMIA

Acute promyelocytic leukemia (5%-10% of AML) is characterized by the cytogenetic abnormality t(15;17),

which results in the *PML-RARα* fusion oncogene and its encoded oncoprotein. The PML-RARα oncoprotein acts as a dominant negative inhibitor of wild type RARα, causing a maturation block and the clinical-pathologic picture of APL.

Historical Perspective With Chemotherapy, ATRA and Arsenic Trioxide

In the 1970s, single-agent anthracyclines (eg, daunorubicin) were first shown to cure APL, at rates of 30% to 40%.[56] Single-agent cytarabine is not curative.[57] The addition of cytarabine to anthracyclines (in the 3+7 regimen) did not increase the cure rate substantially, nor did the addition of maintenance therapy with 6-mercaptopurine-methotrexate combinations.[58,59] A "differentiation syndrome" with chemotherapy was also reported for the first time in this setting.[60] The early mortality from disseminated intravascular coagulopathy (DIC) and bleeding was significant (20%-30%).

In the late 1980s and early 1990s, ATRA and arsenic trioxide were discovered to have major anti-APL activities through their ability to reverse the maturation block, resulting in a gradual differentiation process. Studies from China, India, and Iran that investigated single-agent therapy with ATRA or arsenic trioxide as a frontline therapy showed high CR rates and 5-year disease-free survival rates exceeding 50% to 60%.[61-63] This established arsenic trioxide and ATRA as the most effective anti-APL agents. GO was also found to be highly effective.[64]

Based on the single-agent efficacies of ATRA and arsenic trioxide,[65] both agents were added to chemotherapy during induction and/or consolidation in comparative trials that confirmed their added benefits.[66-70] In the late 1990s, the combination of idarubicin (IDA) and ATRA became the standard of care for APL.[70]

The Era of ATRA and Arsenic Trioxide: A Chemotherapy-Free Regimen

In the early 2000s, MD Anderson decided cautiously to investigate a non-chemotherapy regimen of ATRA plus arsenic trioxide, first as a salvage therapy (in 2001) and then as a frontline therapy (in 2002). GO was added for high-risk disease (white blood cell count $>10 \times 10^9$/L at diagnosis or during induction). Following the demonstration of the high efficacy of this approach,[7,8] randomized studies confirmed the superiority of ATRA plus arsenic trioxide over the combination of ATRA and IDA in low- and intermediate-risk APL.[9,10,71,72] With ATRA plus arsenic trioxide, the CR rate is ≥90% and the cure rate is ≥80%. Induction mortality from DIC is low (~5%), and resistant disease is extremely rare, except in cytogenetic variant APL (translocations between chromosomes 11 and 17 [*PLZF-RARα*] or between chromosomes 5 and 17). Patients with high-risk APL have a worse outcome and may benefit from the addition of GO (or anthracylines).

In the non-chemotherapy regimen, ATRA is administered orally at 45 mg/m^2 daily (in 2 divided doses) during induction until achievement of CR, then daily 2 weeks on and 2 weeks off, for a total of 9 months. Arsenic trioxide is administered intravenously (IV) at 0.15 mg/kg daily during induction until CR, then daily × 5 every week for 4 weeks, every other month, for a total of 4 courses (a total of 80 consolidation doses). At MD Anderson, GO 6-9 mg/m^2 is given for high-risk APL (pretreatment or with rising white blood cell count $>10 \times 10^9$/L pretreatment or during induction) and for *PML-RARα* persistent MRD (documented twice over 1-2 weeks) 2-3 months into CR. For patients who present with the uncommon picture of DIC with thrombosis (rather than bleeding; may be exacerbated by ATRA), GO 6 mg/m^2 × 1 or IDA 6-12 mg/m^2 daily × 1-2 doses are the best emergency interventions.

The Medical Research Council (MRC) comparative trial investigated an intermittent dosing schedule of arsenic trioxide 0.3 mg/kg on days 1-5 of each course, then 0.25 mg/kg twice weekly in weeks 2-8 of course 1 and weeks 2-4 of courses 2-5.[71] Oral formulations of arsenic trioxide may make the treatment of APL more convenient, particularly during the longer-term consolidation.[73,74]

Figure 2 shows the MD Anderson results in APL among younger and older patients, and the significant improvement in outcomes in the era of ATRA and arsenic trioxide.

There are some important yet not well-known considerations in APL management. First, granulocyte colony-stimulating factors (eg, filgrastim, pegfilgrastim) should never be used for the treatment of APL, as they may induce a florid progression and trigger fatal DIC.[75] Second, fluid overload (often confused with "differentiation syndrome") related to ATRA and arsenic trioxide can result in pulmonary failure, as can the use of high-volume blood product transfusions (eg, fresh frozen plasma, platelets) to prevent the complication of consumptive coagulopathy. If not recognized and managed aggressively, pulmonary complications and/or fluid overload may necessitate intensive care, supplemental oxygen, and occasional ventilator support. Interventions include holding ATRA plus arsenic trioxide therapy briefly and

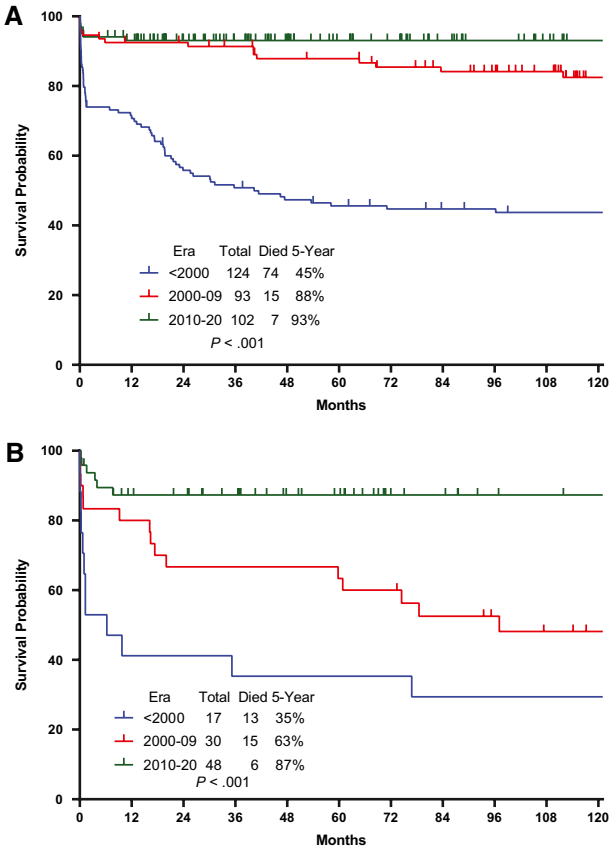

Figure 2. Survival of (A) younger patients (<60) and (B) older patients (≥60) with newly diagnosed acute promyelocytic leukemia treated at MD Anderson over 5 decades.

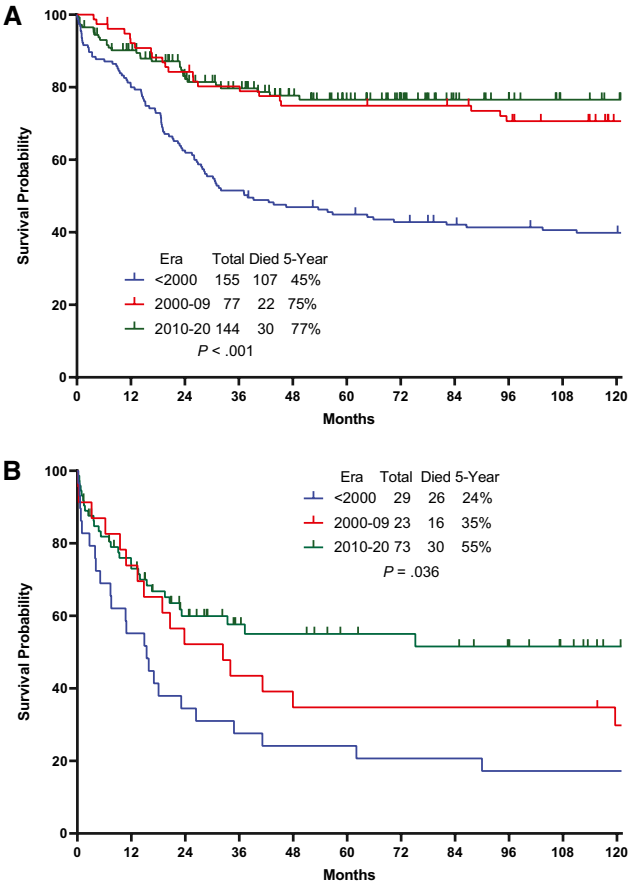

Figure 3. Survival of (A) younger patients (<60) and (B) older patients (≥60) with newly diagnosed core-binding factor acute myeloid leukemia treated at MD Anderson over 5 decades.

using intensive diuresis.[76] Third, a true differentiation syndrome may occur, possibly resulting in the failure of multiple organs. This is preventable with the use prophylactic steroids during induction (together with antibiotics and antifungal prophylaxis) and may be managed with interruptions of ATRA and arsenic trioxide therapy during acute episodes. Fourth, among patients with central nervous system bleeding at diagnosis, the risk of central nervous system leukemia may increase; 2 spaced intrathecal cytarabine injections in CR may eliminate this rare complication.

CORE BINDING FACTOR AML

The CBF-AML subset constitutes approximately 10% to 15% of adult AML and includes the subsets with chromosomal abnormalities involving inv16, t(16;16), and t(8;21).

Historically, CBF-AML was treated with cytarabine/anthracycline induction chemotherapy, followed by 1 to 4 consolidation courses with high-dose cytarabine. The cure rate was 30% to 40% with 1 consolidation and ≥50% with 3 to 4 consolidations.[77,78] Optimizing the combinations of established drugs (fludarabine plus high-dose cytarabine for 5 to 6 courses of induction/consolidation; addition of GO to chemotherapy; monitoring and treatment of persistent measurable molecular disease) gradually improved the cure rate from less than 50% to ≥75%.[11-15] A meta-analysis of 5 randomized trials showed that the addition of GO to chemotherapy improved the estimated 5-year survival from 50% to 75%.[15] Thus, GO now must be considered an integral part of any CBF-AML regimen.

At MD Anderson, we use fludarabine, high-dose cytarabine, filgrastim and GO (FLAG-GO) during induction and consolidations, for a total or up to 6 courses, and modify therapy (eg, allogeneic SCT, azacitidine-GO-venetoclax) for persistent MRD in CR. Results were better when GO replaced IDA, with estimated 5-year survival rates of 80% in both inv16 and t(8;21) AML (Fig. 3),[3,12] and were better in younger patients than in patients aged

≥60 years (Fig. 3). Older patients are treated with lower-dose FLAG-GO. Patients who cannot tolerate this or who have persistent molecular disease may be offered HMA therapy (decitabine, azacitidine) combined with venetoclax/GO (GO 3-6 mg/m^2 per course × 2-3, doses with ursadiol prophylaxis to reduce the risk of veno-occlusive disease), with the treatment duration adjusted according to the MRD results (PCR) or for ≥12 months. MRC trials using the fludarabine, high-dose cytarabine, and IDA combination (FLAG-IDA with or without GO) have also yielded cure rates of ≥80%.[13]

Frequent mutations noted in CBF-AML are *FLT3* (15%-20%), *c-KIT* (25%-30%), *RAS* (30%-50%), and others. Some historical studies have reported that *c-KIT* or multiple mutations are associated with worse outcomes.[40-42] This may be treatment dependent, as it has not been our experience with the FLAG-IDA regimen, which may have overcome the adverse effects of the mutations. Targeted therapies may also be considered (avapritinib or dasatinib for *c-KIT* mutations; FLT3 inhibitors for *FLT3* mutations).[42,43] Recent studies also suggest that epigenetic mutations (*ASXL2* or cohesin/spliceosome mutations) may be adverse.

HOW TO CHOOSE BETWEEN INTENSIVE AND LOWER-INTENSITY CHEMOTHERAPY IN AML?

The median age of patients with AML is 68 to 70 years,[79] yet most of the research with intensive chemotherapy (ie, the 3+7 regimen and its variations) is conducted in younger patients and is recommended for older patients only if they are considered fit for intensive chemotherapy. However, outcomes with this approach in community oncology practices may be significantly inferior to those reported in clinical trials.[79]

In a study of 813 selected patients aged ≥60 years (median age, 67 years) treated with 3+7 (randomization to 2 doses of daunorubicin), the median survival was 7 to 8 months and the estimated 3-year survival was 20%.[6] The early mortality rate was 11% to 12%. These findings and those of other studies[80] (which were carefully controlled studies in selected patients with good performance status, normal organ function, and few comorbidities) have translated poorly to community practice. An analysis of the Surveillance, Epidemiology, and End Results data (a better reflection of real-world experience) in approximately 29,000 patients with AML yielded significantly worse results, even among patients who were treated more recently (2000-2017). Among patients aged 40 to 59 years with de novo AML (excluding APL and CBF-AML), the early (4-week) mortality rate was 27%, and the 5-year survival rate was 40%. Among patients aged ≥70 years, the 4-week mortality rate was 45% to 50% and the 5-year survival rate was <5%.[79]

Evidence suggests that the outcomes of patients with AML may not be equal when comparing the results from National Cancer Institute (NCI)-designated cancer centers or academic institutions with a large volume of such patients with those from smaller community practice settings. In an NCI database of 60,738 patients, the 1-month mortality rate was 16% in academic centers and 29% in nonacademic centers ($P < .001$); the 5-year survival rate was 25% versus 15% ($P < .001$).[81] A second study of 7007 patients reported an early mortality rate of 12% in NCI-designated cancer centers versus 24% in non–NCI-designated cancer centers.[82] At MD Anderson, the 4-week mortality rate with intensive chemotherapy is <5%; the early mortality rate with low-intensity regimens in older patients with AML is 2% to 3%. Whenever logistically possible, we encourage AML treatment in leukemia centers of excellence.

AML is a rare and heterogeneous cancer, the management of which requires cumulative experience in both diagnosis and treatment. It often affects older patients with multiple comorbidities who need intensive chemotherapy in the setting of a compromised marrow and severe cytopenias at diagnosis and throughout therapy. These conditions require the aggressive and consistent use of prophylactic antibiotics, the availability of optimal and prompt supportive care (blood products), skilled emergency centers and treatment facilities, rapid recognition of infections/sepsis and implementation of proper broad-spectrum IV antibiotics, and the timely use of an intensive care unit care when needed. Without these, the risks of serious morbidities, mortality, and treatment abandonment are high.

AML in older patients is associated with a distinct disease biology (high incidence of complex karyotype and cytogenetic abnormalities involving chromosomes 5 and 7 [monosomies] and 17; of multiple mutations including *TP53* [20%]; and of secondary and therapy-related AML [20%-30%]). At MD Anderson, historical studies with intensive chemotherapy in older patients with AML produced CR rates of 40% to 50%, 4- to 8-week mortality rates of 26% to 36%, median survivals of 4 to 6 months, and 1-year survival rates of <30%.[83,84] By multivariate analysis, independent adverse factors predictive of early mortality were: age ≥75 years; adverse karyotype with ≥3 chromosomal abnormalities; presence of an antecedent hematologic disorder; poor performance status (Eastern

Cooperative Oncology Group 2-4); creatinine level 1.3 mg/dL or higher; and induction treatment outside a protected environment. The expected 8-week mortality was 10% to 19% with the presence of 0 to 1 adverse factors, and 36% to 65% with the presence of 2 to 5 adverse factors.[83]

These poor results led us and others to explore lower-intensity therapy in such patients, and raised the question of how to select patients who are unfit for intensive chemotherapy. The prevailing approach relies on the leukemia expert's perception of the patient's condition. This is highly subjective and is the basis of intense discussions among leukemia experts, even within the same institution. At MD Anderson, we use the above model. If the expected 4- to 8-week mortality is less than 10%, patients are offered intensive chemotherapy. If it is more than 10% to 20%, they are offered lower-intensity approaches. Of interest, one-third of patients may have significant abnormalities detected by computed tomography scans of the chest at diagnosis (which may reflect infection, leukemic infiltrate, fluid overload, bleeding, or other findings).[85] Patients with pneumonia at diagnosis have a significantly higher risk of 4-week mortality (15%-20%) with intensive chemotherapy (unpublished data). Future studies may need to incorporate pretreatment routine computed tomography chest findings into the predictive models of early mortality.

Historically, many older patients (age ≥70 years) with a new diagnosis of AML have been offered supportive/palliative or hospice care.[86] An MRC randomized trial in this group of patients demonstrated the superiority of low-dose cytarabine therapy (20 mg subcutaneously twice daily × 10) versus supportive care/hydroxyurea (CR rate 18% versus 1% [$P = .00006$]; longer survival [odds ratio, 0.60; $P = .0009$]).[87] This study emphasized the important message that an active and tolerable treatment can have a significant effect on improving outcome, even among patients deemed only suitable for supportive care.

Next, we discuss the roles of intensive chemotherapy in younger/fit patients and of lower-intensity chemotherapy in older/unfit patients as they apply to current standards of care.

YOUNGER/FIT PATIENTS WITH AML: INTENSIVE CHEMOTHERAPY

Summary of Literature Using the 3+7 Anthracycline-Cytarabine Regimen With High-Dose Cytarabine Consolidation

A series of randomized trials (cytarabine for 5 vs 7 vs 10 days; cytarabine 100 mg/m^2 vs 200 mg/m^2; different anthracyclines and dose schedules; addition of other agents such as etoposide, 6-mercaptopurine, 6-thioguanine to induction/consolidation) established the 3+7 regimen as a standard of care over the past 40 years: daunorubicin 50-60 mg/m^2 IV daily × 3, or IDA 12 mg/m^2 IV daily × 3; cytarabine 100-200 mg/m^2 IV continuous infusion daily for 7 days. A Cancer and Leukemia Group B randomized trial reported superior survival with high-dose cytarabine consolidation therapy (3 g/m^2 IV over 2-3 hours every 12 hours on days 1, 3, and 5) for 4 courses, compared with lower-dose cytarabine schedules.[88] In this study, high-dose cytarabine consolidation was followed by 4 courses of "2+5" chemotherapy, which were omitted in later Cancer and Leukemia Group B studies. This omission may be important, because later studies using this regimen in a control arm reported 5-year survival rates of 20% to 30% rather than 40%.[5] High-dose cytarabine became the consolidation standard of care in AML. Other studies have investigated lowering the dose of cytarabine (1.5 g/m^2), using 4 to 5 courses (vs fewer courses), and the possible benefits of using allogeneic or autologous SCT in first CR.[89] The MRC studies suggested that cytarabine doses of 1.5 g/m^2 and 3 g/m^2 were equivalent and that outcomes with 4 or 5 high-dose cytarabine consolidation courses were also equivalent. A study from Korea indicated that a cytarabine dose of ≥1.5 g/m^2 was better than a dose of 1 g/m^2.[90]

Better Regimens Than the 3+7 Regimen

An increasing body of research indicates that there already may be better anti-AML regimens than the 3+7 regimen. Such regimens incorporate high-dose cytarabine combinations during induction; optimize the choice and dose of the anthracycline (IDA; daunorubicin 60 mg/m^2 daily × 3 vs 45 mg/m^2 or 90 mg/m^2 daily × 3); add adenosine nucleoside analogs (fludarabine, clofarabine, cladribine) to the cytarabine/anthracycline combinations; and include the CD33-targeted monoclonal antibody GO in the treatment of favorable and intermediate-risk disease. More recent regimens also incorporate targeted therapies such as FLT3 inhibitors in *FLT3*-mutated AML (now standard practice), and venetoclax and/or IDH inhibitors in appropriate patients (still investigational). They also now consider the use of oral azacitidine maintenance therapy following its recent FDA approval for maintenance in older patients with AML who are in first CR.

High-dose cytarabine consolidation is standard of care for AML,[88] but is it beneficial during induction? Five studies have reported that it is. A meta-analysis of

3 randomized trials in 1691 patients treated with high-dose cytarabine induction reported improved rates of relapse-free survival (RFS [$P = .03$]), overall survival ($P = .0005$), and event-free survival ([EFS] $P < .0001$).[91] A Southwest Oncology Group randomized trial in patients aged <65 years yielded a better RFS rate with high-dose cytarabine in younger patients (aged <50 years; 4-year RFS, 33% vs 21%) as well as older patients (aged 50 to 64 years; 4-year RFS, 21% vs 9% [$P = .049$]).[92] An Australian randomized trial revealed that high-dose cytarabine induction improved CR duration and RFS.[93] An EORTC-GIMEMA randomized trial in 1942 younger patients (aged ≤60 years) showed that high-dose cytarabine was associated with significantly better rates of CR, EFS, and overall survival among patients aged 15 to 45 years. Among patients aged 45 to 60 years, high-dose cytarabine was also associated with significant improvements in CR and EFS, as well as a trend for better survival among patients with *FLT3*-ITD AML or poor prognosis karyotypes.[94] An Italian randomized trial in 574 patients (median age, 52 years [range, 16-73 years]) showed that sequential high-dose cytarabine induction was associated with significantly higher CR and 5-year survival rates.[95] The MRC trial comparing the FLAG-IDA regimen with the 3+7 regimen with or without etoposide is discussed later.

Two randomized trials reported no benefit with high-dose cytarabine induction, but their design did not actually address this question. Lowenberg et al[96] randomly assigned 858 younger patients (median age, 49 years [range, 18-60 years]) to induction therapy with high-dose cytarabine 1 g/m^2 every 12 hours × 10 versus standard-dose cytarabine 200 mg/m^2 daily × 7, both in combination with IDA. However, all patients received high-dose cytarabine during induction course 2 (either 2 g/m^2 every 12 hours × 8 [total dose, 16 g/m^2] for patients who were randomly assigned to high-dose cytarabine during course 1 or cytarabine 1 g/m^2 every 12 hours x 6 days [total dose, 12 g/m^2] for patients who were randomly assigned to standard-dose cytarabine during course 1). Thus, all patients received high-dose cytarabine in at least 1 of the 2 induction courses. The recent Southwest Oncology Group S1203 trial randomly assigned patients to 1 of 2 arms: 1) 3+7 induction followed by 4 consolidations with high-dose cytarabine (3 g/m^2 twice daily on days 1, 3, and 5 [total cytarabine 18 g/m^2/course × 4 = 72 g/m^2]) or 2) idarubicin and cytarabine (IA) with or without vorinostat (IDA plus continuous high-dose cytarabine [1.5 g/m^2 continuous infusion daily × 4] followed by IA consolidation with cytarabine 0.75 g/m^2 continuous infusion daily × 3 [2.25 g/m^2/course × 4], for a total cumulative cytarabine dose of 15 g/m^2).[97] These 2 arms presumably tested the benefit of high-dose cytarabine induction, but the total dose of cytarabine was 4.5 times higher in the 3+7 arm than in the IA arm. The 3+7 regimen, in fact, delivered more total high-dose cytarabine and was, as expected, superior in the CBF-AML. However, despite the lower total cytarabine dose given in the IA arm, the results of the 2 groups were similar among patients with intermediate or adverse karyotypes. The trial design did not properly address the benefit of high-dose cytarabine added to induction, as the effect was likely nullified by giving more high-dose cytarabine consolidation in the control arm.

The optimal dose schedule of high-dose cytarabine has been investigated for more than 30 years. The established single dose of 3 g/m^2 may not deliver better anti-AML efficacy and may increase toxicity.[89,90] At MD Anderson, we use high-dose cytarabine (1.5-2 g/m^2 daily × 5 [total, 7.5-10 g/m^2 per course]) during induction (3 days during consolidations).

A combination regimen of fludarabine, high-dose cytarabine and idarubicin (FLAG-IDA), or FAI) developed at MD Anderson[98] was later evaluated in a randomized trial (MRC AML 15). The FLAG-IDA regimen consists of cytarabine 2 g/m^2 daily for 5 days, fludarabine 30 mg/m^2 daily for 5 days, and IDA 8-10 mg/m^2 daily for 3 days. Among patients who tolerated 4 courses in the FLAG-IDA arm (2 FLAG-IDA + 2 high-dose cytarabine), the 8-year survival rate was 66% versus 47% in patients who received standard 3+7 with or without etoposide.[13,89,99] The FLAG-IDA/FAI regimen is intensive and requires cumulative expertise to deliver safely. However, it is not more difficult to deliver than allogeneic SCT, and it likely provides a 20% benefit in 8-year survival. Candoni et al[100] treated 130 patients who were newly diagnosed with AML (aged <65 years) with FLAG-IDA and GO. They reported a CR rate of 82% and an estimated 5-year survival of 52% (10-year survival, ~44%). In a retrospective analysis of a single-center experience using 3+7 (n = 86) or FLAG with or without IDA (n = 218), patients who were treated with FLAG with or without IDA were more likely to achieve remission after 1 course of induction (74% vs 62% [$P \leq .001$]), had a faster time to CR (30 vs 37.5 days [$P \leq .001$]), and had significantly better rates of 3-year overall survival (54% vs 39% [$P = .01$]) and disease-free survival (49% versus 32% [$P = .01$]).[101] When delivered effectively, FLAG-IDA/FAI is a multifaceted regimen that explores the benefits of high-dose cytarabine induction/consolidation, the addition of an adenosine nucleoside analog (fludarabine), and the use of

TABLE 2. Summary of Studies Incorporating Strategies Beyond the 3+7 Regimen

Study	N	Comparison	Results
Kern and Etsy[91]	1691	Meta-analysis of 3 studies comparing HiDAC vs SDAC during remission induction	• CR rates: similar • Improved RFS ($P = .03$) and survival ($P = .0005$) with HiDAC
Weick et al[92]	665	SDAC (200 mg/m^2 daily × 7) vs HiDAC (2 g/m^2 × 12), each combined with daunorubicin (45 mg/m^2 × 3)	• CR rates: 45%-58% (no difference between SDAC and HiDAC) • 4-year RFS: 33% (HiDAC) vs 21% (SDAC) among patients aged <50 years • 4-year RFS: 21% vs 9% among patients aged 50-64 years
Bishop et al[93]	301	SDAC (100 mg/m^2 daily × 7) vs HiDAC (3 g/m^2 × 8), each combined with daunorubicin + etoposide	• CR rates: 71%-74%. No difference between SDAC and HiDAC. • 5-year RFS: 49% (HiDAC) vs 24% (SDAC); $P = .0004$
Willemze et al[94]	1942	SDAC (100 mg/m^2 daily × 10) vs HiDAC (3 g/m^2 × 8), each combined with daunorubicin + etoposide	• CR rates: 72% (SDAC) vs 78.7% (HiDAC); $P < .001$ • 6-year OS: 38.7% (SDAC) vs 42.5% (HiDAC); $P = .009$ • 6-year OS: 43.3% (SDAC) vs 51.9% (HiDAC) among patients aged <46 years; $P = .009$
Bassan et al[95]	574	IDA + SDAC (100 mg/m^2 daily × 7) + etoposide vs IDA + HiDAC (2 g/m^2 × 8)	• CR rates: 80.8% (SDAC) vs 83.6% (HiDAC); $P = .38$ • 5-year OS: 39% (SDAC) vs 49% (HiDAC); $P = .045$ • 5-year RFS: 36% (SDAC) vs 48% (HiDAC); $P = .028$
Burnett et al[87]	1983 + 1268	Daunorubicin + SDAC (DA) vs ADE (n = 1983) ADE vs fludarabine + HiDAC + IDA + GCSF (FLAG-IDA) (n = 1268)	• CR rates: 84%-86% (no difference among 3 arms) • 8-year RFS: 45% (FLAG-IDA) vs 34% (ADE); $P = .01$ • Relapse rate reduced (38% vs 55%); $P < .01$ • 8-year OS: 66% vs 47% among patients who could tolerate FLAG-IDA × 2 + HiDAC × 2 vs ADE × 2 + HiDAC × 2; $P < .01$
Garcia-Manero et al[97]	738	3+7 vs IDA + HiDAC (IA) vs IA + vorinostat	• CR rates: 75%, 79%, 77%, respectively (no difference in EFS, RFS, or OS)[a]
Lowenberg et al[96]	860	IDA + SDAC (200 mg/m^2/daily × 7) vs IDA + HiDAC (1 g/m^2 × 10)[b]	• CR rates: 80% (SDAC) vs 82% (HiDAC) between SDAC and HiDAC; $P = .38$ • 5-year OS: 40% (SDAC) vs 42% (HiDAC); P = NS • 5-year EFS: 34% (SDAC) vs 35% (HiDAC); P = NS[a]
Candoni et al[100]	130	FA-IDA + GO	• CR rate: 82% • 3-year DFS: 49.6%; • 5-year OS: 52% • 5-year DFS: 52%
Solh et al[101]	86 (3+7) + 218 (FLAG ± IDA)	Historical comparison of 3+7 vs FLAG ± IDA	• CR rate after 1 course: 74% (FLAG ± IDA) vs 62% (3+7); $P < .001$ • 3-year OS: 46% (FLAG ± IDA) vs 28% (3+7); $P = .007$
Reville et al[114]	31	Cladribine + IDA + HiDAC (CLIA) + venetoclax	• CR rate: 90% • 1-year EFS: 79.3% • 1-year OS: 81%
Lachowiez et al[113]	27	Fludarabine + HiDAC + IDA + GCSF (FLAG-IDA) + venetoclax	• CR rate: 89% • 1-year OS: 80%-100%

Abbreviations: 3+7, 3 days of anthracycline + 7 days of cytarabine; araC, cytarabine; ADE, DA + etoposide; CLIA, cladribine, idarubicin, high-dose cytarabine; CR, complete remission; DA, daunorubicin, cytarabine; DFS, disease-free survival; EFS, event-free survival; FA, fludarabine, high-dose cytarabine; GCSF, granulocyte colony-stimulating factor; GO, gemtuzumab ozogamicin; HiDAC, high dose of cytarabine; IA, idarubicin, high-dose cytarabine; IDA, idarubicin; NS, not significant; OS, overall survival; RFS, relapse-free survival; SDAC, standard dose of cytarabine.

[a]See text for discussion of possible reasons for negative results.

[b]Cycle 2: SDAC patients received total 12 g/m^2 of araC, HDAC patients received total 16 g/m^2 of araC.

IDA rather than daunorubicin. Leukemia management expertise (supportive care; antibiotics and antifungal prophylaxis; timely transfusion support; management of toxicities; and early, aggressive treatment of infections/sepsis) allows safe and full delivery of this regimen in specialized leukemia centers (more than 4-5 leukemia experts in an oncology group; large AML referral volume).

Other adenosine nucleoside analogs (clofarabine, cladribine) also have been explored in combinations with standard chemotherapy. Two randomized trials confirmed the benefit of adding cladribine to the 3+7 regimen. The first study randomly assigned 400 patients to induction with 3+7 with or without cladribine and reported that adding cladribine resulted in higher rates of CR (64% vs 46% [$P = .0009$]) and leukemia-free survival (44% vs 28% [$P = .05$]).[102] The second study compared 3 arms, 1 with 3+7 alone and the other 2 adding cladribine and fludarabine, respectively. The addition of cladribine (but not fludarabine) was associated with higher rates of CR (67.5% vs 56% [$P = .001$]) and 3-year survival (45% vs 33% [$P = .02$])[103] and also improved outcome in *FLT3*-mutated AML.[104]

At MD Anderson, we use regimens that add the adenosine nucleoside analogs to IDA and high-dose cytarabine as frontline induction therapy in younger patients with AML (fludarabine FLAG-IDA/FAI; clofarabine/idarubicin/high-dose cytarabine in CIA; cladribine idarubicin/high-dose cytarabine in CLIA).[105] We are exploring the addition of venetoclax and other targeted therapies (discussed later). Table 2 summarizes the results of some studies that have incorporated novel intensive chemotherapy induction strategies in AML.

The optimal choice and dose schedule of anthracycline has been evaluated in multiple studies. Historically, daunorubicin 30-60 mg/m^2 daily × 3 was used for induction therapy. Daunorubicin 45 mg/m^2 daily × 3 for induction was inferior to 90 mg/m^2 in age-specific subsets,[5,6] but the 60 mg/m^2 dose was equivalent to the latter and was less toxic.[106,107] IDA 12 mg/m^2 daily × 3 is equivalent, or perhaps superior, to daunorubicin. Studies comparing IDA and daunorubicin, including a meta-analysis of 5 randomized trials, suggested that using IDA may be associated with higher CR and survival rates.[108-111] With FLAG-IDA/CLIA, we reduce the IDA dosage to 8-10 mg/m^2 daily × 3 to avoid excessive myelosuppression.

The benefit of GO has been confirmed in a meta-analysis of 5 randomized trials. The drug, which was approved by the FDA in 2000, was withdrawn in 2010 and reapproved in 2017 at a lower dose schedule and in combination with chemotherapy (3 mg/m^2 × 1 during induction and consolidation; 3 mg/m^2 on days 1, 4, and 7 during induction). The negative pivotal trial in the United States (Southwest Oncology Group S0106),[14] which prompted the withdrawal, perhaps had a faulty design. Randomization was to 3+7 with daunorubicin 60 mg/m^2 daily × 3 versus 3+7 with the addition of GO 6 mg/m^2 on day 4, but with daunorubicin at 45 mg/m^2 daily × 3 (presumed to be equitoxic but later found to be suboptimal).[14] The other 4 randomized trials demonstrated a benefit with GO.[15] The meta-analysis involving 3325 patients revealed that the addition of GO reduced the risk of relapse ($P = .0001$) and improved the 5-year survival rate ($P = .01$). The benefit was most significant in patients with favorable cytogenetics (increased 5-year survival rate from 50% to 75% [$P = .0006$]) and intermediate cytogenetics ($P = .005$). The 3 mg/m^2 dose was as effective as the 6 mg/m^2 dose and was associated with fewer early deaths.[15]

An interesting question is the possible role of lomustine, an alkylating agent, in the treatment of AML. In 3 French studies involving 847 patients aged >60 years, the addition of lomustine 200 mg/m^2 orally on day 1 to IDA + cytarabine (n = 508), compared with the latter 2 drugs alone (n = 339), was associated with a higher CR rate (68% vs 58% [$P = .002$]) and longer survival (median 12.7 vs 8.7 months [$P = .004$]). By multivariate analysis, lomustine was a favorable independent treatment variable for CR and survival prolongation.[112]

At MD Anderson, we use intensive chemotherapy regimens for younger/fit patients that incorporate high-dose cytarabine and adenosine nucleoside analogs (fludarabine in FLAG-IDA; cladribine in CLIA) during induction and consolidation and add targeted therapies as indicated: gilteritinib in *FLT3*-mutated AML, and venetoclax (7-14 days) in non–*FLT3*-mutated AML. Allogeneic SCT may be offered to patients who are in CR based on donor availability, patient age and comorbidities, pretreatment AML characteristics (eg, cytogenetic/molecular profiles), and MRD status in CR. Allogeneic SCT in first CR should be considered in patients with high-risk disease based on adverse cytogenetics, high *FLT3* mutation allelic ratio, or MRD positivity by multicolor flow cytometry >0.1% after first consolidation. Otherwise, patients complete 4 to 6 courses of consolidation and are offered maintenance therapy with azacitidine and venetoclax on a clinical trial for ≥2 years or targeted therapies as appropriate (eg, FLT3 inhibitors or IDH inhibitors). With this approach, the CR rate in nonselected younger patients is 70% to 80%, and the long-term survival rate is 40% to 50% (Fig. 1). These results antedate the introduction

of targeted therapies into the frontline intensive chemotherapy regimens (FLAG/IDA and CLIA), which are now combined with venetoclax for 7-14 days during induction and for 5-7 days in maintenance, as tolerated.[113,114]

OLDER/UNFIT PATIENTS WITH AML: LOW-INTENSITY THERAPY

Hypomethylating Agents

The poor results with intensive chemotherapy and low-dose cytarabine in older/unfit patients with AML prompted the search for alternative strategies. Decitabine was originally developed in Europe in the 1970s and 1980s as a cytotoxic drug at doses of 1000 to 2500 mg/m^2 per course.[115] Its development was abandoned because of severe prolonged and unpredictable myelosuppression as well as neurotoxicity. In 1992, awareness of the possible differentiation properties of decitabine led MD Anderson investigators (H.M.K.) to import the drug to the United States as an investigator-initiated investigational new drug. Between 1992 and 2000, it was developed as an epigenetic HMA at 1/20th of the myelosuppressive dose: 10 to 20 mg/m^2 daily × 5-10 days.[116-119] The initial collaboration was with the Dutch company Pharmachemie BV, but in 1999, Teva acquired the company and abandoned decitabine because it was thought to be a cytarabine-like drug. SuperGen then acquired it and continued its development as an HMA. This led to the phase 3 trials in myelodysplastic syndrome (MDS), resulting in its FDA approval for higher-risk MDS in 2006.[119] The phase 3 pivotal trial of decitabine versus low-dose cytarabine in older patients with AML failed to meet the study-designed primary endpoint,[120] although the decitabine arm demonstrated a significant survival benefit with the more mature data. Decitabine was approved by the European Medicines Agency for the treatment of older patients with AML, but not by the FDA. The AML phase 3 study randomly assigned 485 patients aged ≥65 years to decitabine 20 mg/m^2 IV daily × 5 every month versus supportive care or low-dose cytarabine. In a final analysis, the median survival was 7.7 with decitabine vs 5 months with supportive care or low-dose cytarabine (P = .036). Parallel studies were ongoing with azacitidine, resulting in its approval by the FDA for the treatment of higher-risk MDS,[121] but not for the treatment of older patients with AML.[122] The azacitidine phase 3 pivotal study in older patients with AML (AZA-AML-001) randomly assigned 488 patients to azacitidine versus 3 conventional strategies: low-dose cytarabine, intensive chemotherapy, or supportive care. Azacitidine therapy was associated with longer survival (median 10.4 vs 6.5 months; hazard ratio, 0.85 [P = .06]).[122] Today, decitabine and azacitidine are the most commonly used agents for the treatment of older/unfit patients with AML.

Longer durations of decitabine schedules (20 mg/m^2 daily × 10) have also been proposed.[117,123] Recently, the FDA approved an oral formulation of decitabine plus cedazuridine (cytosine deaminase inhibitor; combination bioequivalent to IV decitabine).[124,125] This may result in effective oral therapies for older/unfit patients with AML (decitabine-cedazuridine plus venetoclax) and may improve tolerance and quality of life with effective postremission outpatient consolidation therapy.

Comparison of intensive chemotherapy versus HMA therapy in older patients with AML showed better results with HMAs.[126,127]

Combined Low-Intensity Chemotherapy Regimens

Despite the benefits of HMAs, their value in treating older/unfit patients with AML is modest. Because of the anti-AML efficacy of clofarabine, cladribine, and low-dose cytarabine, we evaluated a 3-drug lower-intensity regimen combining an adenosine nucleoside analog (clofarabine in one study and cladribine in another) with low-dose cytarabine, in alternating cycles with decitabine, over a period of 18 months.[128,129] Among 248 patients (median age, 69 years [range, 48-85 years]) treated with the 2 regimens, the overall response rate was 66%, the CR rate was 59%, the early (4-week) mortality rate was 2%, the median survival was 12.5 months, and the estimated 2-year survival rate was 29%. Among patients with a normal karyotype, the median survival was 19.9 months, and the estimated 2-year survival rate was 45%.[128,129] Compared with single-agent HMAs (considered a standard of care in older/unfit AML), the double-nucleoside analog/HMA lower-intensity therapy suggested improved results and represents a novel, well-tolerated, effective foundation upon which approaches that add venetoclax and other targeted therapies can be built.

EXCITING DISCOVERIES IN AML, PRESENT AND FUTURE

Venetoclax

Venetoclax and HMAs/low-dose cytarabine

One strategy to target AML involves activation of the intrinsic or mitochondrial pathway of apoptosis, regulated by the BCL-2 family of proteins. Survival/

apoptosis involves a dynamic balance of proapoptotic effectors (Bak, Bax) and antiapoptotic proteins (BCL-2, BCL-XL, MCL-1). The latter are overexpressed in AML. Small molecule "BH3 mimetics" bind to the antiapoptotic proteins in the BH3 domain and liberate proapoptotic proteins, thus triggering apoptosis. The earlier generation of BH3 mimetics were associated with unacceptable on-target toxicities, including thrombocytopenia.

The BCL-2 inhibitor venetoclax is a more advanced and highly potent BH3-mimetic molecule that retains specificity for BCL2, but without affinity for BCL-XL or MCL-1. It is active against several cancers (chronic lymphocytic leukemia; other lymphoproliferative disorders) and is under investigation in others (acute lymphoblastic leukemia, MDS, lymphoma, and myeloma subsets). AML blasts and stem cells depend on BCL-2 for survival, and preclinical studies have confirmed the activity of venetoclax in AML,[130] leading to a phase 2 single-agent venetoclax study for relapsed AML that showed modest activity.[131] Responses were more frequent in the *IDH*-mutated subtype, confirming the preclinical hypothesis that *IDH*-mutated AML is particularly venetoclax-sensitive.[131] Venetoclax was then combined with HMAs and low-dose cytarabine in single-arm and, later, randomized trials in older/unfit patients with newly diagnosed AML. The positive results from the single-arm trials (azacitidine/venetoclax combination: overall response rate, 67%; estimated median survival, 17.5 months; 2-year survival, 40%) led to FDA-accelerated approval of venetoclax in combination with HMAs or low-dose cytarabine for the treatment of these patients.[132,133]

The VIALE-A phase 3 pivotal trial randomly assigned newly diagnosed AML patients aged ≥75 years and unfit for intensive chemotherapy to azacitidine with or without venetoclax. Among 431 patients randomly assigned (2:1) to azacitidine plus venetoclax (n = 286) or azacitidine alone (n = 145), those who received venetoclax had significantly improved survival (median survival, 14.7 vs 9.6 months [$P < .001$]). The response rates (66.4% vs 28.3% [$P < .001$]) and CR rates (29.7% vs 17.9% [$P < .001$]) were also better.[134] A second randomized study of low-dose cytarabine with or without venetoclax (211 patients; 2:1 randomization in favor of the combination) showed similar findings (median survival, 8.4 vs 4.1 months [$P = .04$]; overall response rate, 48% vs 13% [$P < .001$]; CR rate, 27% vs 7% [$P < .001$]), all in favor of the combination.[135]

A single-arm trial of decitabine (10-day induction; maintenance 5 d/mo) with venetoclax (14-21 days) in older patients (median age, 72 years [range, 70-78 years]) with newly diagnosed de novo AML showed an overall response rate (CR +CR with incomplete hematologic recovery [CRi]) of 84%, a CR rate of 67%, a 4-week mortality rate of 0%, and a median survival of 18.1 months.[136]

Low-intensity and intensive chemotherapy combinations with venetoclax

A study of the combination of cladribine/cytarabine/venetoclax alternating with azacitidine/venetoclax is ongoing in older/unfit patients with newly diagnosed AML.[137] Among 48 patients treated so far (median age, 68 years [range, 57-84 years]), the CR rate is 77% (overall response rate 94%). The MRD negativity rate is 80%, the 4-week mortality is 0%, and estimated 1-year survival is 70%.

In younger/fit patients with newly diagnosed AML, we are investigating intensive chemotherapy (FLAG-IDA, CLIA) in combination with venetoclax (7-14 days during induction; 5-7 days in maintenance).[113,114] Among 28 patients treated so far with FLAG-IDA/venetoclax, the overall response rate is 93%, and the MRD negativity rate in CR is 92%.[113] Among 31 patients treated with CLIA/venetoclax, the overall response rate is 90%, and the estimated 1-year survival is 78%.[114]

FLT3 Inhibitors

FLT3 inhibitors in AML salvage

Investigations of FLT3 inhibitors have now spanned close to 2 decades. These have included, among others, midostaurin, sorafenib, gilteritinib, and quizartinib. Type 1 inhibitors (midostaurin, gilteritinib) are active against both *FLT3*-ITD and *FLT3*-TKD mutations. Type 2 inhibitors (sorafenib, quizartinib) are effective only against *FLT3*-ITD mutations. Newer FLT3 inhibitors may be more effective than earlier ones.[138]

Therapy with single-agent gilteritinib (type 1 FLT3 inhibitor; dual FLT3-AXL inhibitor) 120 mg/d resulted in composite CR (CRc) rates of 45% to 50% in relapsed/refractory *FLT3*-mutated AML.[139] The phase 3 ADMIRAL trial randomly assigned (2:1) 371 patients with relapsed *FLT3*-mutated AML to gilteritinib 120 mg/d (n = 247) or investigator-choice salvage chemotherapy (both high- and low-dose chemotherapy) (n = 124).[140] Gilteritinib therapy was associated with a significantly longer survival (median survival, 9.3 vs 5.6 months; hazard ratio, 0.637 [$P = .0007$]), and higher rates of CR (21% vs 11% [$P = .013$]), CR vs. CR with partial hematologic recovery (CRh) rate (34% vs 15%), and CRc rate (54% vs 22%).[140] This led to FDA approval of single-agent gilteritinib as salvage therapy

for *FLT3*-mutated AML. Ongoing studies are combining gilteritinib with HMA therapy and with intensive chemotherapy as well as with venetoclax in frontline, salvage, and maintenance strategies.

Quizartinib is a potent type 2 FLT3 inhibitor. In phase 1 studies in relapsed/refractory AML, a maximum tolerated oral dose of 200 mg/d was proposed; the dose-limiting toxicity was prolongation of the QT interval.[141] In *FLT3*-ITD AML, the overall response rate was 50%. This was confirmed in a large phase 2 study in relapsed/refractory older and younger patients with *FLT3*-mutated AML.[142] Later studies evaluated quizartinib 90-135 mg/d, then 30-60 mg/d, to reduce the incidence of prolongation of the QT interval.[143] A total of 67 patients with relapsed/refractory *FLT3*-ITD AML were randomly assigned to quizartinib 30 mg/d or 60 mg/d. The CRc rate was 50% in both arms, and the median survival was 6-8 months. The rate of grade 3 prolongation of the QT interval was 3% in both arms (grade 2, 11%-17%).[143] The randomized phase 3 QUANTUM-R study evaluated quizartinib versus investigator-choice salvage chemotherapy in 367 patients with relapsed/refractory *FLT3*-ITD mutated AML. Quizartinib was better than chemotherapy (CRc rate, 48% vs 27%; median survival, 6.2 months vs 4.7 months [$P = .0177$]). However, quizartinib was not granted FDA approval, due in part to concerns over treatment equipoise and robustness of the survival benefit (it was approved in Japan in 2019). Combination studies of quizartinib in relapsed and frontline *FLT3*-ITD AML are ongoing.

Certain activating point mutations (such as *FLT3*-ITD *F691L*) are resistant to current FLT3 inhibitors. Third-generation compounds (FT10101, crenolanib) are under development potentially to overcome these and other mechanisms of resistance, such as the emergence of MAPK-pathway mutations (eg, RAS, RAF, PTPN11, NF1).[144]

Combination therapy of FLT3 inhibitors with agents that induce apoptosis may enhance cytotoxicity against *FLT3*-mutated and wild-type clones and potentially delay or prevent resistance to FLT3 inhibitor-based therapies. Preclinical data indicated strong synergism between venetoclax and FLT3 inhibitors. Ongoing studies are evaluating combinations of HMAs plus gilteritinib, gilteritinib plus venetoclax, and triplet therapy (HMAs/gilteritinib/venetoclax).

Frontline therapy with FLT3 inhibitors

A phase 2 RATIFY trial randomly assigned 717 younger patients (aged <60 years) with newly diagnosed *FLT3*-mutated AML (median age, 48 years [range, 18-60 years]; 77% *FLT3*-ITD, 23% *FLT3*-TKD) to the 3+7 regimen with or without midostaurin.[145] The addition of midostaurin resulted in a significant survival benefit (median survival, 74.7 vs 25.6 months [$P = .009$]; estimated 5-year survival, 50% vs 42%). The benefit was noted in *FLT3*-ITD low allelic ratio (≤0.70), *FLT3*-ITD high allelic ratio (>0.70), and TKD-mutated AML. At MD Anderson, a matched cohort analysis showed the benefit of adding sorafenib to IDA/cytarabine in *FLT3*-mutated AML.[33] In our study of CLIA + FLT3 inhibitor (sorafenib/midostaurin), the CR rate was 86% and the estimated 1-year survival was 70%.[33]

Several trials are evaluating newer-generation FLT3 inhibitors with intensive chemotherapy. In a study of 79 patients with newly diagnosed AML (56% had *FLT3*-mutated AML) treated with 3+7 plus gilteritinib, the overall response rate was 82%, and the estimated 2-year survival was 72%.[146] Sorafenib added as maintenance therapy after allogeneic SCT in patients with *FLT3*-mutated AML improved survival and/or relapse-free survival.[147,148] The combination of azacitidine and sorafenib in older patients with *FLT3*-ITD AML resulted in a CR-CRi rate of 78%.[149]

Of interest, several nontargeted chemotherapy strategies have shown benefits in *FLT3*-mutated AML, including induction regimens containing high-dose cytarabine, cladribine, and high-dose daunorubicin.[94,104,150]

IDH Inhibitors

The *IDH1-2* mutations induce neomorphic IDH enzyme activity, which causes aberrant production of the 2-hydroxyglutarate onco-metabolite. The 2-hydroxyglutarate competitively inhibits α-ketoglutarate, leads to dysregulated epigenetic function, a hypermethylated phenotype, and a block in maturation leading to AML.[151] Enasidenib and ivosidenib are orally bioavailable small molecule inhibitors of mutant *IDH2* and mutant *IDH1*, respectively.

In a phase 1-2 study, 239 patients with *IDH2*-mutated AML (176 relapsed/refractory) were treated with oral enasidenib 50-650 mg/d continuously. A subset of 109 patients with relapsed/refractory AML received enasidenib at the recommended phase 2 dose of 100 mg/d, with an overall response rate of 40.3%, a CR rate of 19.3%, a median response duration of 5.8 months, and a median survival of 9.3 months.[152] This resulted in the FDA approval of enasidenib 100 mg/d as single-agent therapy in *IDH2*-mutated relapsed/refractory AML. Grade 3/4 adverse effects included elevation of indirect bilirubin (12%) and differentiation syndrome (7%, responsive to steroids).

In a phase 1/2 study, 258 patients with *IDH1*-mutated AML (179 relapsed/refractory) were treated with ivosidenib. In the phase 2 efficacy portion that included 125 patients, ivosidenib 500 mg/d produced an overall response rate of 41.6%, a CR/CRh rate of 30.4%, a CR rate of 21.6%, a median overall response duration of 8.2 months, and a median survival of 8.8 months. Grade 3/4 adverse effects included prolongation of QT interval (7.8%) and differentiation syndrome (3.9%).[153] Based on this, ivosidenib 500 mg/d was approved by the FDA for the treatment of relapsed/refractory *IDH1*-mutated AML (as well as frontline therapy of *IDH1*-mutated AML in patients unfit for intensive chemotherapy).

With both IDH inhibitors, *RAS/RTK* pathway comutations and/or high mutational burden (>6 mutations) were associated with worse results, suggesting the importance of combination therapy.[154]

In a randomized phase 2 study, 101 older patients with newly diagnosed *IDH2*-mutated AML (median age, 74 years [range, 62-85 years]) were randomly assigned (2:1) to azacitidine plus enasidenib (n = 68) versus azacitidine alone (n = 33). The combination produced better results (CR rate, 50% vs 12% [$P = .0002$]; overall response rate, 68% vs 42% [$P = .015$]; median EFS 17.2 vs 10.8 months (hazard ratio, 0.59 [$P = .13$]). The median overall survival was impressive but was similar in both arms (22.0 vs 22.3 months), likely because of the availability of effective salvage options (including enasidenib, which was used in at least 24% of patients on the azacitidine-alone arm).[155]

In another single-arm trial, 134 younger/fit patients with newly diagnosed *IDH*-mutated AML (60 with *IDH1* mutations; 91 with *IDH2* mutations) received 3+7 chemotherapy plus ivosidenib (for *IDH1* mutation) or enasidenib (for *IDH2* mutation).[120] In *IDH1*-mutated AML, the overall response rate was 93% and the estimated 1-year survival was 79%; in *IDH2*-mutated AML, the overall response rate was 73% and the estimated 1-year survival was 75%.[156] A randomized, placebo-controlled trial of intensive chemotherapy with ivosidenib or enasidenib versus placebo is ongoing in Europe.

Other IDH inhibitors are under development. Olutasidenib (FT-2102; IDH1 inhibitor) was investigated in a phase 1/2 trial in patients with *IDH1*-mutated AML. Thirty-two patients were treated with single-agent FT-2102, and 46 were treated with FT-2102 and azacitidine. The overall response rate was 39% (CR 15%) with single-agent FT-2102 and 54% (CR 23%) with the combination.[157,158]

CPX-351

CPX-351 is a nano-scale liposome that contains a fixed 5:1 molar ratio of cytarabine and daunorubicin.[159] Following the encouraging phase 1/2 trial results in the subset of secondary AML, a phase 3 trial in newly diagnosed secondary AML randomly assigned 309 patients to CPX-351 versus 3+7. Therapy with CPX-351 was associated with a significantly longer survival (hazard ratio, 0.69 [$P = .005$]), and better response rates (CR rate 38% vs 26% [$P = .035$]; CR + CRi rate 48% vs 33% [$P = .016$]). CPX-351 was also associated with a longer duration of myelosuppression. The feasibility of later allogeneic SCT was higher in patients achieving CR post CPX-351 (20% vs 12%); their survival was also longer post SCT. This resulted in the FDA approval of CPX-351 as frontline therapy for secondary AML.[160,161] Ongoing studies are combining CPX-351 with venetoclax, GO and other targeted therapies.

Glasdegib

The Hedgehog signaling pathway plays critical roles in embryogenesis and stem cell maintenance. Dysregulation in the Hedgehog pathway can result in the development, maintenance, and expansion of leukemic stem cells, which may play an important role in AML pathogenesis, persistence, and progression.[162]

Glasdegib is an orally bioavailable selective inhibitor of the Smoothened receptor, a component of the Hedgehog signaling pathway. Following preclinical and phase 1/2 trials, a phase 2 study investigated low-dose cytarabine with and without glasdegib 100 mg/d. The addition of glasdegib was associated with significant prolongation of survival (median survival, 8.8 vs 4.9 months; 12-month survival, 59.8% vs 38.2%).[163] The FDA approved glasdegib (with low-dose cytarabine) for the treatment of newly diagnosed AML in unfit patients aged ≥75 years.[164] Glasdegib combinations with azacitidine and intensive chemotherapy are under investigation.

APR-246 in TP53*-Mutated AML*

TP53-mutated AML is associated with older age, therapy-related disease, complex cytogenetics, and poor prognosis. With HMA plus venetoclax therapy in older/unfit patients with *TP53*-mutated AML, the response rate is 55%, but the median survival is only approximately 6 months.[134,136]

The investigational drug APR-246 may restore the transcriptional activity of unfolded wild-type or mutant *p53*, leading to induction of apoptosis in *TP53*-mutated

cancers.[165] The early experience with azacitidine plus APR-246 is producing encouraging results in newly diagnosed older/unfit patients with *TP53*-mutated AML. In a study from the United States of 55 patients with *TP53*-mutated disease (40 with MDS, 11 with AML, and 4 with chronic myelomonocytic leukemia), there were 45 evaluable patients who had an overall response rate of 87%, with 24 of the 39 responders achieving CR (53%), and the median survival was 11.6 months.[166] Another study from France treated 52 patients with *TP53*-mutated disease (34 with MDS, 18 with AML) with the same combination and reported an overall response rate of 58% and a CR rate of 37%; the median overall survival was approximately 12 months.[167] A phase 3 randomized study of azacitidine with or without APR-246 (1:1 randomization) in 154 patients with *TP53*-mutated MDS did not meet the primary endpoint of CR (CR rate, 33.3% with azacitidine + APR246 vs 22.4% with azacitidine alone [$P = .13$].[168]

Magrolimab (CD47 Antibody)

The CD47 protein functions as a macrophage checkpoint, providing a potent "do not eat me" signal. This allows tumor cells to evade detection and immune destruction by macrophages. CD47 is upregulated in AML and is associated with a poor prognosis.[169,170] Magrolimab (Hu5F9-G4) is a humanized monoclonal antibody that binds CD47 and blocks its interaction with SIRPα, its ligand on phagocytic cells, resulting in the elimination of cancer cells.[171]

The combination of azacitidine plus magrolimab was evaluated in older/unfit patients with newly diagnosed AML or with intermediate/high-risk MDS. Among 34 evaluable patients with AML, the objective response rate was 65% (40% CR, 12% CRi). Among patients with abnormal pretreatment karyotype, 50% achieved a complete cytogenetic response. Among patients with *TP53*-mutated AML, the overall response rate was 71% (15 of 21 patients; CR rate, 42%). The estimated median survival was 18.9 months in wild-type patients and 12.9 months in mutated patients.[172]

MAINTENANCE THERAPY

Maintenance therapy is established as beneficial in many cancers, including acute lymphocytic leukemia. However, for many years, studies in AML did not confirm a survival benefit with maintenance therapy. This changed with the recent positive results reported with oral azacitidine (CC-486). In an international multicenter trial (QUAZAR AML-001), 472 older patients (aged ≥55 years; median age, 68 years) with AML (unfavorable karyotype) in first CR for <4 months were randomly assigned to oral CC-486 300 mg × 14 d/mo (n = 238) or placebo (n = 234). The median survival was 24.7 months with CC-486 vs 14.8 months with placebo (hazard ratio, 0.69 [$P = .0009$]). The median RFS was 10.2 vs 4.8 months. As a result, the FDA approved CC-486 as a maintenance therapy for this indication in September 2020.[173]

A second study (HOVON97) randomly assigned 116 older patients (aged ≥60 years) with AML in CR after 2 courses of intensive chemotherapy with subcutaneous azacitidine 50 mg/m^2 × 5 d/mo for 12 courses (n = 56) versus observation (n = 60). The 12-month disease-free survival was 64% with azacitidine versus 42% with observation ($P = .04$).[174]

It is important to emphasize that the 2 FDA-approved oral HMAs, decitabine/cedazuridine and CC-486, are vastly different. Decitabine/cedazuridine is 100% absorbed and approved for the treatment of MDS and chronic myelomonocytic leukemia (a flat dose of 35 mg/d × 5 days per course; presumably as a replacement to IV decitabine) based on a study that was designed specifically to demonstrate dose proportionality. CC-486, on the other hand, is poorly absorbed, producing an area under the curve that is 10% to 30% of IV azacitidine. Its FDA approval is as a 2-week course every month for maintenance therapy in adults with AML in first CR who cannot complete intensive chemotherapy. A formulation of oral azacitidine/cedazuridine that would be 100% absorbed is under development as an alternative to subcutaneous/IV azacitidine. Current studies are investigating the combination of these agents (eg, oral decitabine/cedazuridine + venetoclax) and longer dose schedules (mimicking the decitabine 10-day schedule) in AML.

Maintenance therapy may also be beneficial in the post-SCT setting. In the SORMAIN trial, 83 patients with *FLT3*-ITD AML post–allogeneic SCT were randomly assigned to sorafenib 200-400 mg twice daily versus placebo for 2 years. The 2-year PFS rate was 85% with sorafenib versus 53% with placebo ($P = .04$). Survival was longer with sorafenib (hazard ratio, 0.447 [$P = .03$]).[148] In the pivotal ADMIRAL trial, which evaluated gilteritinib versus salvage chemotherapy in *FLT3*-mutated AML (detailed earlier), 51 patients achieving a response post gilteritinib and undergoing allogeneic SCT either resumed gilteritinib after SCT (n = 35) or did not (n = 16). The median survival was longer with gilteritinib resumption (16.2 vs 8.4 months;

hazard ratio, 0.387 [$P = .024$]).[140] The ongoing randomized RADIUS trial and BMT-CTN 1506 study are prospectively investigating post-SCT maintenance with midostaurin and gilteritinib, respectively, versus the standard of care.

ALLOGENEIC AND AUTOLOGOUS STEM CELL TRANSPLANTATION

A meta-analysis of multiple randomized trials demonstrated, on average, a benefit of allogeneic SCT in AML in first CR.[175] This has been questioned in previous randomized trials for several reasons. The limited number of patients in each study may have overlooked modest but clinically significant benefits with SCT. The lead-time bias to allogeneic SCT and the fact that many patients allocated to allogeneic SCT could not undergo the procedure for various reasons (infections, organ dysfunction, new chemotherapy-related morbidities, AML relapse, others) further confused the analyses. Finally, some patients allocated to chemotherapy in first CR may have benefited from allogeneic SCT in second CR. An MRC study reported that the benefits of chemotherapy versus allogeneic SCT in first CR were similar when the benefit of allogeneic SCT in second CR was considered.[176]

Today, allogeneic SCT is the standard of care in first CR and is considered based on several factors. These include the presence of an adverse karyotype or high *FLT3*-mutated allelic ratio at diagnosis; persistent MRD in CR; and a lower risk of SCT-associated mortality (based on favorable characteristics such as age, comorbid conditions, suitability of donor, and degree of matching).

With the availability of multiple effective targeted therapies in AML, allogeneic SCT should be considered as part of a total strategy of chemotherapy/targeted therapy/SCT/post-SCT maintenance to improve AML cure rates further. Further investigations of post-SCT maintenance strategies to reduce the risk of relapse need to be considered in this continuum, including HMAs (both parenteral and oral), FLT3 and IDH inhibitors, venetoclax, and others.

Allogeneic SCT should be considered in patients with relapsed/refractory AML who achieve subsequent CR, and it may also be the best salvage option in patients with relapsed/refractory AML who have persistent disease with <20% bone marrow blasts (long-term survival, 10%-20%).[177]

Modifications of pre-, peri-, and post-SCT strategies are improving the efficacy and safety of SCT. For example, the use of cyclophosphamide on day 4 after stem cell infusion has rendered haplo-identical SCT safer (reducing graft-versus-host disease complications) and consequently improved the longer-term results of haplo-identical SCT. These findings are encouraging similar modifications across all SCT procedures.[178,179] Autologous SCT is still considered occasionally in the setting of APL and CBF-AML in second CR, with negative molecular studies in collected stem cells. Otherwise, it has been largely abandoned in the United States for AML because of the perceived lack of benefit. Some European researchers consider autologous SCT in first CR based on randomized trials showing that it provides equivalent results to multiple chemotherapy consolidations (usually <4). With increasing knowledge about the negative impact of persistent MRD in CR, it is conceivable that with autologous SCT, host marrows may have been reinfused with significant persistent AML disease burden, thus causing relapses and negating its possible benefit. Future studies should re-evaluate the benefit of autologous SCT using collected MRD-negative cells.

FUNDING SUPPORT

This work was supported in part by the MD Anderson Cancer Center Leukemia SPORE grant (CA100632), the Cancer Center Support Grant (P30CA016672), and the Charif Souki Cancer Research Grant.

CONFLICT OF INTEREST DISCLOSURES

Hagop M. Kantarjian has received research grants from AbbVie, Amgen, Ascentage, Bristol Myers Squibb, Daiichi Sankyo, Immunogen, Jazz Pharmaceuticals, Novartis, Pfizer, and Sanofi; has received honoraria from AbbVie, Adaptive Biotechnologies, Amgen, Aptitude Health, BioAscend, Daiichi Sankyo, Delta-Fly Pharma, Janssen Global, Novartis, Oxford Biomedical, Pfizer, and Takeda Oncology; and has served on the advisory board for Actinium. Tapan M. Kadia has received research grants from AbbVie, Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, Celgene, Cellenkos, Delta-Fly Pharma, Genentech, GenFleet, Jazz Pharmaceuticals, and Pfizer and has received consultant fees from AbbVie, Agios, Jazz Pharmaceuticals, Genentech, Novartis, and Pfizer. Courtney D. DiNardo has received research grants from AbbVie, Agios, Bayer, Bristol Myers Squibb/Celgene, Calithera, Cleave, Daiichi Sankyo, ImmuneOnc, and Novartis; has received honoraria from AbbVie, Agios, Bristol Myers Squibb/Celgene, Daiichi Sankyo, Foghorn, ImmuneOnc, MedImmune, Novartis, and Takeda Oncology; has received consultant fees from AbbVie, Agios, Bristol Myers Squibb/Celgene, Daiichi Sankyo, and ImmuneOnc; and has served on the advisory board for Notable Labs. Farhad Ravandi has received research grants from AbbVie, Amgen, Astex, Bristol Myers Squibb, Macrogenics, Prelude, Orsenix, and Xencor and has received honoraria from AbbVie, Agios, Amgen, AstraZeneca, Astellas, Celgene, Bristol Myers Squibb, Orsenix, Syros, Taiho, and Xencor. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Hagop M. Kantarjian: Conceptualization, writing–original draft, writing–review and editing. **Tapan M. Kadia:** Conceptualization, writing–review and editing. **Courtney D. DiNardo:** Conceptualization, writing–review and editing. **Mary Alma Welch:** Conceptualization, writing–review and editing. **Farhad Ravandi:** Conceptualization, writing–review and editing.

REFERENCES

1. Kantarjian H. Acute myeloid leukemia—major progress over four decades and glimpses into the future. *Am J Hematol*. 2016;91:131-145.
2. Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. *Lancet*. 2018;392:593-606.
3. Kadia TM, Ravandi F, Cortes J, Kantarjian H. Toward individualized therapy in acute myeloid leukemia: a contemporary review. *JAMA Oncol*. 2015;1:820-828.
4. Dohner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. *N Engl J Med*. 2015;373:1136-1152.
5. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009;361:1249-1259.
6. Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361:1235-1248.
7. Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. *J Clin Oncol*. 2009;27:504-510.
8. Abaza Y, Kantarjian H, Garcia-Manero G, et al. Long-term outcome of acute promyelocytic leukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab. *Blood*. 2017;129:1275-1283.
9. Platzbecker U, Avvisati G, Cicconi L, et al. Improved outcomes with retinoic acid and arsenic trioxide compared with retinoic acid and chemotherapy in non-high-risk acute promyelocytic leukemia: final results of the randomized Italian-German APL0406 trial. *J Clin Oncol*. 2017;35:605-612.
10. Burnett AK, Russell NH, Hills RK, et al. Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2015;16:1295-1305.
11. 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;89:964-968.
12. 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(Suppl 1):290.
13. Burnett AK, Hills RK, Milligan D, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. *J Clin Oncol*. 2011;29:369-377.
14. Petersdorf SH, Kopecky KJ, Slovak M, et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. *Blood*. 2013;121:4854-4860.
15. 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;15:986-996.
16. Groschel S, Schlenk RF, Engelmann J, et al. Deregulated expression of EVI1 defines a poor prognostic subset of MLL-rearranged acute myeloid leukemias: a study of the German-Austrian Acute Myeloid Leukemia Study Group and the Dutch-Belgian-Swiss HOVON/SAKK Cooperative Group. *J Clin Oncol*. 2013;31:95-103.
17. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010;116:354-365.
18. National Comprehensive Cancer Network. NCCN guidelines & clinical resources. Adapted from the National Cancer Centers Network (NCCN). 2020. Accessed November 3, 2020. https://www.nccn.org/professionals/physician_gls/default.aspx
19. Schoch C, Schnittger S, Klaus M, et al. AML with 11q23/MLL abnormalities as defined by the WHO classification: incidence, partner chromosomes, FAB subtype, age distribution, and prognostic impact in an unselected series of 1897 cytogenetically analyzed AML cases. *Blood*. 2003;102:2395-2402.
20. Harrison CJ, Hills RK, Moorman AV, et al. Cytogenetics of childhood acute myeloid leukemia: United Kingdom Medical Research Council treatment trials AML 10 and 12. *J Clin Oncol*. 2010;28:2674-2681.
21. Bill M, Mrozek K, Kohlschmidt J, et al. Mutational landscape and clinical outcome of patients with de novo acute myeloid leukemia and rearrangements involving 11q23/*KMT2A*. *Proc Natl Acad Sci U S A*. 2020;117:26340-26346.
22. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374:2209-2221.
23. 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;37:2632-2642.
24. Pastore F, Dufour A, Benthaus T, et al. Combined molecular and clinical prognostic index for relapse and survival in cytogenetically normal acute myeloid leukemia. *J Clin Oncol*. 2014;32:1586-1594.
25. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med*. 2008;358:1909-1918.
26. 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;129:424-447.
27. Pratcorona M, Brunet S, Nomdedeu J, et al. Favorable outcome of patients with acute myeloid leukemia harboring a low-allelic burden FLT3-ITD mutation and concomitant NPM1 mutation: relevance to post-remission therapy. *Blood*. 2013;121:2734-2738.
28. Schlenk RF, Kayser S, Bullinger L, et al. Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. *Blood*. 2014;124:3441-3449.
29. Ho AD, Schetelig J, Bochtler T, et al. Allogeneic stem cell transplantation improves survival in patients with acute myeloid leukemia characterized by a high allelic ratio of mutant FLT3-ITD. *Biol Blood Marrow Transplant*. 2016;22:462-469.
30. DiNardo CD, Ravandi F, Agresta S, et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. *Am J Hematol*. 2015;90:732-736.
31. Seifert H, Mohr B, Thiede C, et al. The prognostic impact of 17p (p53) deletion in 2272 adults with acute myeloid leukemia. *Leukemia*. 2009;23:656-663.
32. 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;122:3484-3491.
33. Boddu P, Kantarjian H, Ravandi F, et al. Outcomes with lower intensity therapy in TP53-mutated acute myeloid leukemia. *Leuk Lymphoma*. 2018;59:2238-2241.
34. Sasaki K, Kanagal-Shamanna R, Montalban-Bravo G, et al. Impact of the variant allele frequency of ASXL1, DNMT3A, JAK2, TET2, TP53, and NPM1 on the outcomes of patients with newly diagnosed acute myeloid leukemia. *Cancer*. 2020;126:765-774.
35. Thol F, Damm F, Ludeking A, et al. Incidence and prognostic influence of DNMT3A mutations in acute myeloid leukemia. *J Clin Oncol*. 2011;29:2889-2896.
36. Mendler JH, Maharry K, Radmacher MD, et al. RUNX1 mutations are associated with poor outcome in younger and older patients with cytogenetically normal acute myeloid leukemia and with distinct gene and MicroRNA expression signatures. *J Clin Oncol*. 2012;30:3109-3118.
37. 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;21:178-184.
38. Welch JS, Petti A, Miller C, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med*. 2016;24:2023-2036.
39. Klossowski S, Miao H, Kempinska K, et al. Menin inhibitor MI-3454 induces remission in MLL1-rearranged and NPM1-mutated models of leukemia. *J Clin Invest*. 2020;130:981-997.
40. Paschka P, Marcucci G, Ruppert AS, et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): a Cancer and Leukemia Group B Study. *J Clin Oncol*. 2006;24:3904-3911.

41. Schnittger S, Kohl TM, Haferlach T, et al. KIT-D816 mutations in AML1-ETO-positive AML are associated with impaired event-free and overall survival. *Blood*. 2006;107:1791-1799.
42. Marcucci G, Geyer S, Zhao J, et al. Adding the KIT inhibitor dasatinib (DAS) to standard induction and consolidation therapy for newly diagnosed patients (pts) with core binding factor (CBF) acute myeloid leukemia (AML): initial results of the CALGB 10801 (Alliance) study. *Blood*. 2013;122:357. doi:10.1182/blood.V122.21.357.357.
43. Gotlib J, Radia D, George T, et al. Avapritinib induces responses in patients (PTS) with advanced systemic mastocytosis (ADVSM), regardless of prior midostaurin therapy. European Hematology Association abstract EP1079. Abstract presented at: European Hematology Association; June 2020; Virtual Meeting.
44. Jongen-Lavrencic M, Grob T, Hanekamp D, et al. Molecular minimal residual disease in acute myeloid leukemia. *N Engl J Med*. 2018;378:1189-1199.
45. Grimwade D, Freeman SD. Defining minimal residual disease in acute myeloid leukemia: which platforms are ready for "prime time"? *Blood*. 2014;124:3345-3355.
46. Pastore F, Levine RL. Next-generation sequencing and detection of minimal residual disease in acute myeloid leukemia: ready for clinical practice? *JAMA*. 2015;314:778-780.
47. Klco JM, Miller CA, Griffith M, et al. Association between mutation clearance after induction therapy and outcomes in acute myeloid leukemia. *JAMA*. 2015;314:811-822.
48. Ravandi F, Jorgensen J, Borthakur G, et al. Persistence of minimal residual disease assessed by multiparameter flow cytometry is highly prognostic in younger patients with acute myeloid leukemia. *Cancer*. 2017;123:426-435.
49. Short NJ, Zhou S, Fu C, et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. *JAMA Oncology*. 2020;6:1890-1899.
50. Hourigan CS, Dillon LW, Gui G, et al. Impact of conditioning intensity of allogeneic transplantation for acute myeloid leukemia with genomic evidence of residual disease. *J Clin Oncol*. 2020;38:1273-1283.
51. Grimwade D, Jovanovic JV, Hills RK, et al. Prospective minimal residual disease monitoring to predict relapse of acute promyelocytic leukemia and to direct pre-emptive arsenic trioxide therapy. *J Clin Oncol*. 2009;27:3650-3658.
52. Yin JA, O'Brien MA, Hills RK, Daly SB, Wheatley K, Burnett AK. Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial. *Blood*. 2012;120:2826-2835.
53. Zhu HH, Zhang XH, Qin YZ, et al. MRD-directed risk stratification treatment may improve outcomes of t(8;21) AML in the first complete remission: results from the AML05 multicenter trial. *Blood*. 2013;121:4056-4062.
54. Kronke J, Schlenk RF, Jensen KO, et al. Monitoring of minimal residual disease in NPM1-mutated acute myeloid leukemia: a study from the German-Austrian acute myeloid leukemia study group. *J Clin Oncol*. 2011;29:2709-2716.
55. Schnittger S, Kern W, Tschulik C, et al. Minimal residual disease levels assessed by NPM1 mutation-specific RQ-PCR provide important prognostic information in AML. *Blood*. 2009;114:2220-2231.
56. Bernard J, Weil M, Boiron M, et al. Acute promyelocytic leukemia: results of treatment by daunorubicin. *Blood*. 1973;41:489-496.
57. Ghaddar HM, Plunkett W, Kantarjian HM, et al. Long-term results following treatment of newly diagnosed acute myelogenous leukemia with continuous-infusion high-dose cytosine arabinoside. *Leukemia*. 1994;8:1269-1274.
58. Kantarjian HM, Keating MJ, Walters RS, et al. Acute promyelocytic leukemia. M.D. Anderson Hospital experience. *Am J Med*. 1986;80:789-797.
59. Kantarjian HM, Keating MJ, Walters RS, Smith TL, McCredie KB, Freireich EJ. Role of maintenance chemotherapy in acute promyelocytic leukemia. *Cancer*. 1987;59:1258-1263.
60. Kantarjian HM, Keating MJ, McCredie KB, et al. A characteristic pattern of leukemic cell differentiation without cytoreduction during remission induction in acute promyelocytic leukemia. *J Clin Oncol*. 1985;3:793-798.
61. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. *Blood*. 1988;72:567-572.
62. Mathews V, George B, Chendamarai E, et al. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: long-term follow-up data. *J Clin Oncol*. 2010;28:3866-3871.
63. Ghavamzadeh A, Alimoghaddam K, Rostami S, et al. Phase II study of single-agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia. *J Clin Oncol*. 2011;29:2753-2757.
64. Lo-Coco F, Cimino G, Breccia M, et al. Gemtuzumab ozogamicin (Mylotarg) as a single agent for molecularly relapsed acute promyelocytic leukemia. *Blood*. 2004;104:1995-1999.
65. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol*. 2001;19:3852-3860.
66. Fenaux P, Chastang C, Chevret S, et al. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood*. 1999;94:1192-1200.
67. Sanz MA, Martin G, Rayon C, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. *Blood*. 1999;94:3015-3021.
68. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. *Blood*. 2002;100:4298-4302.
69. Powell BL, Moser B, Stock W, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. *Blood*. 2010;116:3751-3757.
70. Avvisati G, Lo-Coco F, Paoloni FP, et al. AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. *Blood*. 2011;117:4716-4725.
71. Russell N, Burnett A, Hills R, et al. Attenuated arsenic trioxide plus ATRA therapy for newly diagnosed and relapsed APL: long-term follow-up of the AML17 trial. *Blood*. 2018;132:1452-1454.
72. Lancet JE, Moseley AB, Coutre SE, et al. A phase 2 study of ATRA, arsenic trioxide, and gemtuzumab ozogamicin in patients with high-risk APL (SWOG 0535). *Blood Adv*. 2020;4:1683-1689.
73. Ravandi F, Koumenis I, Johri A, et al. Oral arsenic trioxide ORH-2014 pharmacokinetic and safety profile in patients with advanced hematologic disorders. *Haematologica*. 2020;105:1567-1574.
74. Zhu HH, Wu DP, Du X, et al. Oral arsenic plus retinoic acid versus intravenous arsenic plus retinoic acid for non-high-risk acute promyelocytic leukaemia: a non-inferiority, randomised phase 3 trial. *Lancet Oncol*. 2018;19:871-879.
75. Tsimberidou AM, Estey E, Kantarjian H, Keating MJ, Pierce S, Garcia-Manero G. Granulocyte colony stimulating factor administration associated with cerebral hemorrhage in acute promyelocytic leukemia. *Leukemia*. 2006;20:1452-1453.
76. Chamoun K, Kantarjian HM, Wang X, et al. Unrecognized fluid overload during induction therapy increases morbidity in patients with acute promyelocytic leukemia. *Cancer*. 2019;125:3219-3224.
77. Byrd JC, Ruppert AS, Mrozek K, et al. Repetitive cycles of high-dose cytarabine benefit patients with acute myeloid leukemia and inv(16)(p13q22) or t(16;16)(p13;q22): results from CALGB 8461. *J Clin Oncol*. 2004;22:1087-1094.
78. Paschka P, Du J, Schlenk RF, et al. Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML Study Group (AMLSG). *Blood*. 2013;121:170-177.
79. Sasaki K, Ravandi F, Kadia T, et al. De novo acute myeloid leukemia: a population-based study of outcome in the united states based on the Surveillance, Epidemiology, and End Results (SEER) database, 1980-2017. *Cancer*. 2021; In press.
80. Derolf A, Juliusson G, Benson L, et al. Decreasing early mortality in acute myeloid leukaemia in Sweden 1997-2014: improving performance status is a major contributing factor. *Br J Haematol*. 2020;188:187-191.
81. Bhatt VR, Shostrom V, Giri S, et al. Early mortality and overall survival of acute myeloid leukemia based on facility type. *Am J Hematol*. 2017;92:764-771.

82. Ho G, Wun T, Muffly L, et al. Decreased early mortality associated with the treatment of acute myeloid leukemia at National Cancer Institute-designated cancer centers in California. *Cancer*. 2018;124:1938-1945.
83. Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer*. 2006;106:1090-1098.
84. 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;116:4422-4429.
85. Bitterman R, Hardak E, Raines M, et al. Baseline chest computed tomography for early diagnosis of invasive pulmonary aspergillosis in hemato-oncological patients: a prospective cohort study. *Clin Infect Dis*. 2019;69:1805-1808.
86. Lang K, Earle CC, Foster T, Dixon D, Van Gool R, Menzin J. Trends in the treatment of acute myeloid leukaemia in the elderly. *Drugs Aging*. 2005;22:943-955.
87. 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;109:1114-1124.
88. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med*. 1994;331:896-903.
89. 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;31:3360-3368.
90. Park Y, Kang G, Kim D, et al. High-dose cytarabine consolidation ($\geq$1.5 g/m^2) might have shown a better outcomes than intermediate-dose cytarabine (1.0 g/m^2) combined with anthracyclines In AML patients who had achieved complete remissions in the first induction by standard 3+7 regimen. *Blood*. 2013;124.
91. Kern W, Estey EH. High-dose cytosine arabinoside in the treatment of acute myeloid leukemia: review of three randomized trials. *Cancer*. 2006;107:116-124.
92. Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. *Blood*. 1996;88:2841-2851.
93. Bishop JF, Matthews JP, Young GA, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. *Blood*. 1996;87:1710-1717.
94. Willemze R, Suciu S, Meloni G, et al. High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: results of the EORTC-GIMEMA AML-12 trial. *J Clin Oncol*. 2014;32:219-228.
95. Bassan R, Intermesoli T, Masciulli A, et al. Randomized trial comparing standard vs sequential high-dose chemotherapy for inducing early CR in adult AML. *Blood Adv*. 2019;3:1103-1117.
96. Lowenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. *N Engl J Med*. 2011;364:1027-1036.
97. Garcia-Manero G, Othus M, Pagel JM, et al. Standard versus high-dose cytarabine with or without vorinostat in acute myelogenous leukemia: results of SWOG 1203. *Leukemia*. 2021; In press.
98. Estey E, Thall P, Pierce S, et al. Randomized phase II study of fludarabine + cytosine arabinoside + idarubicin ± all-trans retinoic acid ± granulocyte colony-stimulating factor in poor prognosis newly diagnosed acute myeloid leukemia and myelodysplastic syndrome. *Blood*. 1999;93:2478-2484.
99. 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;30:3924-3931.
100. Candoni A, Papayannidis C, Martinelli G, et al. Flai (fludarabine, cytarabine, idarubicin) plus low-dose gemtuzumab ozogamicin as induction therapy in CD33-positive AML: final results and long term outcome of a phase II multicenter clinical trial. *Am J Hematol*. 2018;93:655-663.
101. Solh M, Solomon S, Morris L, et al. Improved post remission survival of non-favorable risk acute myelogenous leukemia (AML) patients following initial remission induction therapy with FLAG ± idarubicin versus 3 + 7 (anthracycline + cytarabine). *Leuk Res*. 2020;93:106318.
102. Holowiecki J, Grosicki S, Robak T, et al. Addition of cladribine to daunorubicin and cytarabine increases complete remission rate after a single course of induction treatment in acute myeloid leukemia. Multicenter, phase III study. *Leukemia*. 2004;18:989-997.
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;30:2441-2448.
104. Libura M, Giebel S, Piatkowska-Jakubas B, et al. Cladribine added to daunorubicin-cytarabine induction prolongs survival of FLT3-ITD+ normal karyotype AML patients. *Blood*. 2016;127:360-362.
105. Jabbour E, Short NJ, Ravandi F, et al. A randomized phase 2 study of idarubicin and cytarabine with clofarabine or fludarabine in patients with newly diagnosed acute myeloid leukemia. *Cancer*. 2017;123:4430-4439.
106. Devillier R, Bertoli S, Prebet T. Induction therapy for AML patients with daunorubicin dose of 60 mg/m^2 and 90 mg/m^2 results in similar complete response rate, relapse-free and overall survival. *Blood*. 2013;122:66. doi:10.1182/blood.V122.21.66.66.
107. Burnett AK, Russell NH, Hills RK, Kell J, Cavenagh J, Kjeldsen L, et al. A randomized comparison of daunorubicin 90 mg/m^2 vs 60 mg/m^2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. *Blood*. 2015;125:3878-3885.
108. A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. AML Collaborative Group. *Br J Haematol*. 1998;103:100-109.
109. Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. *J Clin Oncol*. 2010;28:808-814.
110. Gardin C, Chevret S, Pautas C, et al. Superior long-term outcome with idarubicin compared with high-dose daunorubicin in patients with acute myeloid leukemia age 50 years and older. *J Clin Oncol*. 2013;31:321-327.
111. Mandelli F, Vignetti M, Suciu S, et al. Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: the EORTC and GIMEMA Groups Study AML-10. *J Clin Oncol*. 2009;27:5397-5403.
112. Pigneux A, Harousseau JL, Witz F, et al. Addition of lomustine to idarubicin and cytarabine improves the outcome of elderly patients with de novo acute myeloid leukemia: a report from the GOELAMS. *J Clin Oncol*. 2010;28:3028-3034.
113. Lachowiez C, Konopleva M, Kadia T, et al. Interim analysis of the phase 1b/2 study of the BCL-2 inhibitor venetoclax in combination with standard intensive AML induction/consolidation therapy with FLAG-IDA in patients with newly diagnosed or relapsed/refractory AML. *Blood*. 2020;136. Abstract 332.
114. Reville PK, Kantarjian H, Borthakur G. Cladribine, idarubicin, cytarabine (ara-C), and venetoclax in treating patients with acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood*. 2020;136. Abstract 2854.
115. Willemze R, Stegman APA, Colly LP. The use of 5-aza-2'-deoxycytidine (DAC) in adult patients with acute leukaemia [abstract]. *Haematologica*. 1990;76:43.
116. Kantarjian HM, O'Brien S, Cortes J, et al. Results of decitabine (5-aza-2'deoxycytidine) therapy in 130 patients with chronic myelogenous leukemia. *Cancer*. 2003;98:522-528.
117. Issa JP, Garcia-Manero G, Giles FJ, et al. Phase 1 study of low-dose prolonged exposure schedules of the hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) in hematopoietic malignancies. *Blood*. 2004;103:1635-1640.
118. Kantarjian H, Oki Y, Garcia-Manero G, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood*. 2007;109:52-57.
119. Kantarjian H, Issa JP, Rosenfeld G, et al. Decitabine improves patient outcomes in myelodysplastic syndrome. *Cancer*. 2006;106:1794-1780.
120. 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;30:2670-2677.
121. Silverman L, Demakos E, Peterson B. Randomized controlled trial of azacitidine in patients with the myelodysplastic sundrome: a study of the Cancer AND Leukemia Group B. *J Clin Oncol*. 2002;20:2429-2440.
122. 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;126:291-299.
123. Blum W, Garzon R, Klisovic RB, et al. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proc Natl Acad Sci U S A*. 2010;107:7473-7478.
124. Savona MR, Odenike O, Amrein PC, et al. An oral fixed-dose combination of decitabine and cedazuridine in myelodysplastic syndromes: a multicentre, open-label, dose-escalation, phase 1 study. *Lancet Haematol*. 2019;6:e194-e203.
125. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. *Blood*. 2020;136:674-683.
126. Quintas-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;120:4840-4845.
127. Takahashi K, Kantarjian H, Garcia-Manero G, et al. Clofarabine plus low-dose cytarabine is as effective as and less toxic than intensive chemotherapy in elderly AML patients. *Clin Lymphoma Myeloma Leuk*. 2016;16:163-168; e1-e2.
128. 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:e411-e421.
129. 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;121:2375-2382.
130. Pan R, Hogdal LJ, Benito JM, Bucci D, Han L, Borthakur G, et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. *Cancer Discov*. 2014;4:362-375.
131. 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;6:1106-1117.
132. 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;133:7-17.
133. Wei AH, Strickland SA Jr, Hou JZ, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. *J Clin Oncol*. 2019;37:1277-1284.
134. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383:617-629.
135. 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;135:2137-2145.
136. DiNardo 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:e724-e736.
137. Kadia T, Cortes J, Konopleva M, et al. Venetoclax combined with cladribine+low dose AraC (LDAC) alternating with 5-azacytidine produces high rates of minimal residual disease (MRD) negative complete remissions (CR) in older patients with newly diagnosed acute myeloid leukemia (AML). *Blood*. 2020;136. Abstract 25.
138. Alfayez M, Kantarjian H, Ravandi F, et al. Outcomes with subsequent FLT3-inhibitor (FLT3i) based therapies in FLT3-mutated (mu) patients (pts) refractory/relapsed (R/R) to one or more prior FLT3 inhibitor based therapies: a single center experience. *Blood*. 2018;132. Abstract 663.
139. Perl AE, Altman JK, Cortes J, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1-2 study. *Lancet Oncol*. 2017;18:1061-1075.
140. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381:1728-1740.
141. Cortes JE, Kantarjian H, Foran JM, et al. Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status. *J Clin Oncol*. 2013;31:3681-3687.
142. Cortes J, Perl AE, Dohner H, et al. Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukaemia: an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2018;19:889-903.
143. Cortes JE, Tallman MS, Schiller GJ, et al. Phase 2b study of 2 dosing regimens of quizartinib monotherapy in FLT3-ITD-mutated, relapsed or refractory AML. *Blood*. 2018;132:598-607.
144. Alotaibi A, Yilmaz M, Kanagal-Shamanna R, et al. Patterns of resistance differ in patients with acute myeloid leukemia treated with type I versus type II FLT3 inhibitors. *Blood Cancer Discov*. Published online January 19, 2021. doi:10.1158/2643-3230.BCD-20-0143
145. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377:454-464.
146. Pratz K, Cherry M, Altman J, et al. A Phase 1 study of gilteritinib in combination with induction and consolidation chemotherapy in patients with newly diagnosed AML: final results. *Blood*. 2020;136. Abstract 24.
147. Xuan L, Wang Y, Huang F, et al. Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. *Lancet Oncol*. 2020;21:1201-1212.
148. Burchert A, Bug G, Fritz LV, et al. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with FLT3-internal tandem duplication mutation (SORMAIN). *J Clin Oncol*. 2020;38:2993-3002.
149. 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;93:1136-1141.
150. Choi EJ, Lee JH, Lee JH, et al. Comparison of anthracyclines used for induction chemotherapy in patients with FLT3-ITD-mutated acute myeloid leukemia. *Leuk Res*. 2018;68:51-56.
151. Amatangelo MD, Quek L, Shih A, et al. Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response. *Blood*. 2017;130:732-741.
152. Stein E, DiNardo C, Pollyea D, et al. Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130:722-731.
153. 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;378:2386-2398.
154. Choe S, Wang H, DiNardo CD, et al. Molecular mechanisms mediating relapse following ivosidenib monotherapy in IDH1-mutant relapsed or refractory AML. *Blood Adv*. 2020;4:1894-1905.
155. DiNardo C, Schuh A, Stein E. Enasidenib plus azacitidine significantly improves complete remission and overall response compared with azacitidine alone in patients with newly diagnosed acute myeloid leukemia (AML) with isocitrate dehydrogenase 2 (IDH2) mutations: interim phase II results from an ongoing, randomized study. *Blood*. 2019;134. Abstract 643.
156. Stein EM, DiNardo CD, Fathi AT, et al. Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: a phase 1 study. *Blood*. Published online October 5, 2020. doi:10.1182/blood.2020007233
157. Watts JM, Baer MR, Yang J, et al. Phase 1 study of the IDH1m inhibitor FT-2102 as a single agent in patients with IDH1m acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). *J Clin Oncol*. 2018;36.
158. Watts JM, Baer MR, Yang Y, et al. Olutasidenib (FT-2102), an IDH1m inhibitor as a single agent or in combination with azacitidine, induces deep clinical responses with mutation clearance in patients with acute myeloid leukemia treated in a phase 1 dose escalation and expansion study. *Blood*. 2019;134 (Suppl 1):231. doi:10.1182/blood-2019-123920.
159. Feldman EJ, Lancet JE, Kolitz JE, et al. First-in-man study of CPX-351: a liposomal carrier containing cytarabine and daunorubicin in a fixed 5:1 molar ratio for the treatment of relapsed and refractory acute myeloid leukemia. *J Clin Oncol*. 2011;29:979-985.

160. Lancet JE, Cortes JE, Hogge DE, et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. *Blood*. 2014;123:3239-3246.
161. 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;36:2684-2692.
162. Jamieson CH, Martinelli G, Papayannidis C, et al. Hedgehog pathway inhibitors: a new therapeutic class for the treatment of acute myeloid leukemia. *Blood Cancer Discov*. 2020;1:134-145.
163. 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;33:379-389.
164. Norsworthy KJ, By K, Subramaniam S, et al. FDA approval summary: glasdegib for newly diagnosed acute myeloid leukemia. *Clin Cancer Res*. 2019;25:6021-6025.
165. Lehmann S, Bykov VJ, Ali D, et al. Targeting p53 in vivo: a first-in-human study with p53-targeting compound APR-246 in refractory hematologic malignancies and prostate cancer. *J Clin Oncol*. 2012;30:3633-3639.
166. Sallman D, DeZern AE, Garcia-Manero G, 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. Abstract 676.
167. 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 Myelodysplasies (GFM) A. European Hematology Association abstract S181. Abstract presented at: European Hematology Association; June 2020; Virtual Meeting.
168. Aprea Therapeutics announces results of primary endpoint from phase 3 trial of eprenetapopt in TP53 mutant myelodysplastic syndromes (MDS). Press release. Aprea Therapeutics; December 28, 2020.
169. Jaiswal S, Jamieson CH, Pang WW, et al. CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. *Cell*. 2009;138:271-285.
170. 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;138:286-299.
171. Advani R, Flinn I, Popplewell L, et al. CD47 Blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. *N Engl J Med*. 2018;379:1711-1721.
172. Sallman D, Asch A, Kambhampati S, et al. The first-in-class anti-CD47 antibody magrolimab in combination with azacitidine is effective in AML patients: phase 1b results. *Blood*. 2020;136. Abstract 330.
173. Wei A, Dohner H, Pocock C, et al. Oral azacitidine maintenance therapy with CC-486 for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383:2526-2537.
174. Huls G, Chitu DA, Havelange V, et al. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. *Blood*. 2019;133:1457-1464.
175. 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;301:2349-2361.
176. Burnett AK, Wheatley K, Goldstone AH, et al. The value of allogeneic bone marrow transplant in patients with acute myeloid leukaemia at differing risk of relapse: results of the UK MRC AML 10 trial. *Br J Haematol*. 2002;118:385-400.
177. Kantarjian HM, DiNardo CD, Nogueras-Gonzalez GM, et al. Results of second salvage therapy in 673 adults with acute myelogenous leukemia treated at a single institution since 2000. *Cancer*. 2018;124:2534-2540.
178. Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood*. 2015;126:1033-1040.
179. Robinson TM, Fuchs EJ, Zhang MJ, et al. Acute Leukemia Working Party of the European Society for Blood and Marrow Transplant and the Center for International Blood and Marrow Transplant Research. Related donor transplants: has posttransplantation cyclophosphamide nullified the detrimental effect of HLA mismatch? *Blood Adv*. 2018;2:1180-1186.