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Current status and research directions in acute myeloid leukemia

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The understanding of the molecular pathobiology of acute myeloid leukemia (AML) has spurred the identification of therapeutic targets and the development of corresponding novel targeted therapies. Since 2017, twelve agents have been approved for the treatment of AML subsets: the BCL2 inhibitor venetoclax; the CD33 antibody drug conjugate gemtuzumab ozogamicin; three FLT3 inhibitors (midostaurin, gilteritinib, quizartinib); three IDH inhibitors (ivosidenib and olutasidenib targeting *IDH1* mutations; enasidenib targeting *IDH2* mutations); two oral hypomethylating agents (oral poorly absorbable azacitidine; fully absorbable decitabine-cedazuridine [latter approved as an alternative to parenteral hypomethylating agents in myelodysplastic syndrome and chronic myelomonocytic leukemia but commonly used in AML]); and CPX-351 (encapsulated liposomal 5:1 molar ratio of cytarabine and daunorubicin), and glasdegib (hedgehog inhibitor). Other targeted therapies (menin inhibitors, CD123 antibody-drug conjugates) are showing promising results. To achieve optimal results in such a rare and heterogeneous entity as AML requires expertise, familiarity with this rare cancer, and the access to, and delivery of disparate therapies under rigorous supportive care conditions. In this review, we update the standard-of-care and investigational therapies and outline promising current and future research directions.

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INTRODUCTION

A better understanding of the pathobiology of acute myeloid leukemia (AML) has accelerated the progress of translational-clinical research and therapeutic applications [1–6]. Even though the first AML therapeutic building blocks were established five decades ago, cytarabine (ara-C) and anthracyclines combined into "7 + 3" (7 days of cytarabine, 3 days of daunorubicin) is still considered the standard of care by many AML experts and in community practices [1–6]. Yet it is a poor standard of care since the long-term cure rate is 40% or less in younger patients fit for intensive chemotherapy (younger/fit), as reported in trials with strict inclusion/exclusion criteria [7]. These trials exclude "treated secondary AML" (AML progression from myelodysplastic syndrome [MDS] post treatment with hypomethylating agents [HMAs]; about 20% of AML; poor prognosis). In patients older than 60 years and fit for 7 + 3 intensive chemotherapy, the median survival is about 9 months, and the 5-year survival rate is 10% or less [8]. These figures also discount older patients unfit for intensive chemotherapy (older/unfit) because of age (>75–80 years), poor performance status, co-morbidities, or organ dysfunctions. This population may constitute 30–40% of all patients since the median age in patients with AML is 68–70 years. Before the advent of epigenetic therapies (HMA-based), older/unfit patients with AML were offered supportive care or hospice care and had a median survival of 2–6 months. Today, most older/unfit patients are offered epigenetic/lower-intensity therapies. Thus, we believe there are better regimens using intensive chemotherapy plus targeted agents for younger/fit AML, and better regimens using lower-intensity chemotherapy plus targeted agents for older/unfit AML [1–6]

The clinical, morphologic, cytogenetic, and molecular heterogeneity of AML is consequential at multiple levels. It provides prognostic information, allows the incorporation of targeted therapies, and guides the optimal therapy in many AML subsets. The latter is illustrated by the treatment of acute promyelocytic leukemia (APL) and core-binding factor (CBF) AML. In APL, the chemotherapy-free regimen of all trans-retinoic acid (ATRA) and arsenic trioxide produces cure rates of 95 + % [9–13]. In CBF AML, combining gemtuzumab ozogamicin (GO; CD33-targeted antibody-drug conjugate with a calicheamicin payload) with high-dose cytarabine based regimens increased the long-term survival rate from 50% to 75–80% [14–17].

Distinguishing the pathophysiologic-molecular entities in AML resulted in the regulatory approval of 12 novel agents since 2017, and more importantly, their rapid incorporation into highly effective regimens (Table 1). Venetoclax, a first-in-class B-cell leukemia/lymphoma 2 (BCL2) inhibitor, was approved in combination with epigenetic therapy/HMA (azacitidine and decitabine) or low-dose cytarabine for the treatment of newly diagnosed older/unfit AML, and is now being investigated as an addition to intensive chemotherapy in younger/fit AML as well as in triple-combination regimens (adding a targeted therapy such as a fms-like tyrosine kinase 3 [FLT3] or isocitrate dehydrogenase [IDH] inhibitor to the HMA-venetoclax backbone), or with the "triple-

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Table 1. Recent food and drug administration drug approvals (since 2017) in acute myeloid leukemia.

Treatment (approval date)	Description	Indication
Midostaurin (April 2017)	Multi-kinase FLT3 inhibitor	Newly diagnosed *FLT3*-mutated (as detected by FDA-approved test) AML, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
Gemtuzumab ozogamicin (September 2017)	Anti-CD33 antibody drug conjugate	Adults with newly diagnosed CD33-positive AML; refractory-relapsed CD33-positive AML in patients ≥ 2 years of age
CPX-351 (August 2017)	Liposomal cytarabine and daunorubicin at a fixed 5:1 molar ratio	Newly diagnosed therapy-related AML, secondary AML or AML with myelodysplasia-related changes
Glasdegib (November 2018)	Hedgehog pathway inhibitor	Newly diagnosed AML aged ≥ 75 years or with comorbidities that preclude the use of intensive induction chemotherapy (in combination with low-dose cytarabine)
Venetoclax (November 2018)	BCL2 inhibitor	In combination with azacitidine or decitabine, or low-dose cytarabine in newly diagnosed AML aged ≥ 75 years or with comorbidities that preclude the use of intensive induction chemotherapy
Enasidenib (August 2017)	IDH2 inhibitor	Relapsed or refractory *IDH2*- mutated (as detected by FDA-approved test) AML
Ivosidenib (July 2018) (May 2019)	IDH1 inhibitor	1. Relapsed or refractory *IDH1*-mutated (susceptible mutation, as detected by FDA-approved test) AML. 2. First line treatment of *IDH1*-mutated AML (as detected by FDA-approved test), patients ≥ 75 years old or ineligible to receive intensive chemotherapy.
Gilteritinib (November 2018)	FLT3 inhibitor	Patients with relapsed or refractory *FLT3*-mutated AML (as detected by FDA-approved test)
CC-486 (September 2020)	Oral azacitidine hypomethylating agent (30% absorption)	Continued treatment of adult patients with AML who achieved first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and who are not able to complete intensive curative therapy
Oral decitabine-cedazuridine (July 2020)	Oral hypomethylating agent (100% absorption)	Alternative to parenteral decitabine for the treatment of adults with MDS (pretreated/untreated; denovo/secondary)
Olutasidenib (December 2022)	IDH1 inhibitor	Relapsed or refractory *IDH1*-mutated (susceptible mutation, as detected by FDA-approved test) AML.
Quizartinib (July 2023)	FLT3 inhibitor	Newly diagnosed *FLT3*-ITD mutated (as detected by FDA-approved test) AML, in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and maintenance monotherapy following consolidation chemotherapy.

nucleoside" regimen in older AML regardless of fitness for intensive chemotherapy. Three FLT3 inhibitors are now approved for different indications in *FLT3*-mutated AML: gilteritinib as a single agent for refractory-relapsed, *FLT3*-mutated AML; midostaurin and quizartinib in combination with intensive chemotherapy for frontline therapy of *FLT3*-mutated (midostaurin) or *FLT3*-internal tandem duplication (ITD)-AML (quizartinib). Sorafenib, another FLT3 and multikinase inhibitor, is approved as a kinase inhibitor for solid tumor indications (renal cell and hepatocellular carcinoma), and is used, particularly as maintenance post allogeneic hematopoietic stem cell transplantation (HSCT), in *FLT3*-ITD AML. Three IDH inhibitors are approved in *IDH*-mutated AML: ivosidenib and olutasidenib targeting *IDH1* mutations; enasidenib targeting *IDH2* mutations. Enasidenib and olutasidenib are approved as salvage single-agent therapy for refractory-relapsed disease. Ivosidenib is approved in refractory relapsed disease, but also as frontline therapy as a single-agent therapy (frail patients) or in combination with azacitidine. Investigation of combinations of the IDH inhibitors with intensive chemotherapy and with HMA-venetoclax are ongoing. Other approved agents are: (1) Gemtuzumab ozogamicin (GO); approved in 2002, withdrawn from the market in 2010, and re-approved in 2017, based on a meta-analysis of 5 randomized trials showing its significant benefit in favorable-risk and intermediate-risk AML (17) (2) A poorly absorbable oral formulation of azacitidine (300 mg orally [PO] twice daily x 14 days every month) as maintenance therapy in AML patients in complete remission (CR) who are not candidates for allogeneic hematopoietic stem cell transplantation (HSCT) [18] (3) CPX-351 (liposomal encapsulated cytarabine-daunorubicin 5:1 molar ratio) for adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes (AML-MRC) [19]; and (4) glasdegib (hedgehog inhibitor) in combination with low-dose cytarabine for newly-diagnosed AML in patients 75+ years or who have comorbidities. (5) Decitabine-cedazuridine, a highly absorbable (99% absorption) oral formulation of decitabine, is approved as an alternative to parenteral HMAs in myelodysplastic syndrome and chronic myelomonocytic leukemia (MDS, CMML), and is used commonly in AML in combinations with venetoclax ± other targeted therapies, offering a total AML oral regimen (reducing hospitalizations and clinic visits, decreasing some costs of care and improving quality of life) [20]. Promising investigational strategies (nearing community practice application) include (1) the menin inhibitors in mixed lineage leukemia (*MLL1*)-rearranged, referred later to as *KMT2A*-rearranged acute leukemia, nucleophosmin1 exon-12 gene (*NPM1)*-mutated AML and AML with HOX-A9/MEIS upregulation (could be 40–50% of all AML; "menin-like signature"?) [21, 22]; (2) CD123-targeting antibody drug conjugates (ADCs); (3) and perhaps natural killer (NK) cell immunotherapy for AML with residual measurable disease (MRD)/high-risk AML.

Comparing this AML review to ones published in 2016 and 2021 (1,2) illustrates profoundly how rapid AML research progress has been. And this rapid pace of discovery highlights a weakness in some clinical trial designs. With so many therapeutic tools, randomized trials comparing one such agent added to a standard-of-care regimen may produce positive results, but ones

Table 2. Cytogenetic-molecular entities in acute myeloid leukemia.

A) NCCN classification

NCCN	Cytogenetics	Molecular abnormalities
Better risk	-Inversion (16) or translocation (16;16) -Translocation (8;21) -Translocation (15;17)	Normal cytogenetics: *NPM1* mutation in the absence of *FLT3*-ITD; bzip in-frame *CEBPA* mutation
Intermediate risk	-Normal cytogenetics -Trisomy 8 alone -Translocation (9;11) -Other non-defined	- *NPM1*-mutated and FLT3-*ITD* mutated - NPM1-wild type and FLT3- wild type
Poor risk	-Complex (≥ 3 clonal chromosomal abnormalities) -Monosomal karyotype: -5, 5q-, 7, 7q- -11q23 – non translocation (9:11) -Inversion (3), translocations of (3;3) -Translocation (6;9) or (9;22) or (8;16)	- *TP53*-mutated - Mutation of *RUNX1, ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1*, and/or *ZRSR2* - NPM1-wildtype and *FLT3*-ITD mutated (high allelic ratio)

B) ELN classification 2022

Risk category	Genetic lesion
Favorable	t(8;21)(q22;q22); *RUNX1::RUNX1T1* inv(16)(p13.1q22); *CBFB::MYH11* Mutated *NPM1* without *FLT3*-ITD bZIP in-frame mutated *CEBPA*
Intermediate	Mutated *NPM1* with *FLT3*-ITD Wild type *NPM1* with *FLT3*-ITD t(9;11)(p21.3;q23.3); *MLLT3::KMT2A* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK::NUP214* t(v;11q23.3); *KMT2A*-rearranged t(9;22)(q34.1;q11.2); *BCR::ABL1* inversion(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *MECOM(EVI1)* -5 or del(5q); −7; −17/abnormality (17p) Complex karyotype (≥ 3), monosomal karyotype Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSF2* Mutated *TP53*

gNotes related to the NCCN and ELN Risk classification.
1) The NCCN and ELN risk classifications are applicable to younger patients with AML (age up to 60–65 years old) and in de novo AML treated with 7 + 3 regimens. Older patients with AML and patients with secondary (progression to AML from myelodysplastic syndrome, particularly if treated; or from myeloproliferative neoplasm) or therapy related AML have significantly poorer outcome within each of the NCCN or ELN risk categories (the exception being possibly APL).
2) At MD Anderson, all translocations involving 11q23 are considered adverse. Also, in updated analyses, a translocation (9;11) may be intermediate risk only in de novo younger AML (but not in older or secondary/therapy-related AML).
3) The differential effect of mutations is particularly notable in patients with diploid or intermediate risk karyotype, but not in patients with better or poor risk karyotypes.
NCCN=National Cancer Centers Network.
Adapted from National Cancer Centers Network (NCCN) Version 3.2024. Accessed June 28, 2024. https://www.nccn.org/.
ELN =European Leukemia Net. Dohner. Blood; 2022;140: 1345–1377.

that are obsolete by the time the data are reported, oftentimes 5–15 years later. We address this by proposing to use single-arm trials of biomarker-driven AML subsets, with Bayesian designs (incorporating previous knowledge) and comparisons to contemporary historical controls (propensity score matching, synthetic control groups, real-world data) until optimized regimens combining several novel agents are identified and can be compared to an acceptable standard of care [23].

In this review, we outline the patient- and leukemia-associated characteristics that lend themselves to target-focused regimens and identify novel therapeutic approaches that will likely become standards of care within the next 5 years.

CYTOGENETIC AND MOLECULAR ABNORMALITIES

While the spectrum of cytogenetic-molecular abnormalities in AML may seem complex, they are in fact relatively simple. (Table 2) The cytogenetics can be grouped in the following categories: (1) favorable cytogenetics. These include APL with the characteristic translocation 15;17 [t(15;17) (q22,q21)]; and CBF AML, with inversion 16 [inv 16(p13; q22)] or translocation 16;16 [t(16;16) (p13;q22)] and translocation 8;21 [t(8;21)(q22;q22)]; (2) intermediate cytogenetics, most commonly a diploid karyotype (about 40–50% of patients); (3) unfavorable cytogenetics with a complex karyotype, particularly with 3+ abnormalities, loss of chromosome 17p (encoding the locus for the TP53 gene), and/or translocation/inversion 3q26 (*MDS1/EVI1* complex locus on chromosome 3q26.2; MECOM rearrangement); and (4) other cytogenetic/molecular abnormalities [24–30]. The unfavorable category varies in different trials and classifications (Table 2). Also, some subsets, such as Philadelphia chromosome (Ph)-positive AML and *KMT2A*-rearranged AML may shift categories if the promising novel targeted agents (third-generation BCR::ABL1 tyrosine kinase inhibitors; menin inhibitors) combined with standard chemotherapy improve

their prognosis [31]. This happened with the addition of FLT3 inhibitors to standard intensive chemotherapy, which resulted in improved outcomes in *FLT3*-ITD AML and subsequently led to its reassignment in younger AML on intensive chemotherapy (<60 years) to the" intermediate" risk group in the most recent European LeukemiaNet (ELN) 2022, regardless of the *FLT3* allelic ratio or *NPM1* co-mutation [28]. AML with *TP53* loss (either due to a mutation or loss of chromosome 17p) or with *MECOM* rearrangement is associated with a particularly poor prognosis with standard chemotherapy [26].

Next-generation sequencing (NGS) detects recurrent somatic mutations in 90% of patients with AML [27, 32]. Frequently mutated genes (>5%) are *FLT3, NPM1, DNMT3A, IDH1, IDH2, TET2, RUNX1, TP53, NRAS, CEBPA, WT1* [30, 32–51]. The frequencies of many of these mutated genes are different in younger versus older patients (e.g., *FLT3* mutations more common in younger AML and *TP53* mutations more common in older AML) [30]. Along AML pathways of clonal dominance and shifts, the mutations show patterns of co-occurrence or mutual exclusivity, which may help optimize the future development of more rational targeting therapies and effective target-based therapeutic combinations. Molecular aberrations in AML can be prognostic (in the setting of standard intensive chemotherapy), predictive (when therapies such as venetoclax, FLT3, IDH1/2, BCR::ABL1, and menin inhibitors are combined with standard chemotherapy), and targetable (as shown with *NPM1, FLT3, IDH1/2* mutations, *BCR::ABL1* fusions and *KMT2A* rearrangements). Understanding the significance of the cytogenetic/molecular findings and acting on that knowledge is rapidly evolving and confusing at times; hence, a simplified explanation can help make practical treatment decisions (discussed later).

The predictive significance of mutations is most valuable in the subset of patients with intermediate cytogenetics (diploid or "others") [29, 52]. The presence of unfavorable cytogenetics (complex, chromosome 17p loss, *MECOM*) generally supersedes mutations. Mutations in the subset of favorable karyotypes (APL, CBF AML) may not carry an unfavorable impact (e.g., *FLT3* mutations in APL; *C-KIT, FLT3 or NRAS* mutations in CBF AML) with modern therapeutic regimens (discussed later).

A mutation of *NPM1* is considered favorable in younger patients with AML and normal karyotype [32, 33]. They respond well to high-dose cytarabine, to venetoclax-based regimens [53], to gemtuzumab ozogamicin [54] and to menin inhibitor-based combinations [35–38]. Mutations and/or deletions of the tumor suppressor gene *TP53* (located on the short arm of chromosome 17) occur in 2–20% of patients, are more common in those who are older and have secondary (following an antecedent hematologic disorder) or therapy-related disease, and are associated with complex cytogenetics (90%) and poor prognosis (except the 10–15% of cases of *TP53*-mutated AML that have the uncommon *TP53* monoallelic mutation, VAF < 20%, and diploid karyotype) [39–41]. In newly diagnosed AML, *NRAS* mutations may predict for good outcome if treated with high-dose cytarabine regimens [42, 43]. But *RAS*-pathway mutations (including *NRAS, KRAS, PTPN11, NF1*) are often clonally selected (via either mutational acquisition or clonal expansion) as a resistance mechanism in AML relapse, particularly in patients receiving low intensity therapies such as with *FLT3*-mutated AML on FLT3 inhibitor-based regimens, *IDH*-mutated AML on IDH inhibitor-based regimens, as well as after HMA-venetoclax therapy [44, 55]. Surprisingly, *BCR::ABL1* fusions occasionally appear in the relapse setting after failure of targeted therapies (especially described after therapy with FLT3 inhibitors), suggesting this fusion be tested for in relapsed disease status post targeted therapy, since such patients may respond to combination therapies containing BCR::ABL1 inhibitors [45].

Among patients with a diploid karyotype, single mutations may have different predictive values than combinations [29, 46]. For example, an *NPM1* mutation without a *FLT3* mutation is associated with a more favorable outcome. If a *FLT3*-ITD mutation is present (50% of diploid karyotype with *NPM1* mutation), historically the outcome was substantially worse, but is now improved with FLT3 inhibitors [47–50]. Other mutational interactions to be clarified in the context of modern regimens that incorporate targeted therapies include: *NPM1* and/or *FLT3*-ITD mutations co-occurring with one or more of following: *DNMT3A, WT1, RUNX1, IDH1/2*, or others.

The predictive significance of mutations is context dependent (associated mutations, AML subset, size of mutated clone, and intended therapy), and evolving as more large-scale analyses are performed. A good analogy is to consider mutations as actors in different roles and in different plays. The particular outcome of the AML/patient (play) depends on which mutations co-exist (different actors in the play or in other plays), their size or variant allelic frequency (VAF) (how big a role the actor has), and the treatment given (the creator and director/manager of the play). A few examples are illustrative. In the ELN 2022 classification, which pertains to younger/fit AML on 7 + 3 regimens, the relevant mutations are: *NPM1* without *FLT3* (favorable), bZIP in-frame mutated *CEBPA* (favorable); and *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2, TP53* (all unfavorable). This classification was not predictive of outcome in older/unfit AML on HMA-venetoclax regimens and was replaced with a proposal of a 4-gene molecular classification incorporating *NRAS, KRAS, FLT3*-ITD, *TP53*, which was confirmed independently when using HMA-venetoclax [56, 57], but not with cladribine-low dose cytarabine-venetoclax alternating with HMA-venetoclax (unpublished). In the MD Anderson studies, multivariate analyses have identified independent significant mutations after complex cytogenetics and the patient- and leukemia-associated features are considered [58–60]. In younger/fit AML, *NPM1* mutations were favorable, and *TP53* and *PTPN11* mutations were unfavorable [52, 59, 61, 62]. Once FLT3 inhibitors were added to frontline regimens and allogeneic HSCT was implemented in first CR, *FLT3* mutations were no longer unfavorable [47–50]. In older patients, mostly treated with low-intensity therapy, *NPM1* and *IDH2* mutations were favorable, and *TP53* mutations were unfavorable [60] Another example is in favorable risk AML (ELN 2022), where secondary-type mutations (*SRSF2, STAG2, ASXL1, EZH2, SF3B1, BCOR, U2AF1, ZRSR2*) occur in 15% of patients and are associated with worse CR rate (82% versus 93%; $P = 0.002$) and survival (5-year rate 48% versus 68%; $P = 0.0001$) [63].

As the dust settles and with the implementation of more effective treatment regimens incorporating venetoclax and other targeted therapies, these predictive models will also evolve. Thus, as a cautionary statement, we highlight the currently consistent adverse factors across analyses that should be considered in clinical practice: elderly age (75–80+ years); poor performance status and organ dysfunctions; complex karyotype; and *TP53* mutations (and likely also *MECOM* fusions and *PTPN11* mutation). Important and clinically relevant mutations are highlighted in Table 3.

The significance of a mutation is impacted by the size of the mutant clone [58]. In all mutations except *FLT3*, the clone size is expressed as "variant allele frequency" (VAF; the ratio of the number of copies of the variant allele/total number of copies of all alleles). In *FLT3*-mutated AML, it has been expressed historically as *FLT3* allelic ratio (AR) [28, 47, 48], which refers to the ratio of the area under the curve of *FLT3*-ITD divided by the area under the curve of FLT3-wild type using a semi-quantitative DNA fragment analysis [28]. This is confusing, and it is perhaps time to change the *FLT3*-mutated AML clone quantification to VAF, as is being applied more often in recent studies.

An inherited predisposition to leukemia may be present is as much as 10% of AML, highlighting that some mutations may be germline. Examples include Li-Fraumeni syndrome (germline *TP53* mutation) and *DDX41* mutation, among others. Germline

Table 3. Clinically relevant aberrations in acute myeloid leukemia.

Mutation	% Incidence (with diploid karyotype)	Comments
FLT3-ITD	20 (30–35)	-Intermediate risk in current era with use of frontline FLT3 inhibitors and allogeneic hematopoietic stem cell transplant (allo-HSCT) in first complete remission (CR1) -FLT3 inhibitors (quizartinib, midostaurin, gilteritinib) should be added to frontline intensive chemotherapy (IC) -*FLT3*-ITD mutated patients should considered for transplant in CR1 although emerging *FLT3*-MRD data suggests we may safely identify patients who may not need alloHSCT in CR1, but this is too early for routine practice in our opinion -Adding FLT3 inhibitors (ideally gilteritinib or quizartinib, sorafenib option as well) as post HSCT maintenance recommended -Less sensitive (short EFS, OS) to hypomethylating agents plus venetoclax (HMA-VEN). Triplets adding gilteritinib/quizartinib to HMA-VEN in frontline and salvage ongoing
FLT3-TKD	5–10	-Prognostic significance uncertain; recommend addition of type I FLT3 inhibitors like gilteritinib and midostaurin to frontline therapy -*FLT3*-TKD with concomitant *NPM1* mutations have favorable outcome; HSCT in CR1 not mandatory; could be monitored longitudinally using *NPM1* high-sensitivity PCR -Neutral sensitivity to HMA-VEN. Triplets adding Gilteritinib to HMA-VEN in frontline and salvage ongoing
NPM1	30 (40–50)	-FLT3 wild-type *NPM1*-mutated = favorable prognosis. Prognosis of *NPM1* mutation with concomitant secondary type mutations unclear (one report suggesting adverse, and another neutral impact) -Sensitive to cytarabine, gemtuzumab ozogamicin (GO), menin inhibitors. Numerous trials evaluating adding these agents to frontline IC for *NPM1*-mutated AML. -Older patient with *NPM1*-mutated AML = very sensitive to HMA-VEN with high rates of CR, MRD-, and survival. Trial evaluating addition of menin inhibitors to HMA+venetoclax
KMT2Ar	10–12%	Adverse prognosis; more common in young – decreases with age; menin inhibitors (4 in advanced development) showing encouraging activity in salvage and frontline trials of IC and of HMA-VEN + menin inhibitors, recommend prophylactic intrathecal therapy prophylaxis 2–4
CEBPA	<5	Biallelic mutations and bZIP type mutations = better prognosis (if without concomitant unfavorable mutations)
DNMT3A	20 (30–35)	Associated with *NPM1*- and *FLT3*-ITD mutations Adverse prognosis, especially with concomitant *FLT3* mutations in the setting of frontline IC but not in the setting of targeted Rx like gilteritinib
RUNX1	10	Adverse prognosis
ASXL1	10–15	Adverse prognosis
KIT	5	Incidence higher in CBF-AML; unfavorable outcome in CBF-AML with 3 + 7 based induction (? need for c-KIT inhibitors), but with FLAG-GO (overcomes adverse outcome). Benefit from addition of GO
NRAS	10–15	40–50% of inversion16 AML; no definite prognostic association. Mechanism of resistance to BCL2, IDH, and FLT3 inhibitors (especially Type I) at the time of relapse. Multiple RAS/MEK-inhibitors evaluated in clinical trials but none approved or in advance development currently.
IDH2	10–20 (20–30)	Therapy with enasidenib and high sensitivity to venetoclax based combinations. Triplets adding enasidenib to HMA-VEN in frontline and salvage ongoing
IDH1	7–10 (10–15)	Therapy with ivosidenib and sensitive to venetoclax based combinations (but not as sensitive as IDH2). Triplets adding ivosidenib to HMA-VEN in frontline and salvage ongoing
TET2	10–15	Adverse prognosis; epigenetic modulation
TP53	2–20	High incidence (70%) in complex karyotype; very adverse prognosis; limited benefit of IC among patients with allelic frequency of ≥ 40%, complex karyotype. Investigational approaches strongly considered in frontline setting

Prognostic impact of mutations mostly in the context of normal karyotype.

mutations may be suspected either by the type (e.g., *DDX41* mutation at ~50% heterozygous frequency) or when multiple cancers occur in a patient and family, or in the setting of certain genotype-phenotype associations (e.g., lifelong thrombocytopenia and a *RUNX1*, *ANRKD26* or *ETV6* mutation; recurrent infections or immunodeficiency and *GATA2* or *SAMD9* or *SAMD9L* mutations). Germline variants should be suspected when the VAF is high (>40–50%), especially if this high VAF remains stable in AML morphologic CR. The presence of a germline mutation is significant and should be evaluated because it may have therapeutic implications: ability to tolerate intensive chemotherapy in the setting of inherited bone marrow failure syndromes like Fanconi anemia or telomere biology disorders; optimal donor selection if an allogeneic HSCT is indicated; choice of therapy. For instance, in *DDX41*-mutated AML, the addition of venetoclax to chemotherapy improves outcome [64].

Translating the cytogenetic-molecular knowledge

Translation of this molecular knowledge to clinical practice currently should focus on the addition of FLT3 inhibitors in *FLT3*-mutated AML (30%); treatment of *NPM1*-mutated AML (40–50% of normal karyotype) with high-dose cytarabine, HMA-venetoclax, or menin inhibitors; addition of IDH inhibitors in *IDH1/2*-mutated AML (20%); and treatment of *KMT2A*-rearranged AML with

regimens that include menin inhibitors (Table 3). However, as with Philadelphia-like acute lymphoblastic leukemia, it is possible that a FLT3-like signature (40–50% of FLT3 wild-type AML) may emerge as clinically relevant and targetable with FLT3 inhibitors [65, 66], and that menin inhibitors may be effective in AML with HOXA9/MEIS1 signature (30–40%) [21, 22].

In addition to *FLT3*-ITD mutation, *FLT3* point mutations within the tyrosine kinase domain can occur (*FLT3*-TKD mutations, 5–7% of AML; outcome more favorable than *FLT3*-ITD mutated AML; D835 most common). Midostaurin and gilteritinib, type I FLT3 inhibitors, are active against both *FLT3*-ITD and *FLT3*-TKD mutations. Sorafenib and quizartinib, type II FLT3 inhibitors, only target *FLT3-ITD*. Combinations of HMAs with venetoclax or enasidenib are effective in *IDH2*-mutated AML, although only HMA+venetoclax regimens confirmed a survival advantage in a randomized study [67, 68]. Combinations of HMAs with ivosidenib may be more effective than with venetoclax in *IDH1*-mutated AML [69, 70]. Building on these combinations, triple-drug regimens incorporating HMA-venetoclax with either FLT3 inhibitors or IDH1/2 inhibitors are showing positive results [71–73]. While associated with higher CR rates and MRD negative rates, they are also more myelosuppressive and require refining the dose schedules (such as shorter venetoclax durations based on induction Day 14 marrow results), and adjusting the doses and schedules of all agents, especially FLT3 inhibitors.

In CBF AML, mutations in *c-KIT* have been associated with worse outcome with 7 + 3 regimens [74], but this has not been the case with the fludarabine-cytarabine-GO-based regimens [14, 15]. It may be useful to investigate the addition of a c-KIT inhibitor (avapritinib, dasatinib) to chemotherapy as would be the use of sorafenib [75–77]. *FLT3* mutations are common in APL (40%) and in CBF AML, and are associated with leukocytosis at presentation, but FLT3 inhibitors have not been shown to be of benefit in these two subsets.

KMT2A-rearranged AML is historically associated with a poor outcome, a high incidence of disseminated intravascular coagulopathy (DIC) and bleeding in active disease and during induction, and high incidence of central nervous system (CNS) and extramedullary involvement [78, 79]. As noted above, its outcome may improve significantly with the use of combination therapies that incorporate menin inhibitors in frontline and salvage therapy. Current menin inhibitors under investigation include revumenib (Syndax), ziftomenib (Kura), bleximenib (JNJ-75276617; Johnson and Johnson), and enzomenib (Sumitomo) [35–38].

MEASURABLE RESIDUAL DISEASE IN COMPLETE MORPHOLOGIC REMISSION

Detectable MRD in AML in morphologic CR is associated with a high relapse rate and poor survival. Methodologies used to measure MRD include: (1) multicolor flow cytometry (MFC-MRD; sensitivity 10^{-4}); (2) reverse-transcriptase quantitative polymerase-chain reaction (RTq-PCR) assay (when optimized, sensitivity 10^{-5}); (3) standard next-generation sequencing (NGS) panels which have variable sensitivity (usually only 1%); and (4) ultrasensitive error-corrected and mutation-specific PCR-NGS assays [80–96]. PCR is routinely used for quantitative monitoring of AML-defining translocations and mutations in APL, CBF AML, and *NPM1*-mutated and *FLT3*-mutated disease. In APL, PCR quantification of promyelocytic leukemia-retinoic acid receptor alpha (*PML-RARα*) may detect early molecular relapse [87]. The cytogenetic abnormalities inversion 16 and t (16;16) result in the formation of the CBF beta/myosin heavy chain 11 (*CBFB/MYH11*) fusion gene. The t (8;21) involves the fusion of the runt-related transcription factor 1 (RUNX1) and the runt-related transcription factor 1; translocated to 1(RUNX1T1). This creates the *RUNX1/RUNX1T1* fusion gene. Detection of MRD by quantitative PCR in the form of molecular fusion genes in CBF AML (especially inversion 16) predicts for relapse [88, 89].

In other subsets of AML, MFC-MRD positive status in CR is associated with a high relapse rate (80%). However, MFC-MRD negative status is not very reassuring, since it is still associated with a relapse rate of 30–40%, even though it is often cited as a justification to avoid allogeneic HSCT in first CR. Monitoring mutational MRD by high-sensitivity RTq-PCR or error-corrected mutation-specific PCR-NGS assays (in *NPM1*-mutated and *FLT3*-mutated AML) is more informative and predictive. Molecular monitoring or *NPM1* MRD in *NPM1*-mutated AML using RTq-PCR assay (sensitivity 10^{-4}) was highly predictive for the risk of relapse and probability of long-term survival. (83) [97] Similarly persistence of *NPM1* or *FLT3*-ITD mutations pre-HSCT using targeted error-coded NGS (10^{-4}) was associated with increased relapse and worse survival among patients undergoing HSCT in first CR [96]. Recent data suggests that patients achieving *NPM1* MRD clearance by RT-qPCR (10^{-5}) after 2 courses of intensive induction chemotherapy may not benefit from HSCT in CR1 (3-year OS 79% vs 82%). Even when the analysis was restricted to *NPM1*-mutated patients with coexisting *FLT3*-ITD HSCT in first CR did not improve OS in patients with *NPM1* RT-qPCR MRD clearance after two courses of intensive chemotherapy [95]. Patients with *FLT3*-ITD, AML and error-corrected ultra-sensitivity PCR-NGS (10^{-6}) MRD negativity immediately pre- or post-allogeneic HSCT (peri-transplant MRD) may not benefit from post-transplant maintenance with FLT3 inhibitors such as gilteritinib [98]. Similar ultra-sensitive novel PCR-NGS assays for *NPM1* mutations are now available. Importantly, the commonly available routine non-ultra-sensitive NGS molecular panels used at diagnosis to identify and monitor mutations on therapy have a low sensitivity (1–2%) and should not be relied upon for MRD assessment for decisions concerning allogeneic HSCT or maintenance therapy (also the challenge of discriminating residual clonal hematopoiesis versus residual AML MRD), although studies have shown that persistence of mutations detected by these panels at the time of CR is associated with a higher likelihood of relapse. Combining MFC and novel molecular MRD assays (RT-qPCR or ultra-sensitive PCR-NGS) may further improve the ability to predict relapse [80]. The significance of persistent DTA mutations (*DNMT3A, TET2, ASXL1*; i.e., mutations often associated with clonal hematopoiesis) in CR has been debated, with some suggesting persistence did not predict for relapse, and others concluding it did [80, 95].

With detection of MRD in CR comes the need to consider options for therapeutic intervention. In APL, treatment at detection of molecular relapse improved outcomes compared with intervention at hematologic relapse [87]. In CBF AML, allogeneic HSCT for persistent MRD improved survival. (82) Important interventions in MRD-positive AML may include allogeneic HSCT; regimens with intensive chemotherapy or HMAs/low-dose cytarabine (plus venetoclax and/or applicable targeted therapies [FLT3 or IDH inhibitors]); antibody therapies (e.g., CD123 or CD33 antibody-drug conjugates [ADCs]); and immune therapies (e.g., NK cellular therapy).

TREATMENT OF AML

Subsets of AML require thoughtful selection of treatments. Figure 1A, B shows the outcomes in de novo AML (excluding APL and CBF AML) at MD Anderson from 1980 to 2023 by age among patients treated on protocol therapies. There has been a steady improvement in survival over the decades, more noticeably so in younger patients and in the last decade. Figure 1C, D shows the oucomes of patients treated on protocol or off protocol therapies, demonstrating slightly inferior overall outcomes. Off protocol therapy may be due to various reasons including the patient's request, socioeconomic reasons, distant geographies from MD Anderson requiring continuation of therapy closer to home, insurance issues and networks, organ dysfunction (cardiac, pulmonary, hepatic, renal), and others.

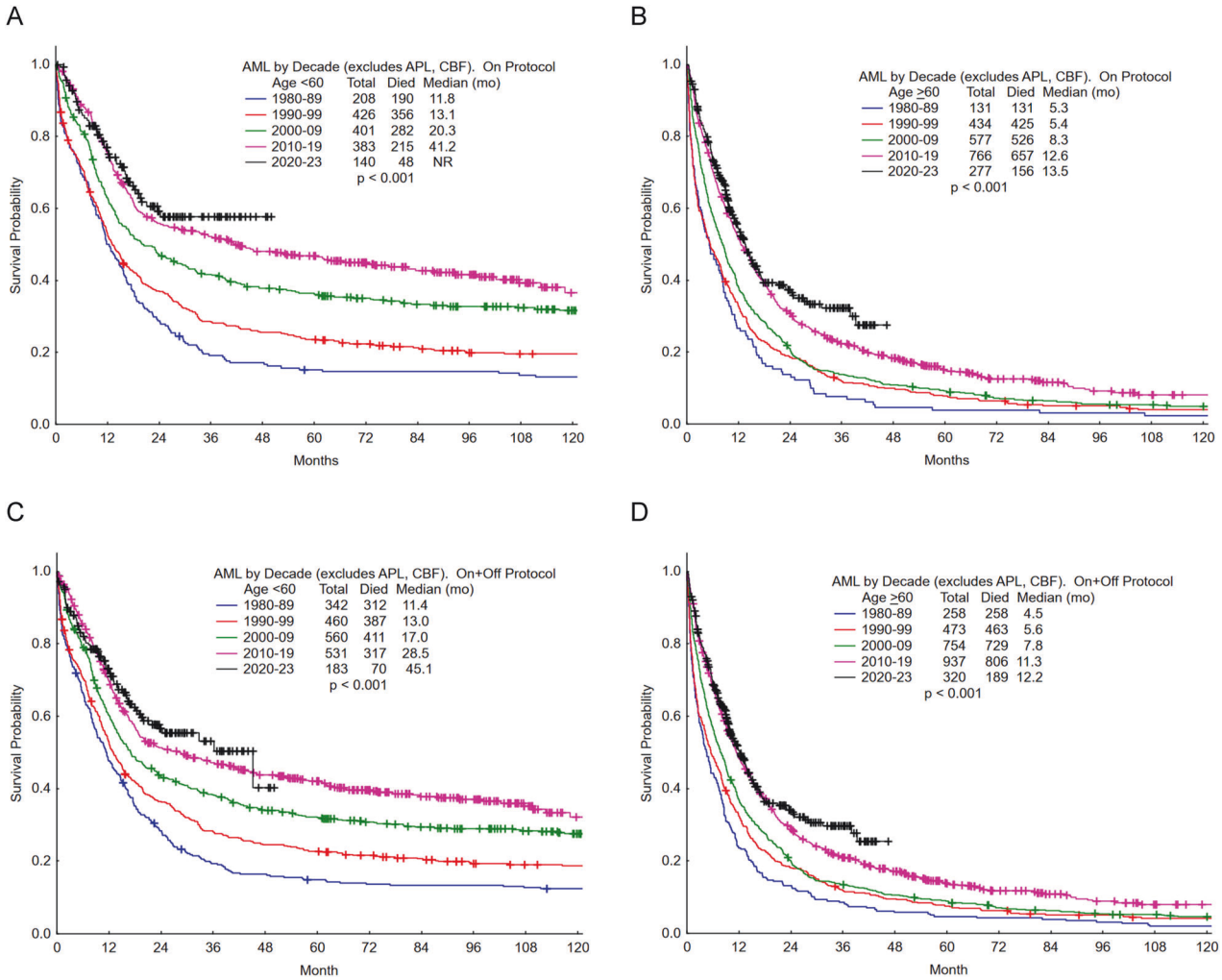

Fig. 1 Survival of de novo acute myeloid leukemia at MD Anderson (1980–2023) on protocol therapies by age and treatment era. A Age <60 years; **B** age 60+ years. Survival of patients on- and off-protocol therapies: **C** age <60 years; **D** age 60+ years. Reasons for off protocol vary: patient choice, socioeconomic reasons, geography, insurance.

Next we detail therapeutic strategies: (1) regimens for the highly curable leukemias, APL and CBF AML; (2) intensive chemotherapy regimens in younger/fit AML; (3) lower-intensity regimens in older AML (whether fit or unfit for intensive chemotherapy), and perhaps even in younger/fit patient with AML features that result in low cure rates with current intensive chemotherapy; and (4) the addition of targeted therapies (venetoclax, FLT3 inhibitors, IDH inhibitors, menin inhibitors) to standard regimens.

ACUTE PROMYELOCYTIC LEUKEMIA

Acute promyelocytic leukemia comprises about 5–10% of AML. It is defined by the cytogenetic abnormality t (15;17), which results in the *PML-RARa* fusion oncogene and its encoded oncoprotein. The PML-RARa oncoprotein acts as a dominant negative inhibitor of wild-type *RARa*, causing a maturation block and the clinical-pathologic picture of APL.

In the 1970s, treatment with anthracyclines alone or in combination with cytarabine resulted in a cure rate of 30–40% [99, 100]. The early mortality from DIC and bleeding was significant, 10–20%. The most potent anti-APL drugs today are arsenic trioxide, followed by ATRA, GO, and anthracyclines [101–103]. High-dose cytarabine and maintenance chemotherapy (POMP) have modest anti-APL efficacy [99, 100].

Based on their single-agent efficacies in APL, ATRA and arsenic trioxide [102, 103] were first combined with standard chemotherapy in induction and consolidation, demonstrating improvements in overall survival (OS) and event-free survival (EFS) [104, 105]. In the late 1990s, the combination of ATRA and idarubicin (AIDA regimen) or other anthracyclines was declared a new standard of care [105].

Chemotherapy-free regimen: ATRA and arsenic trioxide

The non-chemotherapy regimen of ATRA, arsenic trioxide and GO was first investigated in 2001 at MD Anderson and reported to be highly effective [9, 11]. It was subsequently confirmed to be more effective than AIDA or other standard regimens in both high- and low-risk APL in randomized trials in Italy/Germany, England, the US, and in databases in France and Europe [10–13, 106–109]. In long-term follow-up studies, the 10-year survival rate with ATRA-arsenic is 90 + % versus 75% with AIDA. The induction mortality, mostly from DIC-associated fatal bleeding, is now 5% or less [9–13]. Resistant disease is extremely rare, except in molecular variants (translocations between chromosome 11 and 17 [*PLZF-RARa*] or between chromosomes 5 and 17).

A general approach to induction therapy is ATRA 45 mg/m2 PO daily in 2 divided doses and arsenic trioxide 0.15 mg/kg IV daily (see capped dose below). GO is added (6–9 mg/m2) in high-risk APL, defined as a WBC > 10×10^9/L at presentation or during

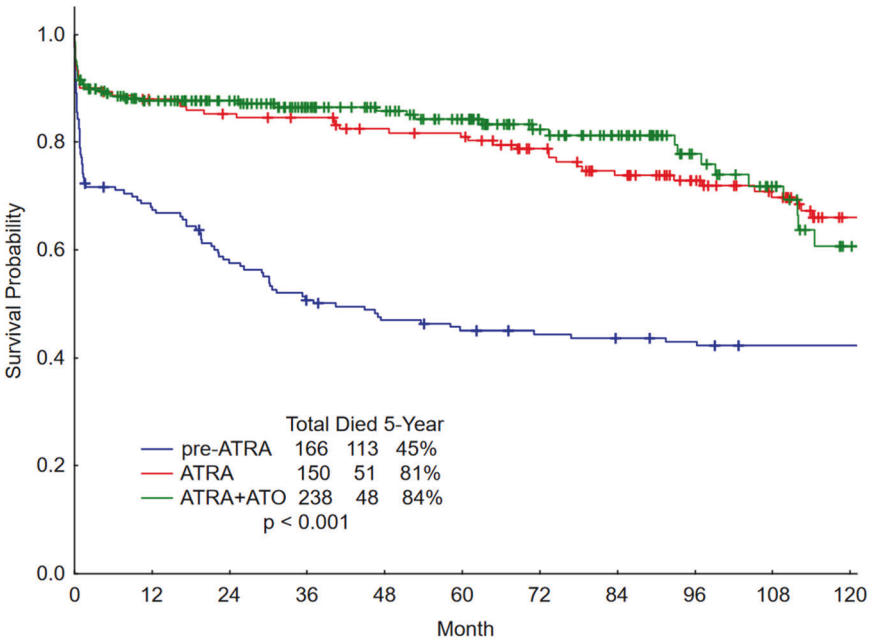

Fig. 2 Survival of acute promyelocytic leukemia at MD Anderson (1980–2023).

induction. Once in CR (usually 3–4 weeks), patients are consolidated with ATRA 2 weeks on 2 weeks off for 8 months and arsenic trioxide 5 days per week for 4 weeks (20 doses) every other month for 4 courses (80 doses; total with induction, approximately 110 doses). The GO also may be added in consolidation if PCR studies demonstrate MRD-positive disease 3+ months into CR (rare; document at least twice because of the possibility of false positivity).

There are several important considerations that help optimize therapy and improve the cure rate: (1) *Never* use granulocyte-colony stimulating factors (filgrastim, pegfilgrastim), as APL is the one leukemia that is exquisitely and dangerously sensitive to them, and their use can result in a sudden rise in blast count and fatal DIC [110] (2) Watch for fluid overload (often confused with, and exacerbated by the "differentiation syndrome") related to ATRA and arsenic trioxide (and the transfusion of high-volume blood products such as fresh frozen plasma to prevent the complication of consumptive coagulopathy). This can lead to a significant rate of pulmonary and multiorgan failure during induction and is managed with aggressive diuresis and by holding ATRA-arsenic trioxide therapy briefly (there should be no concern about APL progression 10–14 days into treatment, since resistant APL is rare) [111] (3) Watch for the development of a "differentiation syndrome" with possible respiratory symptoms/pulmonary and multi-organ failure; this is best prevented by using prophylactic steroids during induction (e.g. dexamethasone 10 mg IV daily x 14; with surveillance blood cultures, and antibacterial, antiviral, and antifungal prophylaxis). (4) CNS leukemia is rare in APL, and its risk may increase if bleeding in the brain occurs during induction. In such patients, CNS prophylaxis with the administration of two intrathecal doses of cytarabine once in marrow CR may help prevent this rare complication. (5) In some studies, arsenic trioxide 0.15 mg/kg was used without a capped daily dose. APL has been associated with obesity, at least in the US, and we identified a rare increased incidence of renal failure in morbidly obese patients who received a daily dose of 20 mg or more [112], such that we recommend capping at 15 mg daily. In India, it is given as a flat 10 mg daily dose (for economic reasons) with great success (Dr Vikram Matthews; personal communication). (6) Watch for signs of increased intracranial pressure (severe headaches, papilledema), a rare complication of ATRA therapy. This can be successfully managed by reducing the ATRA dose, giving steroids (dexamethasone, prednisone) and acetazolamide (125–250 mg PO 2–4x daily), or placing a cerebrospinal-pleural shunt (anecdotal need in severe instances). If ATRA has to be discontinued, then GO replacement therapy (3 mg/m2 every 6 weeks x 6; total 18 mg/m2) is effective. (7) Rarely, APL can present with predominant DIC thromboses rather than bleeding events. We have observed that using idarubicin or GO can abrogate immediately the thrombotic DIC (while ATRA may worsen it).

A trial from the United Kingdom investigated a different dose schedule of arsenic trioxide consisting of 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. The daily dose is higher, but the total number of doses is lower. Reviewing the data for the occurrence of renal failure may be of interest [106].

Oral formulations of arsenic trioxide appear to be as effective as intravenous (IV) arsenic trioxide but are not yet commercially available. They would render the treatment of APL more convenient, particularly during consolidation [113, 114].

Figure 2 demonstrates the significant survival improvement in APL since the introduction of ATRA-arsenic trioxide therapy. It includes patients treated on or off protocols to provide a realistic estimate of survival in APL since some patients may encounter early DIC related issues and mortality and may not end up on protocol therapies. Also, in the longer term follow up, some patients may die from causes other than APL (older age, second cancers, other medical conditions).

CORE BINDING FACTOR ACUTE MYELOID LEUKEMIA

The CBF AMLs constitute about 10–15% of adult AML and 20–30% of childhood AML. The two subsets are inversion 16/ t (16;16) and t (8; 21). Inversion 16 AML is associated with eosinophilia; t (8;21) AML often expresses CD19.

Standard chemotherapy regimens with high dose-cytarabine during induction-consolidation and the addition of GO have improved the cure rate in CBF AML from <50% to 75 + % [13–17]. The cure rate increased from 30–40% with one high-dose cytarabine consolidation to 50 + % with 3–4 consolidations [115]. Induction-consolidation combinations with high-dose

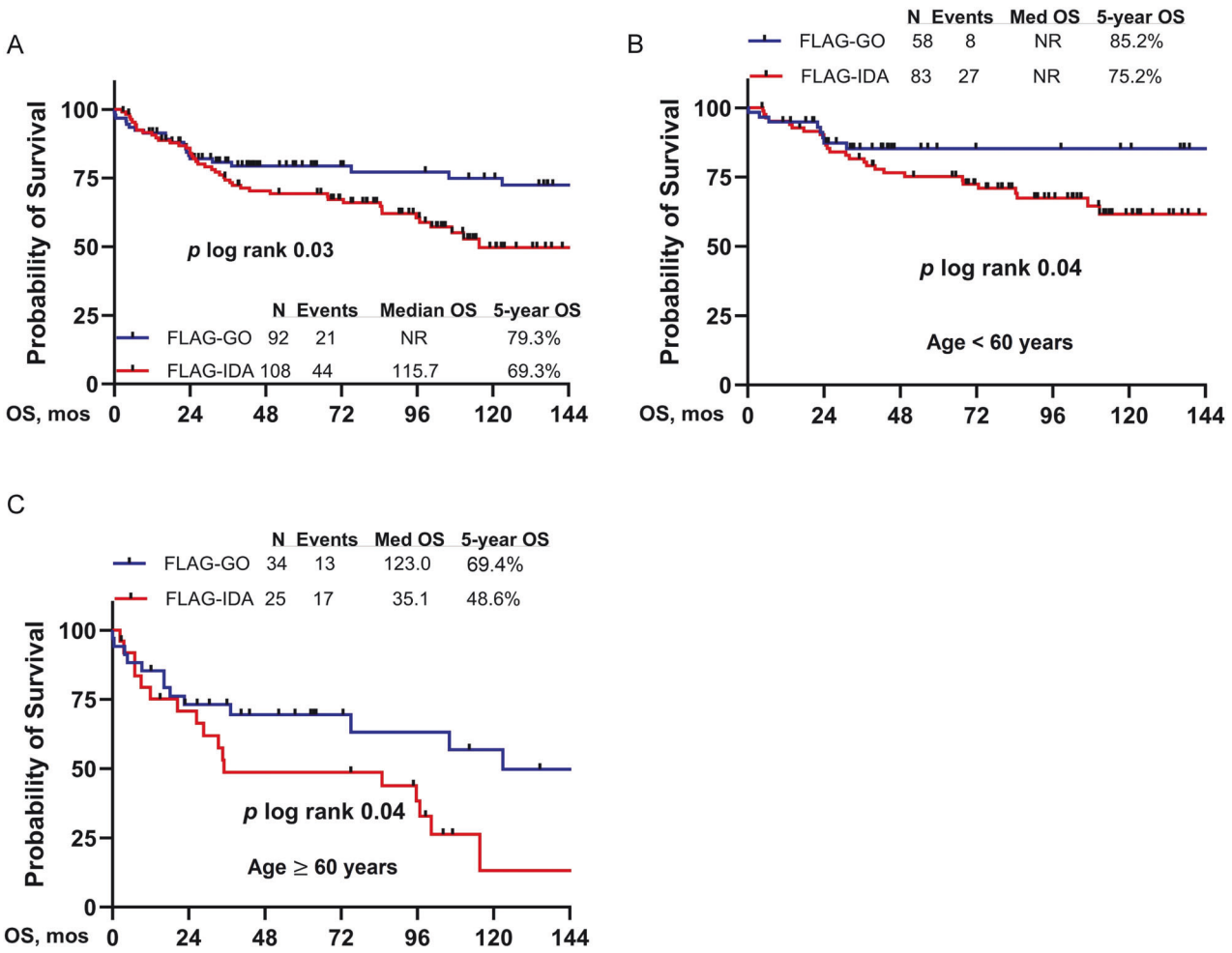

Fig. 3 Survival of core-binding factor acute myeloid leukemia at MD Anderson with FLAG-GO versus FLAG-IDA. A Overall; **B** age <60 years; **C** age 60+ years.

cytarabine and fludarabine and idarubicin, and with the addition of GO 3 mg/m^2 x 1 during induction-consolidation (SWOG and MRC studies), resulted in 5-year survival rates of 75 + % [13–17]. At MD Anderson, we use fludarabine, high-dose cytarabine and GO (i.e., FLAG-GO) during induction and consolidations, for up to 7 courses (3 with GO 3 mg/m^2). The results were better when GO replaced idarubicin. The FLAG-GO regimen resulted in a 5-year survival rate of 80%. (Fig. 3) [3, 15]. The MRC trials using fludarabine, high-dose cytarabine and idarubicin (FLAG-IDA) +/- GO reported similar long-term survival rates [16]. A meta-analysis of 5 studies randomizing patients to standard chemotherapy ±GO reported the addition of GO improved the 5-year survival rate from 50 to 75% [17].

Mutations in *FLT3* (15–20%), *c-KIT* (29–30%), *NRAS* (15–20%), *ASXL2* (15%), *ASXL1* (11%), *TET2* (7%) and others are common in AML; their prognostic significance depends on the treatment used. Some studies using 7 + 3 regimens have reported worse outcomes with *C-KIT* or multiple mutations [74, 116]. A recent Harmony database from Europe included 520 annotated cases with t (8;21) treated mostly with 7 + 3 (only 13% received GO). It reported a CR rate of 94% and a 5-year survival rate of 63%. A multivariate analysis identified a high *c-KIT* VAF (25 + %), *FLT3*-ITD and *TET2* mutations to be associated with worse survival [117]. This was not the case with the FLAG-GO [14, 15]. Older patients with CBF AML are treated with adjusted-dose FLAG-GO. Patients who cannot tolerate FLAG-GO, or who have persistent molecular MRD positivity, may be offered HMA therapy (decitabine, azacitidine) and venetoclax/GO, with the treatment duration of 12+ months (tailored to MRD results). Though the data are scant, targeted therapies may also be considered (avapritinib, novel c-KIT inhibitors, or dasatinib for *c-KIT* mutations; FLT3 inhibitors for *FLT3* mutations) [75, 76].

YOUNGER/FIT PATIENTS WITH ACUTE MYELOID LEUKEMIA (AND OLDER/FIT FOR INTENSIVE CHEMOTHERAPY)

The median age in AML is 68 years [118]. Most of the research with 7 + 3 and other intensive chemotherapy regimens was conducted in younger patients (usual upper age limit 60–65 years). Hence, the published literature may not reflect the results in the community practice (discussed later) [118].

The 7 + 3 anthracycline-cytarabine regimens; high-dose cytarabine consolidations

Since the discovery in the 1970s of the activity of cytarabine and anthracyclines in the treatment of AML, a series of randomized trials evaluated different doses and schedules of cytarabine (5 versus 7 versus 10 days; 100 mg/m^2 versus 200 mg/m^2) in combination with anthracyclines, and the addition of other agents (e.g., etoposide, lomustine, others). These established the 7 + 3 regimen (cytarabine 100–200 mg/m^2 continuous infusion daily for 7 days; daunorubicin 60 mg/m^2 intravenously [IV] daily x 3, or idarubicin 12 mg/m^2 IV daily x 3) as a standard of care that has persisted for half a century. Randomized trials of consolidation

therapies confirmed the benefit of high dose cytarabine (3 g/m^2 IV over 2–3 h twice daily x 3 days, often on Days 1, 3 and 5) [110–113]. Later studies showed cytarabine 1.5 g/m^2/dose to be as effective as 3 g/m^2/dose., investigated a daily dose x 5 days as an alternative schedule; and explored 4 versus 5 courses (4 courses shown to be as effective) [119]. Several studies also showed the benefit of allogeneic HSCT in first remission as better on average than consolidation strategies. The benefit of allogeneic HSCT appears to be highest in the intermediate-high risk AML subsets and depends on the MRD status prior to SCT.

Are there more effective intensive regimens than 7+3?

Several regimens, each discussed in more detail below, have incorporated modifications that have resulted in better outcomes than with 7 + 3: (1) High-dose cytarabine combination during induction; (2) daunorubicin (60-mg/m^2 daily x 3, versus 45 mg/m^2 or 90 mg/m^2 daily x 3; or idarubicin 12 mg/m^2 daily x 3; (3) addition of adenosine nucleoside analogs (fludarabine, clofarabine, cladribine) to cytarabine-anthracyclines; (4) addition of GO; (5) addition of the BCL-2 inhibitor venetoclax; (6) addition of FLT3 and IDH inhibitors when corresponding mutations are present; and 7) maintenance therapy with oral azacitidine.

High-dose cytarabine induction

High-dose cytarabine consolidation is an established standard of care [119–122]. Several studies evaluated high-dose cytarabine during induction. A SWOG trial in patients <65 years old compared standard-dose cytarabine (200 mg/m^2 daily x 7) to high-dose cytarabine (2 g/m^2 every 12 h x 12) during induction (both with daunorubicin) showed a higher 4-year relapse-free survival (RFS) rate with high-dose cytarabine in patients <50 years old (RFS rate 33% versus 21%) and in patients 50–64 years old (RFS rate 21% versus 9%; $p = 0.049$) [121]. An Australian study in patients 60 years and younger comparing high-dose cytarabine (3 g/m^2 every 12 h x 8) to standard-dose cytarabine (both with daunorubicin and etoposide induction) reported high-dose cytarabine to significantly improve the CR duration (median 45 versus 12 months; $p = 0.0004$) and 5-year RFS rate (49% versus 24%). (122) A meta-analysis of 3 trials comparing induction with high-dose versus standard-dose cytarabine reported high-dose cytarabine to improve the 4-year rates of RFS ($p = 0.03$), survival ($p = 0.0005$) and EFS ($p < 0.0001$) [123].

The EORTC-GIMEMA group randomized 1,942 younger patients (≤60 years) to receive daunorubicin plus etoposide and either high-dose cytarabine (3 g/m^2 every 12 h x 8) or standard-dose cytarabine (100 mg/m^2 daily x 10). They reported that in patients 15–45 years, high-dose cytarabine was associated with higher rates of CR (82% versus 76%; $p = 0.01$), 6-year EFS (44% versus 35%; $p = 0.003$), and 6-year survival (52% versus 43%; $p = 0.009$). In patients 45–60 years, high-dose cytarabine also resulted in significantly better CR and 6-year EFS rates, and a trend for better survival among patients with *FLT3*-ITD AML or poor prognosis karyotypes [124].

An Italian study randomized 574 patients (median age 52 years; range 16 to 73 years) to idarubicin-cytarabine-etoposide (ICE) or sequential idarubicin and high-dose cytarabine (2-weekly 3-day blocks of cytarabine 2 g/m^2 twice daily x 2 days plus idarubicin). The latter induction resulted in a higher CR rate post Course 1 (81% versus 69%; p = 0.02), and a better 5-year survival (49% versus 39%; $p = 0.045$) and RFS rates (48% versus 36%; $p = 0.028$) [125].

In a study by Lowenberg and colleagues comparing induction therapy with high-dose cytarabine (1 g/m^2 every 12 h x 10) versus standard-dose cytarabine (both with idarubicin), the outcomes were similar, possibly because both groups received high-dose cytarabine in Course 2 of the induction [126].

The SWOG-1203 trial randomized patients to: (1) 7 + 3 induction followed by four consolidations with high-dose cytarabine (3 g/m^2 twice daily on Days 1, 3, and 5—total consolidation cytarabine 18 g/m^2/course x 4 = 72 g/m^2); (2) idarubicin plus continuous high-dose cytarabine (1.5 g/m^2 continuous infusion daily x 4; total 6 g/m^2; IA) followed by IA consolidations with cytarabine 0.75 g/m^2 continuous infusion daily x 3 days (2.25 g/m^2/course) for 4 cycles (total cytarabine 16 g/m^2); (3) IA + vorinostat [127] The latter two arms, presumably testing the benefit of high-dose cytarabine induction, had lower total doses of cytarabine than in the 7 + 3 regimen. Hence, not surprisingly, the 7 + 3 regimen produced better outcomes in CBF AML. The results of 7 + 3 and the IA arms were similar in AML with intermediate or adverse karyotypes, despite the lower total cytarabine dose in IA. The trial design impeded the ability to assess the benefit of high-dose cytarabine during induction.

Addition of nucleoside analogs

Preclinical studies by Plunkett and colleagues at MD Anderson led to the development of the regimen combining fludarabine, high-dose cytarabine and idarubicin (FLAG-IDA or FAI) [128–130]. The MRC AML 15 trial randomized younger patients to FLAG-IDA or 7 + 3 (with or without etoposide). This FLAG-IDA regimen used cytarabine 2 g/m^2 daily for 5 days, fludarabine 30 mg/m^2 daily for 5 days, and idarubicin 8–10 mg/m^2 daily for 3 days. Among patients who completed four courses on FLAG-IDA (2 FLAG-IDA + 2 high-dose cytarabine), the 8-year survival rate was 66% versus 47% in the 7 + 3 arm [119]. FLAG-IDA/FAI is an intensive, difficult to deliver regimen due to myelosuppression-associated side effects, but worth considering in view of a 20% advantage in the 8-year survival rate. It may be most effectively administered at specialized leukemia centers using triple antibiotic prophylaxis (anti-bacterial, anti-fungal, anti-viral) and providing the infrastructure to offer comprehensive supportive care with timely transfusion support, management of toxicities and rapid and aggressive treatment of infections/sepsis and other complications.

Even after 30+ years of investigations, the optimal high-dose cytarabine dose-schedule is still being debated. High-dose cytarabine 1.5–2 g/m^2 may be as effective and less toxic than the original proposed dose of 3 g/m^2 [119, 131]. The ongoing MD Anderson trials use 1.5–2 g/m^2 daily x 5 (total 7.5- 10 g/m^2 per course) during induction and consolidations.

Other adenosine nucleoside analogs (clofarabine, cladribine) also have been explored in combinations with standard chemotherapy. In two randomized trials, Polish investigators reported the benefit of cladribine when added to frontline 7 + 3 induction [132, 133].

In the current MD Anderson trials in younger/fit patients, we use regimens that combine idarubicin and high-dose cytarabine with adenosine nucleoside analogs (fludarabine in the FLAG-IDA regimens; cladribine in the CLIA regimens). These regimens now include venetoclax (for only 7 days during induction and 5–7 days during consolidations) in all patients without a guiding mutation, or a FLT3 inhibitors in *FLT3*-mutated AML (gilteritinib, quizartinib). Adding both venetoclax and a FLT3 inhibitor in *FLT3*-mutated patients is associated with severe myelosuppression-related complications and may increase the induction mortality. We are also exploring the potential value in the frontline setting of the IDH1/2 inhibitors in *IDH1/2*-mutated AML, and of the menin inhibitors in *KMT2A*-AML and *NPM1*-mutated AML. Patients with a FLT3-like signature may also benefit from the addition of quizartinib (or possibly other FLT3 inhibitors). Patients with a menin-like signature (or HOXA9/MEIS1 signature) may benefit from the addition of menin inhibitors.

Choice of anthracycline

Historically, daunorubicin 30–60 mg/m^2 daily x 3 was used during induction therapy. Randomized trials showed that 90 mg/m^2 daily x 3 was better than 45 mg/m^2 daily x 3 (in combination with cytarabine) [7, 8]. Daunorubicin 30–45 mg/m^2 daily x 3 may be

substandard. Comparative trials showed that daunorubicin 60 mg/m^2 daily x 3 is as effective and less toxic than 90 mg/m^2 daily x 3 [134, 135].

Several randomized trials and a meta-analysis of five trials in AML comparing idarubicin to daunorubicin suggested that idarubicin (12 mg/m^2 daily x 3) may be as effective or more effective. At MD Anderson, we use idarubicin 8–10 mg/m^2 daily x 3 in the FLAG-IDA/CLIA regimens.

Gemtuzumab ozogamicin

This CD33 antibody-drug conjugate bound to calicheamicin has had a rough journey. It initially received accelerated approval by the Food and Drug Administration (FDA) in May 2000 for first salvage therapy of older AML based on three phase 2 studies in 142 patients with relapsed AML (response rate 30%; CR rate 16%).[136]Several studies then explored lower- and fractionated-dose schedules in frontline, randomized trials (3 mg/m^2 x 1 during induction and consolidation; 3 mg/m^2 on Days 1, 4 and 7 during induction). The SWOG pivotal trial in the US [17], which randomized patients to 7 + 3 +/- GO, used a suboptimal daunorubicin dose (45 mg/m^2 daily x 3) in the GO arm, which may have contributed to the negative overall results, and the withdrawal of GO from the US market in 2010. Four other randomized trials that matured later showed a benefit with GO, either overall or in subsets [17, 119, 136–138]. A meta-analysis of these five trials (3,325 patients) showed the addition of GO reduced the risk of relapse ($p = 0.0001$), and improved the 5-year survival rate ($p = 0.01$). The benefit of GO was most pronounced in AML with favorable cytogenetics (>20% improvement in 5-year survival rate from 50 to 75%, $p = 0.0006$; and ~5% improvement in 5-year survival rate in intermediate cytogenetics, $p = 0.005$). Gemtuzumab ozogamicin 3 mg/m^2 was safer than 6 mg/m^2 and equally effective [17]. The FDA re-approved GO at the lower dose schedules in 2017. An important research question is how to integrate GO safely into regimens such as FLAG-IDA and CLIA that are more intensive than 3 + 7 and that include venetoclax or FLT3/IDH inhibitors.

The MD Anderson approach in 2024

With 12 novel therapeutic agents approved for the treatment of AML since 2017 (including oral decitabine for MDS/CMML, which also can be used as an oral alternative to parenteral HMAs in AML), the optimal frontline therapy for younger/fit AML is evolving rapidly. The 7 + 3 regimen remains an often-used standard of care, but its results in younger and older/fit AML are suboptimal. As discussed earlier, better intensive regimens have emerged as frontline and salvage regimens that incorporate high-dose cytarabine in induction and consolidations, add nucleoside analogs and lower-dose GO (induction-consolidation in CBF and intermediate-karyotype AML) [53, 139–151]. These regimens, as well as the 7 + 3 regimens, are now including targeted therapies [152–154]. The investigation of other biologic signatures may lead to the inclusion of targeted therapies in other subsets (e.g., in FLT3-like and HOXA9/MEIS1 signatures).

The current MD Anderson regimens for younger/fit patients with AML are FLAG-IDA plus venetoclax and CLIA plus venetoclax (7 days during induction; 5–7 days during consolidations). In *FLT3*-mutated AML, FLT3 inhibitors (gilteritinib, quizartinib) are used instead of venetoclax [152–154]. Whether these regimens can incorporate more than one targeted therapy (such as venetoclax with GO or a FLT3 or IDH inhibitor) remains an important research question in view of the significant complications associated with myelosuppression and potential mortality. Because we use azole anti-fungals as part of triple antibiotic prophylaxis, certain dose adjustments of targeted therapies are necessary: reduce daily dose of venetoclax from 400 mg daily to 50 mg daily with posaconazole, 100 mg daily with voriconazole, 200 mg with isavuconazole; increase the dose of venetoclax to 600 mg daily with ivosidenib combinations [155, 156]. Once in CR, patients may be offered allogeneic HSCT based on the following considerations: donor availability; patient age, performance status and co-morbidities; pretreatment AML characteristics (karyotype, mutation profile); and MRD status in CR. Generally, patients are considered for allogeneic HSCT in first CR if they have intermediate- or high-risk AML based on adverse cytogenetics, *FLT3*-ITD/other adverse mutations, or persistent MRD. Otherwise, they continue with 4 consolidation courses and are offered maintenance therapy with HMA-venetoclax or the appropriate targeted therapy regimen (e.g FLT3 inhibitors if *FLT3*-mutated; IDH1 inhibitors if *IDH1*-mutated; IDH2 inhibitor or venetoclax if *IDH2*-mutated AML) (Fig. 4). Patients 50 years or older are offered induction therapy in a hospital protected environment (laminar air-flow rooms, enhanced infection precautions, no live plants/flowers, limited visitation) to reduce induction mortality **(**Table 4**)**. In the community practice, similar isolation/protection strategies could be implemented [155, 156].

With this approach, the CR/marrow CR rate in non-selected younger/fit patients with AML is 80–90%, and the long-term survival rate is 50 + % (excluding AML post MDS treated with HMAs, or "treated secondary AML") (Fig. 1). Incorporating targeted therapies (venetoclax, FLT3 inhibitors, IDH inhibitors, GO, novel CD33 monoclonal antibodies, menin inhibitors) will hopefully further improve outcomes.

Some AML subsets remain truly resistant to current chemotherapy-based strategies: treated secondary; *TP53*-mutated; *MECOM*. These constitute a significant proportion of patients (5–25%), and they should be referred to centers that offer investigational approaches and analyzed separately. Including them in current trials of AML may mask the potential value of novel strategies.

Since the 2016 and 2021 AML reviews [1, 2], many previously investigational agents are now FDA approved and utilized as standards of care in approved indications or in combination strategies that optimize their potential benefits and cost-effectiveness. Below, we summarize the novel combined targeted therapies with intensive chemotherapy and venetoclax, FLT3 inhibitors and IDH inhibitors, as frontline therapies in younger/fit AML.

Intensive chemotherapy plus venetoclax

The MD Anderson frontline trials combining FLAG-IDA and CLIA with venetoclax (7 days during induction; 5 days during maintenance) are showing positive results compared with historical data using the same intensive regimens without venetoclax: improved OS and EFS, but on average, the results are better with allogeneic HSCT in first CR, particularly in intermediate-adverse risk groups [152–154]. In the most recent update of CLIA-venetoclax, among 95 patients treated (median age 48 years; range 18–64 years), the CR rate was 84%, the CR+CRi rate was 95%, and the MFC-MRD negativity rate was 90%. The 3-year OS rate was 82%, and induction mortality was 1%. Allogeneic HSCT was performed in first CR in 66% of patients [153]. Triple antibiotic prophylaxis, treatment in a protected environment, prompt supportive care, and the use of growth factors as indicated are important elements that reduced the morbidity/mortality related to myelosuppression-associated complications (infections, bleeding) [153]. Other investigators have also used 7 + 3 or 5 + 2 (in older/fit patients) and reported encouraging preliminary results [157, 158].

Intensive chemotherapy plus FLT3 inhibitors

The phase III RATIFY trial (CALGB 10603) randomized 717 younger patients (<60 years; median age 48 years; range 18–59 years) with newly diagnosed *FLT3*-mutated AML (*FLT3*-ITD 73%; *FLT3*-TKD 23%)to 7 + 3 +/- midostaurin [47]. The addition of midostaurin improved the CR rates (59% versus 54%; $p = 0.045$) and survival

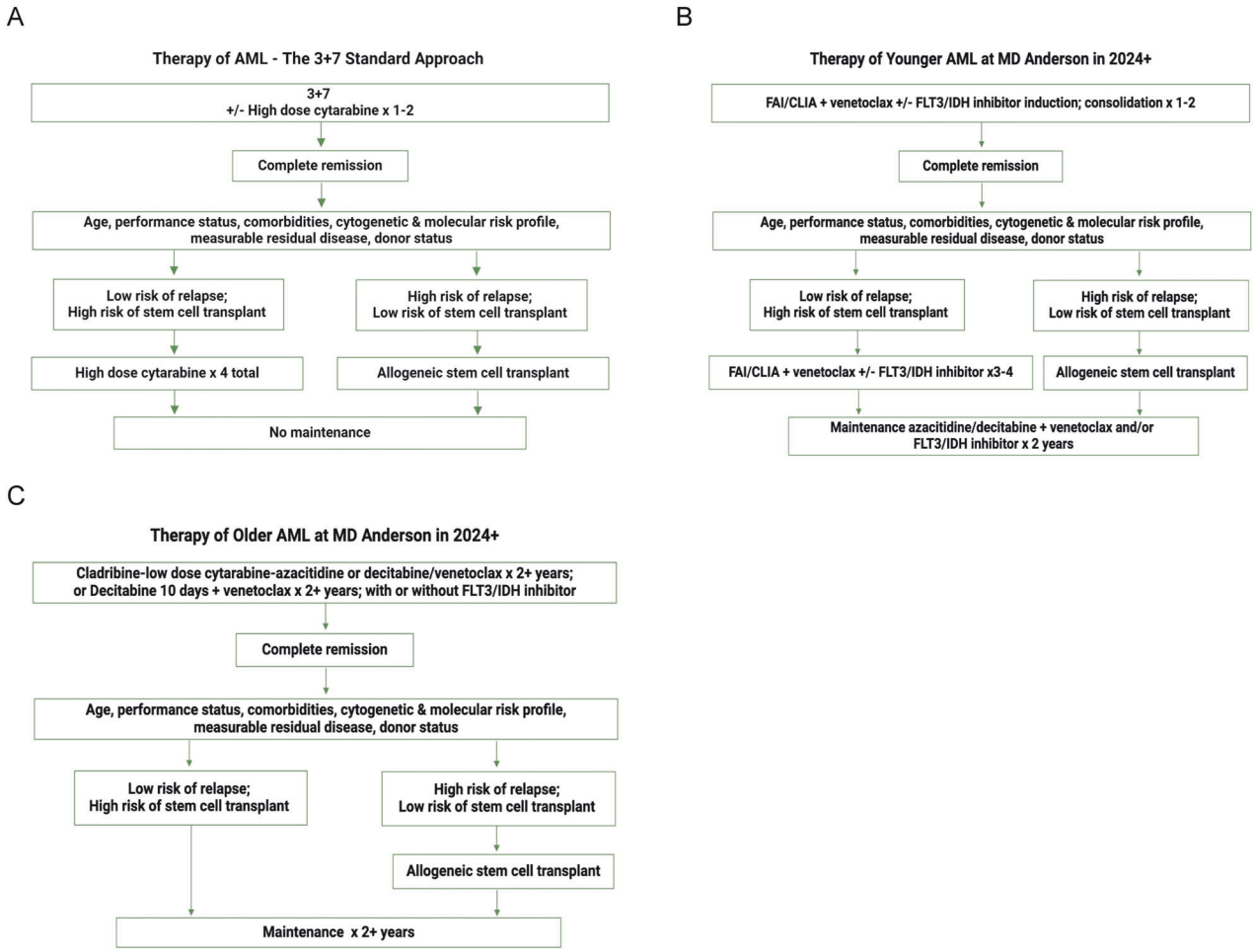

Fig. 4 Therapy of AML. A With 3+7 standard of care; **B** in younger AML at MD Anderson; **C** in older AML at MD Anderson.

(median OS 74.7 versus 25.6 months; $p = 0.009$; estimated 5-year survival rate 50% versus 42%) [47].

The QuANTUM-First phase 3 trial screened 3,468 patients, found 864 (25%) *FLT3*-ITD mutated, and randomized 539 patients (62% of eligible; 16% of total) to 7 + 3 with quizartinib or placebo. The CR rates were similar (55%). The induction mortality rate was slightly higher with quizartinib (30-day mortality 6% versus 3%; *p* not significant). The median OS was 31.9 months versus 15.1 months ($p = 0.032$; HR 0.78) (3-year OS rate 50% versus 42%). The 3-year cumulative incidence of relapse was 34% versus 45% [48].

Pratz and colleagues treated 36 patients with newly diagnosed *FLT3*-mutated AML with 7 + 3+ gilteritinib, and reported a CR rate of 83% and a 3-year OS rate of 50% (60% in patients ≤60 years) [159]. Two randomized studies of 7 + 3+gilteritinib versus 7 + 3+midostaurin are in progress in Europe and the US.

Several historical comparisons in real-world settings have also confirmed the benefits of adding FLT3 inhibitors in *FLT3*-mutated AML [6, 50].

Post allogeneic HSCT maintenance therapy with sorafenib or gilteritinib in *FLT3*-mutated AML was associated with a reduction in the relapse rate and an improvement in OS in several randomized trials, particularly among patients with PCR-NGS MRD-positive status in the period peri-HSCT [160, 161].

An important recent study randomized 284 patients (age range 18–70 years) with wild-type FLT3 (2:1) to 7 + 3 with quizartinib ($n = 180$) or placebo ($n = 93$) and reported the addition of quizartinib to improve OS: 2-year rate 63% versus 47% ($p = 0.004$) [65]. The same investigators later identified a FLT3-like genomic signature in 50% of patients who benefited from the addition of quizartinib, showing improvements is OS, RFS and EFS [66]. If the FLT3-like signature can be simplified and reproduced, and the reported results confirmed, then not only will the 25–30% of patients with *FLT3*-ITD AML benefit from quizartinib (and perhaps other FLT3 inhibitors), but up to 60–65% of patients, including those with the FLT3-like signature. Whether intensive chemotherapy + quizartinib in this "FLT3-like" population would lead to outcome benefits over and above those of intensive chemotherapy + venetoclax is an important question.

While FLT3 inhibitors have become standard of care in *FLT3*-mutated AML (usually in combinations), several non-targeted strategies have also improved the outcomes in this AML subset, such as chemotherapy regimens that include high-dose cytarabine, cladribine, high-dose daunorubicin, and GO [141, 162–164].

Intensive chemotherapy plus IDH inhibitors

Stein and colleagues treated 151 patients (median age 62 years; range 24–73 years) with de novo AML and *IDH1/2* mutations with 7 + 3 and ivosidenib (*IDH1*-mutated AML; n = 60) or enasidenib (*IDH2*-mutated AML; $n = 93$). With 7 + 3+ivosidenib, the CR rate was 70%, the overall response rate was 78%, and the 3-year OS rate was 67%. With 7 + 3+enasidenib, the CR rate was 57%, the overall response rate was 74%, and the 3-year OS rate was 61% [165]. These outcomes are impressive when considering the median age of these patients receiving intensive chemotherapy, and that > 1/3 of patients had secondary AML [165]. The HOVON and German study groups have now completed accrual on a

Table 4. General approach to patients with AML at MD Anderson in 2024.

Disease	Therapy and comments	% 5-year survival
APL	-ATRA plus arsenic trioxide -GO 3–6 mg/M^2 (usually round to 4.5- 9 mg flat dose) added for high risk APL (WBC > 10×10^9 at any time during induction) or persistent molecular disease ≥ 2–3 months into CR	>90
CBF AML	-FLAG-GO induction + 5/6 consolidations, plan 3 total doses of GO across induction and consolidation cycles, each dose 3 mg/M^2 (capped at 4.5 mg) -age ≥ 60 years: adjusted dose FLAG-GO -Intolerance to FLAG-GO: decitabine or azacitidine x 12 (according to molecular MRD) ± targeted therapies (ie. GO as tolerated) -Monitor response with real-time qPCR testing (Goal: >3-log reduction by end of cycle 3 of FLAG-GO)	80–85
AML in younger patients	-FLAG-Ida +venetoclax, CLIA + venetoclax induction + 3–4 consolidations -*FLT3*-ITD AML: add FLT3 inhibitor (quizartinib or gilteritinib on frontline clinical trials). We are currently not adding both venetoclax and FLT3inhibitors to intensive chemotherapy backbone due to the risk of severe, cumulative myelosuppression. -Future: activity of FLT3 inhibitors regardless of *FLT3*-mutated status ("FLT3-like AML?") under evaluation; IDH inhibitors + chemotherapy in *IDH1/2*-mutated AML under evaluation	50+
AML in older patients (age > 60–70 years; 8-week mortality ≥ 20–30%)	-Cladribine-low dose cytarabine- venetoclax alternating with azacytidine/ decitabine + venetoclax: the "triple-nucleoside-venetoclax regimen" - "Triplet" combinations on clinical trials (mutation specific): Decitabine/azacitidine + venetoclax + quizartinib/gilteritinib (*FLT3*-ITD and/or *FLT3*-TKD mutated) Azacitidine + venetoclax + IDH inhibitor (*IDH*1/2- mutated) Azacitidine/decitabine + venetoclax + menin inhibitors (several) in *KMT2A*-rearranged AML, *NPM1*-mutated AML, *NUP98*-rearranged AML; potentially in other "menin-like" with HOXA/MEIS1 up-regulation Azacitidine/decitabine + venetoclax + investigational agents ADCs, phase I-Other investigational agents	30+
Allogeneic HSCT	-In CR1 if poor cytogenetics, secondary/therapy-related AML, *FLT3*-ITD, adverse mutations (including secondary type mutations), MRD-positive, and low anticipated treatment-related mortality of HSCT procedure we recommend SCT in CR1 -In intermediate risk AML, excluding above mentioned, with MRD-negative CR1 after intensive chemotherapy, consider proceeding to HSCT versus maintenance with oral decitabine +/- venetoclax or +/-targeted therapy - In CR2 and beyond: all potential patients	
Salvage therapy	-CRD1 ≥ 12 months: high-dose cytarabine-based regimens with addition of VEN (FLAG-Ida-venetoclax); or addition of FLT3inhibitor, IDH1/2 inhibitor, or menin-inhibitor (if target identified) OHMA-VEN-targeted therapy triplet if suitable target identified (FLT3, IDH1/2, menin target genes) -CRD1 < 12 months: phase 1–2 trials; OR azacytidine/decitabine-venetoclax-targeted therapy triplet if suitable target identified -Always recheck for mutations (next generation sequencing), particularly for *FLT*3, *IDH1/2, KMT2A, NPM1, NUP98, other MEIS1/HOXA9* activating menin sensitive mutations; if targetable mutations/molecular aberrations, then target-based therapy	
Supportive measures	-Antibiotic/antifungal/antiviral prophylaxis for all patients -Day 21 bone marrow on HMA-VEN, breaks for count recovery, growth factor use if delayed count recovery or infections once marrow remission confirmed. Decrease venetoclax to 5–10 days or less in subsequent cycles after remission with 5–6 week cycles allowance for suitable count recovery between cycles. -Protected environment/reverse isolation if age ≥ 50 years + intensive chemotherapy, or if age ≥ 60 years + low-intensity therapy	

APL acute promyelocytic leukemia, *ATRA* all-trans retinoic acid, *GO* gemtuzumab ozogamicin, *FLAG-Ida* fludarabine, high-dose cytarabine, idarubicin, *CLIA* cladribine, high-dose cytarabine, idarubicin.

phase 3 randomized placebo-controlled trial comparing 7 + 3 with or without ivosidenib/enasidenib in younger/fit AML.

Intensive chemotherapy plus menin inhibitors

The *MLL/KMT2A*-rearranged and mutant *NPM1* AML are driven by elevated expression of *HOX* genes, which are dependent on the menin-KMT2A interaction. This aberrant gene expression can be reversed by disrupting the binding of menin to *KMT2A*. Preclinical studies confirmed the efficacy of menin inhibitors in multiple subsets: *KMT2A*-rearranged, NPM*1*-mutated, *NUP98*-fusion, and possibly HOXA9/MEIS1 signatures. Several menin inhibitors under development: revumenib (Syndax), ziftomenib (Kura), bleximenib (Johnson & Johnson), and enzomenib (Sumitomo). Single-agent phase 1–2 studies have documented the efficacy of several of the

menin inhibitors, reporting overall response rates of 40–50%. Serious side effects attributed to a differentiation syndrome (resulting in multi-organ failure and occasional deaths) have been noted with some, requiring dose interruptions/reductions, and the use of cytoreducing agents (hydroxyurea, cytarabine) and steroids. Responses with single-agent menin inhibitors are usually short, lasting 3–12 months, and resistance is often associated with the development of acquired somatic mutations in the *MEN1* gene (40% of cases detected at low levels; commonly M327 and G331) that impede the interaction of the menin inhibitor with the W346 residue (key to the binding). Investigations of combinations of menin inhibitors with chemotherapy are emerging rapidly, with exciting results. Regimens combining them with fludarabine/high-dose cytarabine, 7 + 3, and lower-intensity therapies are ongoing in AML. They are also being tested in acute lymphoblastic leukemia (ALL; with ALL-type chemotherapy) [21, 22, 36–38]. The more mature results from these studies are eagerly awaited to elucidate efficacy and durability, side-effects, mechanisms of resistance, and the ability of novel menin inhibitors to overcome the *MEN1* mutation resistance.

OLDER PATIENTS WITH ACUTE MYELOID LEUKEMIA (OR YOUNGER PATIENTS NOT FIT FOR INTENSIVE CHEMOTHERAPY)

Intensive chemotherapy

While the median age in AML is 68–70 years, most of the experience with 7 + 3 and other intensive chemotherapy regimens is in patients ≤60 years. Yet, the belief is that the results from cooperative trials, as poor as they are, are acceptable and reproducible in the community practice. For example, in the study by Lowenberg and colleagues investigating 7 + 3 with daunorubicin 45 mg/m^2 versus 90 mg/m^2 daily x 3, in 813 selected patients ≥60 years (median age 67 years), the median survival was only 7–8 months and the 3-year OS rate 20% [7]. The early mortality rate was 11–12%. At MD Anderson, intensive chemotherapy regimens used historically in older patients (60–65 years or older) resulted in CR rates of 40–50%, 4–8 week mortality of 26–36%, and median survival of 4–6 months (1-year survival <30%) [166, 167]. By multivariate analysis, factors independently associated with early mortality with intensive chemotherapy were: age 75+ years; complex karyotype (3+ chromosomal abnormalities); antecedent hematologic disorder; poor performance status (ECOG 2–4); creatinine >1.3 mg/dl; and treatment outside of a protected environment. The expected 8-week mortality was 10–19% with 0–1 adverse factors, and 36–65% with 2–5 adverse factors [166]. In the SEER 2010–2017 data, reflective of the community practice, the 4-week mortality was 24% in patients 60–69 years old and the 5-year survival was 18%. In patients 70+ years (45% of all AML), the 4-week mortality rate was 44% and the 5-year survival rate was only 4% [118] While 7 + 3 remains a standard of care, and supportive care/hospice was a common recommendation in more than 2/3 of patients before 2000, neither approach is good.

Today, older AML is likely the most difficult leukemia to treat: patients have multiple co-morbidities (cardio-pulmonary, hepatic, and renal dysfunction; hypertension; diabetes), poor performance status and intolerance to intensive chemotherapy In addition, the disease biology (high incidences of complex karyotype, *TP53* mutations, and secondary/therapy-related AML) is resistant to the current standard intensive chemotherapy. What is the solution?

Epigenetic and low-intensity therapy

In the 1990 s, lower-intensity strategies emerged as potential therapies in older/unfit AML. These included low-dose cytarabine, HMAs, and targeted therapies (monoclonal antibodies; more recently, FLT3 inhibitors and IDH 1/2 inhibitors). The question then is—What is younger/fit versus older/unfit AML? In clinical practice, oncologists often use the "oculometric approach" (evaluating the patient and deciding subjectively, based on intuition, experience, and perception of the patient's condition). At MD Anderson, we use the early-mortality risk model detailed above to select older patients who are unfit for intensive chemotherapy, and we consider an early mortality rate above 10% too high for intensive chemotherapy [59, 60]. We have also shown over time, and with the addition of venetoclax to lower-intensity therapy, that such regimens may result in equal or superior efficacy compared with intensive chemotherapy, not only in older/unfit AML, but also in older AML regardless of fitness [168, 169]. An important question for the future is whether such lower-intensity combination regimens (lower-intensity chemotherapy plus one or more targeted therapies) could replace intensive chemotherapy regimens in selected younger patients [170].

A fraction of patients who present without fever and with normal chest radiographs may have significant abnormalities on computed tomography (CT) scans (e.g., infections, fluid overload, bleeding, nodular lesions suggestive of fungal pneumonia or other pathologies) [171]. Patients with AML and either pneumonia or another pulmonary pathology at diagnosis who receive intensive chemotherapy have a higher risk of induction mortality [59]. A routine pretreatment chest CT may help deciding more objectively on the treatment approach. In addition, a pretreatment measurement of the cardiac ejection fraction (echocardiogram, cardiac scan) will assess a potential cardiac co-morbidity (low ejection fraction) that would favor lower intensity therapy over intensive chemotherapy.

Historically, older patients (age ≥70) with AML were often offered palliative or hospice care [172]. The MRC AML14 randomized trial showed that, compared with hydroxyurea/supportive care, low-dose cytarabine 20 mg subcutaneously twice daily x 10 days was associated with a higher CR rate (18% versus 1%; $p = 0.00006$) and with longer survival (odds ratio: 0.60; $p = 0.0009$) [173]. This study delivered the important message that an effective anti-AML treatment could reduce early mortality (the mixed result of both active disease and poorly tolerated chemotherapy) and prolong survival, even in patients considered historically to be only suitable for hospice/ supportive care. In 1992, we began developing the concept of epigenetic therapy in leukemia at MD Anderson, repurposing the dose schedule of decitabine in investigator-initiated studies. In the 2000s, single-arm and randomized trials with HMAs (decitabine; azacitidine [developed independently by Lewis Silverman and colleagues]) demonstrated the benefits of both in higher-risk MDS (regulatory approval) and in older/unfit AML (decitabine approved in Europe, but not in the US) [174, 175]. The phase 3 randomized trial in older AML (patients ≥65 years) of decitabine 20 mg/m^2 IV daily x 5 every month versus supportive care or low-dose cytarabine resulted in median survivals of 7.7 months versus 5 months ($p = 0.036$). This led to the European Medicines Agency (EMA) approval of decitabine for the treatment of older patients with AML [174]. The phase 3 randomized trial (AZA-AML-001) of azacitidine ($n = 241$) versus three conventional regimens ($n = 247$; low-dose cytarabine, intensive chemotherapy, supportive care) showed a longer survival with azacitidine (median 10.4 versus 6.5 months; $p = 0.06$; hazard ratio 0.85) [175].

Extended schedules of decitabine (20 mg/m^2 daily x 10) [176] are being explored, as well as combinations of HMAs with targeted therapies (venetoclax; FLT3, IDH, and menin inhibitors; CD123 antibody-drug conjugates; others) in couplets and, more recently, in triplets. A highly absorbable oral formulation of decitabine plus oral cedazuridine (cytosine deaminase inhibitor; oral combination bioequivalent to intravenous decitabine) has been approved as an alternative to parenteral HMAs therapy in MDS and CMML [20] Oral decitabine combinations with other oral targeted therapies offer the future possibility of fully oral combination therapy (e.g., oral decitabine + venetoclax+ other

oral targeted therapies) in both frontline and salvage AML. Such therapies could conceivably be delivered in the outpatient setting, improving the patient quality of life and reducing the costs associated with hospitalization and frequent clinic visits for treatment. The oral decitabine (and, perhaps soon, highly absorbable oral azacitidine) must be distinguished from the currently approved oral azacitidine (only 10–15% absorption; approval as 300 mg twice daily x 14 days, every month), which is indicated only as maintenance therapy in patients with AML in first CR who cannot undergo allogeneic HSCT or complete the full curative consolidation therapy (discussed later) [18].

Prior to the discovery of the efficacy of the HMA-venetoclax regimens in AML, MD Anderson investigators developed "triple-nucleoside" lower-intensity regimens that showed favorable efficacy and safety in older AML. The regimens combined an adenosine nucleoside analog (clofarabine or cladribine) with low-dose cytarabine, and alternated this with decitabine [177–179]. Among 248 patients treated (median age 69; range 48–85 years), the overall response rate was 66%, the early (4-week) mortality rate was 2%, the median OS was 12.5 months, and the 2-year OS was 29%. In normal-karyotype AML, the median OS was 19.9 months and the 2-year OS rate was 45% [179]. Other investigators reported the benefit of such regimens in AML frontline and salvage therapy (the latter with venetoclax) [180, 181]. Venetoclax is now added to this combination in what is referred to as the "triple-nucleosides-venetoclax" lower-intensity regimen (discussed later).

Hypomethylating agents plus venetoclax in older/unfit AML

One targeted therapeutic strategy in leukemia involves the activation of the intrinsic or mitochondrial pathway of apoptosis, regulated by the BCL2-family of proteins. This pathway involves a dynamic balance between pro-apoptotic (Bak, Bax) and anti-apoptotic proteins (BCL2, BCL-XL, MCL-1). In a balanced state, the anti-apoptotic proteins bind to, and sequester the pro-apoptotic proteins, thus preventing them from triggering apoptosis. The anti-apoptotic proteins are overexpressed in many cancers, including leukemia. Small-molecule "BH3-mimetics" were developed that could bind to the anti-apoptotic proteins in the BH3 domain and liberate pro-apoptotic proteins. The earlier generation of BH3-mimetics bound efficiently to multiple anti-apoptotic proteins but were associated with unacceptable toxicities, including thrombocytopenia.

Venetoclax (BCL2 inhibitor) was developed as a more selective BH3-mimetic that retained affinity for BCL2, but not for BCL-XL or MCL-1. It has revolutionized the treatment of chronic lymphocytic leukemia and is being explored in other tumors (ALL, MDS and CMML, lymphoma and myeloma subsets). The AML blasts and stem cells depend on BCL2 for survival, but normal hematopoietic stem cells depend on MCL-1. This presented the rationale for investigating venetoclax in AML. The preclinical studies demonstrated the anti-AML activity of venetoclax [182]. The trial of single-agent of venetoclax in refractory-relapsed AML showed only modest activity [183], but the single-arm frontline combination trials of HMA-venetoclax showed high efficacy, which led to the phase 3 randomized trials that resulted in the regulatory approval of this combination as a treatment for older/unfit AML [184–188].

The VIALE-A pivotal trial randomized (2:1) 431 older/unfit patients (≥ 75 years; or unfit for intensive chemotherapy) to azacitidine plus venetoclax ($n = 286$) or azacitidine ($n = 184$). The addition of venetoclax was associated with a significantly longer survival (median survival 14.7 versus 9.6 months; $p < 0.001$), as well as higher composite remission (CR/CRi)rate (66.4% versus 28.3%; $p < 0.001$) and CR rate (29.7% versus 17.9%; $p < 0.001$) [186]. The longer follow-up on the study reported 3-year survival rates of 25% with azacitidine/venetoclax versus 10% with azacitidine [187]. A similar randomized study (211 patients; 2:1 randomization) of low-dose cytarabine with venetoclax versus low-dose cytarabine alone showed a median survival of 8.4 versus 4.1 months ($p = 0.04$), an overall response rate of 48% versus 13% ($p < 0.001$), and a CR rate of 27% versus 7% ($p < 0.001$) [188].

A single-arm trial from our institution investigated the use of decitabine for a 10-day induction with venetoclax (followed by maintenance with monthly decitabine for 5 days and venetoclax for 14–21 days). Among 70 older patients (median age 72 years; range 70–78 years) with newly diagnosed de novo AML, the overall response rate (CR+CRi) was 84%, the CR rate 67%, the 4-week mortality 0%, and the median survival 18.1 months. It appears that, on average, decitabine 10-day regimens may not offer much better outcomes than 5-day regimens [189].

The original HMA-venetoclax trials used a continuous 28-day schedule of venetoclax, but many patients required venetoclax duration reductions to 14–21 days and often 5–6 week cycle lengths with GCSF support. Recent studies have suggested that shorter dose schedules (7–14 days) may be as effective and less toxic [190–192] This will allow for safer designs of the triplet regimens (discussed later).

Lower-intensity therapy with "triple-nucleosides" plus venetoclax

One of the current frontline trials in older (and younger unfit) AML at MD Anderson explores the triple-nucleoside combination of cladribine-cytarabine-venetoclax alternating with azacitidine (or decitabine)-venetoclax [193, 194]. Among 141 patients treated so far (median age 68 years; range 47–84 years), 103 (73%) achieved CR, and 120 (85%) achieved CR-CRi. An MRD-negative status was noted in 93 patients (78%). Two patients (1%) died within 4 weeks of induction and 4 (3%) died within 8 weeks. The 4-year survival rate was 52% overall, 79% for patients who underwent allogeneic HSCT and 42% among those who did not.

Herein a note of concern: It took more than 2 decades to establish HMAs as a reasonable approach for older/unfit AML, and a decade to move from HMA single-agent therapy to the combination of HMA-venetoclax, and to discuss the value of intensive chemotherapy versus lower-intensity therapy [195]. While the latter is a now standard of care, it is a poor one (3-year survival rate 25%). Attempts to explore the cladribine/low-dose cytarabine +/- venetoclax regimens (without combining them with HMA-venetoclax) have started. The triple-nucleoside-venetoclax regimen has not been investigated yet outside MD Anderson. We hope it will not take another decade to establish or reject it as a regimen in AML.

Doublet versus triplet regimens

Doublet combinations of HMAs and FLT3 or IDH inhibitors showed favorable results [67, 69, 196, 197]. Preclinical studies reported a synergistic efficacy of the combination of FLT3 inhibitors and venetoclax. This led to triplet regimens combining HMAs, venetoclax, and FLT3 inhibitors. Among 30 older patients (median age 71 years) with newly diagnosed *FLT3*-mutated AML, the combination of azacitidine (7 days induction; 5 days consolidation), venetoclax (14 days induction, 7 days maintenance) and gilteritinib 80 mg daily (14 days induction; 80 mg daily maintenance) resulted in a CR rate of 90%, an MRD-negativity rate of 93% in responders, and a 1.5 year survival rate of 72% [73] The regimen was myelosuppressive, requiring limiting the induction days of venetoclax-gilteritinib to 14 days, and reducing venetoclax to 7 days/cycle in maintenance, as well as adjusting the gilteritinib dose to 80 mg daily. The future challenge is to develop potentially more curative quadruplet regimens that can be delivered safely and that incorporate HMA-venetoclax with FLT3 and IDH inhibitors/menin inhibitors/CD123 antibodies/NK antibodies or NK cellular therapy. This is possible if studies continue to suggest that 7 days of venetoclax is as effective as longer-duration venetoclax schedules in such combinations.

Combinations of HMAs and IDH inhibitors have shown encouraging results in frontline older AML. While the HMA-venetoclax combination is particularly effective in *IDH2*-mutated AML, ivosidenib may be preferred over venetoclax in *IDH1*-mutated AML [69, 186, 198]. In the subset analysis of VIALE-A of *IDH2*-mutated AML (40 patients on azacitidine-venetoclax, 18 patients on azacitidine), the median OS was 27.5 months vs 13.0 months with azacitidine alone ($p < 0.05$) [68]. Comparably, the combination of azacitidine-enasidenib resulted in a median survival rate of 22 months, although no different than azacitidine alone (median OS of 22 months) in the frontline 2:1 randomized (but not blinded) trial of azacitidine-enasidenib versus azacitidine alone [67]. In the subset analysis of VIALE-A of *IDH1*-mutated AML (23 patients on azacitidine-venetoclax, 11 patients on azacitidine), long-term follow up demonstrates the median OS was only 10.2 months with venetoclax versus 2.2 months [68]. In the AGILE study, 146 patients (median age 76 years) with older/unfit *IDH1*-mutated AML were randomized (1:1) to azacitidine-ivosidenib ($n = 72$) or azacitidine ($n = 74$). The CR rate was 47% versus 15% (p< .0001). The median survival was 29 months versus 7.9 months ($p = 0.001$) [199].

Triplet regimens combining HMAs with venetoclax and IDH inhibitors are ongoing and yielding exciting results. In a study of oral decitabine, venetoclax and the appropriate IDH1/2 inhibitor, among patients with newly diagnosed *IDH*-mutated AML treated (10 *IDH1*-mutated, 14 *IDH2*-mutated), the CR rate was 90–100%, the MRD-negativity rate was 80–93%, and the 1.5-year survival rate was 75%. In such regimens, because of the interaction of ivosedenib and venetoclax (ivosidenib is a CYP inducer, reducing the venetoclax AUC) the dose of venetoclax was increased to 600 mg daily (if no azole prophylaxis) [70].

Older patients (≥65 years) and patients not fit for intensive chemotherapy (based on predicted high early mortality) should be considered for lower-intensity strategies, for example combinations of cladribine and low-dose cytarabine alternating with decitabine (favoring oral decitabine for convenience) or azacitidine, together with venetoclax; and other triplet regimens of HMAs plus venetoclax-based combinations that also incorporate FLT3 inhibitors (if *FLT3*-mutated), IDH inhibitors (if *IDH*-mutated), menin inhibitors (if *KMT2A*-rearranged or *NPM1*-mutated), and other targeted /immune investigational agents (Table 4).

Menin inhibitors—beyond single agents

In older AML with *KMT2A*-rearrangement, *NPM1* mutation and *NUP98* fusions, frontline studies are exploring the value of menin inhibitor-based combinations. In a study of oral decitabine-venetoclax with revumenib in refractory-relapsed AML with *KMT2A* rearrangement, *NPM1* mutation or *NUP98r* fusion (median 3 prior lines of therapy), all 9 patients treated achieved a response [200]. This study is now part of the frontline approaches in older AML with these abnormalities [35–38]. Another study reported on 26 patients with newly diagnosed *KMT2A*-rearranged (35%) or *NPM1*-mutated AML (65%) (median age 70 years; range 60–85 years) treated with azacitidine for 7 days every month, venetoclax daily, and revumenib 113–163 mg daily. Overall, 18/26 patients (69%) achieved CR and 23/26 (88%) achieved a composite CR. MRD-negative status in CR was documented in 22/26 (85%). The estimated 1-year OS was 62% (3 relapses; 6 deaths).(38) A third study treated 60 patients with refractory-relapsed AML (*KMT2A*-rearrangement 50%, *NPM1* mutation 50%; 2 median prior lines of therapy) with azacitidine for 7 days/month, bleximenib daily, and venetoclax daily. Among 34 patients treated with bleximenib 50+mg twice daily, 27 /34 (79%) had an overall response, and 14/34 (41%) had a CR-CRh-I [37].

CPX-351 in older AML

CPX-351 is a dual-drug liposomal encapsulation containing a fixed 5:1 molar ratio of cytarabine and daunorubicin. Based on the preclinical and phase 1–2 trials in the subset of secondary AML, a pivotal phase 3 trial in newly diagnosed secondary AML randomized 309 patients to CPX-351 or 7 + 3. Therapy with CPX351 was associated with a significantly longer survival (hazard ratio 0.69; $p = 0.005$), and with higher rates of CR (38% versus 26%; $p = 0.035$) and CR+CRi (48% versus 33%; $p = 0.016$). More patients achieving CR post CPX-351 underwent allogeneic HSCT (20% versus 12%); their survival was also longer post SCT. This resulted in the FDA approval of CPX-351 as frontline therapy for secondary AML [19]. Ongoing studies are investigating combinations of CPX-351 with venetoclax, GO, and other targeted therapies.

MAINTENANCE THERAPY IN ACUTE MYELOID LEUKEMIA

While maintenance therapy is an established approach in many cancers (including ALL), older studies did not report a benefit in AML until the recent positive trial with oral azacitidine (CC-486; poorly absorbed; AUC 10–15% of intravenous azacitidine). In QUAZAR AML-001, 472 older patients (≥55 years; median age 68 years) with AML in first CR for <4 months and not eligible for an intensive curative strategy (allogeneic HSCT; high-dose cytarabine consolidations) were randomized to oral azacitidine 300 mg orally daily x 14 every month ($n = 238$), or placebo ($n = 234$). The median survival was 24.7 months with oral azacitidine versus 14.8 months with placebo (hazard ratio 0.69; $p = 0.0009$). This resulted in its FDA approval in 2020 as maintenance therapy for this indication [18].

The HOVON97 trial randomized 116 older patients (≥ 60 years) in CR post two courses of intensive chemotherapy to azacitidine (50 mg/m^2 subcutaneously daily x 5/monthly for 12 cycles; $n = 56$) or observation ($n = 60$). The 12-month DFS rate was 64% versus 42% ($p = 0.04$) [201].

At MD Anderson, patients not eligible for allogeneic HSCT in first remission and with expected suboptimal outcome are offered maintenance therapy with HMA (usually oral decitabine) and venetoclax. In an ongoing phase 2 trial, in which we treated 25 patients with newly diagnosed AML in CR (not candidates for allogeneic HSCT) with azacitidine-venetoclax, the 2-year RFS rate was 65% [202]. Other targeted therapies are also considered as indicated by the molecular profile (FLT3, IDH1/2 and menin inhibitors at present).

Maintenance therapy post allogeneic HSCT using FLT3 inhibitors in *FLT3*-mutated AML (particularly If MRD-positive in the peri-HSCT period), or with HMA +/- venetoclax in other patients, is gaining ground. Post HSCT maintenance with other targeted therapies such as IDH and menin inhibitors, or with immune therapies such as multiple donor lymphocyte infusions or NK therapy, are being investigated.

TRANSLATING THE PUBLISHED LITERATURE INTO REAL-WORLD EXPERIENCE

The Surveillance, Epidemiology, and End Results (SEER) data give a better reflection of the results in US community practice. A SEER analysis of about 29,000 patients with AML showed that the outcomes are worse than those reported from single-institution and cooperative studies. This may be attributable to several factors such as the meticulous selection of patients on clinical trials (exclusion of patients who are older, those with treated secondary AML, or those with poor performance status and organ dysfunctions), the kind of regimens offered (standards of care versus investigational), the supportive care infrastructures, and the leukemia expertise. The SEER data does show significant improvements in patient outcome since 2000 in certain subsets: APL (5-year survival about 60+ %; incorporation of ATRA and arsenic trioxide into the APL regimens); CBF AML (5-year survival 50 + %; addition of GO and high-dose cytarabine plus monitoring for MRD by PCR); younger patients (addition of several targeted

therapies, improved supportive care measures). However, even in the newer era (2000–2017), the 4-week mortality in patients 40–59 years with de novo AML (excluding APL and CBF AML) is 27%, and the 5-year survival rate is 40%. Among patients ≥70 years, the 4-week mortality rate is 45–50%, and the 5-year survival rate is <5% [118].

Unlike the common solid tumors, AML is a relatively rare cancer. Since it involves the bone marrow, it causes severe compromise of normal hematopoiesis, myelosuppression, and life-threatening complications such as infections and bleeding. Its treatment is complex, particularly intensive in younger patients, and requires long-term expertise and familiarity with the disease and complications, as well as the availability of prompt supportive care measures. The particularities of AML require the use of triple antibiotic prophylaxis; ready access to transfusion of blood products; prompt availability of skilled emergency facilities; quick recognition of infections and sepsis in order to implement optimal broad-spectrum intravenous antibiotics; and the timely use of the intensive care unit when needed. Thus, the risks of serious morbidities, mortality and treatment abandonment are high [203].

While it has long been assumed that the care of AML can be delivered as optimally in the oncology community practices as in leukemia centers of expertise, this may not be the case for the reasons detailed above. The SEER data and several AML cooperative trials report rates of early mortality (at 4 or 8 weeks) with induction therapy that vary significantly, both in younger and older AML. Several studies have reported significantly different early mortality rates in patients treated in non-academic versus academic centers, and in non-NCI-designated versus NCI-designated cancer centers [204] In the National Cancer Database of 60,738 patients with AML, the 4-week mortality rate was 16% in academic centers and 29% in non-academic centers ($p < 0.001$); the 5-year survival rates were 25% and 15%, respectively ($p < 0.001$) [204]. A study from California in 7007 patients with AML reported an early mortality rate of 12% in NCI-designated cancer centers versus 24% in non-NCI-designated cancer centers [205]. At our institution, the early mortality with intensive chemotherapy in younger AML is less than 5%; the early mortality with low-intensity regimens in older AML is 1–2%.

Because of the circumstances outlined above (rarity, marrow compromise, intensity of care, supportive care needs, cumulative expertise), and the rapidly evolving knowledge and treatment strategies, we believe AML may be better managed in specialized leukemia centers rather than in the oncology community practice.

ALLOGENEIC AND AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

The benefit of allogeneic HSCT in AML first CR was difficult to demonstrate in earlier randomized trials because of: (1) the limited number of patients in each study (may not detect modest but significant benefits); (2) the lead-time bias to allogeneic HSCT; (3) the fact that many patients allocated to HSCT ultimately could not undergo it (due to infections, organ dysfunction, morbidities, AML relapse, etc); (4) patients allocated to chemotherapy in first CR may have benefited from undergoing the HSCT post first relapse. A meta-analysis of multiple randomized trials demonstrated, on average, a significant survival benefit in performing allogeneic HSCT in first remission [206]. A study by the MRC reported that the survival with chemotherapy versus allogeneic HSCT in first CR was similar when the benefit of a later HSCT was considered [207].

Allogeneic HSCT should be considered as an optimal option in first CR (1) in patients who do not have favorable-risk AML (exclude CBF, *NPM1*-mutated without other high-risk mutations, and other favorable risk subsets being defined over time); (2) patients with AML in morphologic CR but persistent MRD. With the availability of venetoclax, FLT3 and IDH inhibitors, and possibly other targeted therapies such as menin inhibitors, the role of allogeneic HSCT in first remission needs to be re-evaluated continuously. Additional considerations for the feasibility of HSCT are the patient age and co-morbidities, donor availability, degree of matching, center expertise/results with HSCT, and patient wishes.

Allogeneic HSCT is not a one-time self-contained procedure, but part of the continuum approach during which the physician considers chemotherapy, targeted therapy, HSCT, post HSCT maintenance. Multiple strategies are being evaluated post allogeneic HSCT to reduce the risk of relapse, including HMA-venetoclax, FLT3 and IDH inhibitors, menin inhibitors, repeated sequential DLIs, and other forms of immunotherapy.

Autologous HSCT has been largely abandoned in in AML in the US (except in APL and CBF AML in second CR) because of the lack of demonstrable benefit in randomized trials. It continues to be used in Europe as an equivalent alternative to multiple chemotherapy consolidations in first CR. A recent update of the PETHEMA Spanish data of 1300 patients with AML in first CR who underwent autologous SCT ($n = 658$ patients) or further chemotherapy ($n = 652$) showed a benefit for autologous SCT in younger patients (< 65 years) with a median OS of 153 months versus 71 months (HR 0.72; $P = 0.02$) [208]. Recognizing, based on recent deeper MRD detection measures (PCR-NGS for *NPM1* and *FLT3* mutations), that many previously infused autologous cells were contaminated with AML residual disease that might have contributed to relapse, future research may investigate autologous HSCT using MRD-negative infusions as an alternative to multiple chemotherapy consolidations-maintenance, or to allogeneic HSCT. At our institution, autologous HSCT is still considered occasionally in APL and CBF AML in second CR and with negative molecular MRD in collected stem cells.

SALVAGE THERAPY

Salvage therapies are multiple in refractory-relapsed AML, and their rates of success/cure depend on the context, including the AML type, prior therapies, prior HSCT, duration of first CR, and the definition of refractoriness.

Salvage therapy in APL (using longer durations of ATRA and arsenic trioxide ±chemotherapy or autologous HSCT) is associated with a high cure rate [209]. Cure rates may also be significant following salvage therapy in CBF-AML (fludarabine/high-dose cytarabine, GO, autologous or allogeneic HSCT) and in AML with relapse following a long first CR duration (2–3 years).

The outcome in non-APL/CBF salvage is very much context dependent. For example, patients are sometimes labeled to have refractory AML based on a Day 14–21 marrow that shows persistent disease after 7 + 3. Such patients may have residual disease that continues to respond to treatment and resolves on later marrow analyses or may respond effectively to salvage therapy and later allogeneic SCT. Patients who relapse after 2+ years of a first CR have a cure rate of 30–50% with effective salvage therapy. In contrast, patients who are resistant to frontline FLAG-IDA-venetoclax or CLIA-venetoclax, or those who relapse after 7 + 3 with a first CR duration < 6–12 months have a cure rate of 20% or less [210].

Some patients relapse with targetable clones (*FLT3*- or *IDH*-mutated AML) that may not have been addressed with prior regimens. Combinations of targeted therapies plus standard chemotherapy followed by allogeneic HSCT may also result in reasonable cure rates. It is thus essential to repeat genomic analysis at relapse, as clonal selection is common during treatment resistance, and resistant new clones may emerge that were not apparent at initial diagnosis (e.g., new *FLT3, IDH1/2*, or *BCR::ABL1* clones).

Often forgotten is the experience that the best curative therapy in AML salvage is allogeneic HSCT in active disease, when the AML burden is minimal (marrow blasts < 20%). Such a strategy may

result in a cure rate of 10–20%. But transplant experts do not like these odds, and often reject such patients for allogeneic HSCT, unless they can achieve CR/MRD-negative status (frequently almost impossible), because of the associated low cure rate/high mortality rate. And accepting such patients may tarnish the reputation of the transplantation center (and lead to its exclusion from insurance networks) [211].

The more common scenario in AML salvage is a patient who is referred with truly resistant AML following effective frontline therapy, with high-risk disease (complex karyotype, *TP53* or other adverse mutations), no targetable mutations and short first CR duration. Such patients may be considered good candidates for investigational therapies, or reasonably be offered supportive/hospice care.

Based on the above discussion, the choice of salvage therapy in AML depends on multiple factors: patient age and wishes, co-morbidities, salvage status, prior therapies, duration of prior response, exposure to allogeneic HSCT, leukemia characteristics, and availability of investigational therapies. Since AML experts and leukemia centers of expertise have different guidelines and pathways in AML salvage, we will restrict our discussion to those at MD Anderson, and address some approved therapies.

Patients in relapse are always evaluated for emerging or persistent targetable mutations or abnormalities amenable to novel therapies (FLT3, IDH1/2 or menin inhibitors). If such mutations/abnormalities are noted (*FLT3* mutations, *IDH1/2* mutations, translocation 11q32, *NPM1* mutations, *NUP98* fusion), patients are considered for investigational combinations that incorporate the corresponding targeting strategies, for example HMA-venetoclax-FLT3 inhibitors, HMA-venetoclax-IDH1/2 inhibitors, HMA-venetoclax-menin inhibitors.

In young/fit patients with AML and failure to respond to or relapse post 7 + 3 regimens, salvage therapy depends on the duration of first CR. If less than 1 year, we offer HMA-venetoclax-based regimens that incorporate an additional investigational agent (antibodies, others). If longer than 1 year, we offer intensive chemotherapy with FLAG-IDA-venetoclax or CLIA-venetoclax. Several studies, including some at MD Anderson, have shown these regimens to result in high CR rates, to bridge safely to allogeneic HSCT, and to offer a reasonable chance of a cure [145–147, 212]. Patients in second salvage or beyond are offered phase 1–2 investigational approaches, or supportive care/hospice.

All patients achieving a subsequent CR or even persistent minimal disease (marrow blasts < 20%) should be offered immediate allogeneic HSCT, provided they are cognizant of the potential low cure rates and risks of the procedure, including high risk of mortality and relapse.

An interesting study from Germany attracted a lot of interest [213]. In this phase 3 trial, 281 patients (median age 61 years; range 18–75 years) with AML refractory to one course of frontline intensive chemotherapy ($n = 183$; which may have enriched for patients with residual sensitive disease post 14–28 days of 7 + 3) or in first relapse ($n = 98$), were randomized to reinduction with intensive chemotherapy (mitoxantrone plus high-dose cytarabine) followed by allogeneic HSCT in remission ($n = 141$), or "disease control" and immediate allogeneic HSCT ($n = 140$). The study showed similar outcomes in both arms: 4-year OS rate 49% versus 46%. What may not have been noticed was that the immediate allogeneic HSCT group received additional therapy with fludarabine, high-dose cytarabine and amsacrine (FLAMSA) on days −12 to −9, followed by fludarabine-alkylator-based reduced intensity conditioning before HSCT (essentially a double intensive/ablative regimen). Along these lines, we are investigating a regimen of sequential intensive chemotherapy, with the application of allogeneic HSCT, often with haplo-identical donors (more readily available, less delays) at the time of marrow aplasia (Day 21–35 of chemotherapy) rather than after achievement of CR (low probability; <10–20% in most situations).

EXPANDING ON TOPICS OF INTEREST IN AML

Antibodies targeting AML surface molecules

Antibodies targeting cluster designation (CD) surface molecules CD33, CD123, CD70, CLL1 (or CLEC12a), TIM3, WT1 and others, may have anti-AML efficacy. These antibodies may be unconjugated; conjugated to immunotoxins; or bispecific antibodies directing killer CD3 T-cells or NK cells to different AML surface markers. Unconjugated monoclonal antibodies have shown minimal or no benefit. Monoclonal antibodies conjugated to immunotoxins, however, have shown good efficacy; for example, GO targeting CD33; tagraxofusp (SL401) and pivekumab sunirine (IMGN632) targeting CD123 in blastic plasmacytoid dendritic cell neoplasm (BPDCN). Combinations of pivekumab sunirine or tagraxofusp with standard chemotherapy are ongoing in AML [214]. Among 50 patients with older/unfit AML treated with pivekumab sunirine and azacitidine-venetoclax, 54% achieved CR; the composite CR rate was 68% [215].

Studies are also evaluating the delivery of radioisotopes using antibodies that target AML surface antigens. The most advanced among them is the use of CD45-targeted antibodies (e.g., Iomab-B or 90Y-BC8-DOTA). As CD45 is ubiquitously expressed in the hematopoietic system, CD45-targeting may lead to significant myeloablation; hence, these studies are being done as part of pre-HSCT conditioning in transplant-eligible patients. An ongoing randomized phase 3 trial is evaluating Iomab-B versus investigator choice salvage therapy prior to HSCT in relapsed-refractory AML [216, 217].

The bispecific T-cell engaging (BiTE) antibody constructs recruit CD3-effector T cells or NK cell to target AML cells (CD33, CD123, CD70). These include AMG330, AMG673, AMG427, XmAb14045, AMV564, SAR443579 (CD123-NK engager) and others. Several have shown some activity (response rates 20% to 30%) but were associated with serious side-effects (cytokine release syndrome with fever). They may ultimately show a good benefit in AML in CR with MRD-positive disease.

CAR-T cellular therapy in AML

The tremendous success of immunotherapy in cancer (checkpoint inhibitors in solid tumors; chimeric antigen receptor [CAR]-T cellular therapy in ALL, lymphoma and myeloma) led to interest in developing similar immune therapies in AML. The studies with checkpoint inhibitors did not demonstrate improved efficacies and were associated with serious toxicities (organ "itis"). Trials with autologous and allogeneic CAR-T cells (targeting CD123, CD33 and CLL1), and with NK cellular therapies, are ongoing. However, multiple studies of such cellular therapies in AML have not produced clear positive trends so far.

SUMMARY

Several therapeutic strategies discussed as promising investigational approaches in the previous two AML reviews of 2016 and 2021 are therapeutic realities in 2024 and are used in standard-of-care therapeutic regimens in both frontline and later-line AML: GO, venetoclax, FLT3 inhibitors (midostaurin, gilteritinib, quizartinib), IDH inhibitors (ivosidenib, enasidenib, olutasidenib), oral decitabine and oral azacitidine. Others have fallen by the wayside, as is expected in cancer research (APR246, magrolimab). And yet, others, surprisingly and unexpectedly, are emerging with force, for example the promising novel (yet still investigational at the time of this writing) menin inhibitors. The wealth of positive data will continue to reshuffle what is, or what might soon become, a new standard of care (induction, consolidation, HSCT, maintenance) in younger and older patients with AML.

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AUTHOR CONTRIBUTIONS

HK designed, conceived, and wrote the review. All authors, GB, ND, CDD, GI, EJ, TK, KS, NS, MY, FR reviewed, revised and approved the final review.

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ADDITIONAL INFORMATION

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