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How I treat AML incorporating the updated classifications and guidelines

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The European LeukemiaNet recently revised both the clinical (2022) and measurable residual disease testing (2021) guidelines for acute myeloid leukemia (AML). The updated World Health Organization and International Consensus Classification for myeloid neoplasms were also published in 2022. Together, these documents update the classification, risk stratification, prognostication, monitoring recommendations, and response assessment of patients with AML. Increased appreciation of the genetic drivers of AML over the past decade and our increasingly sophisticated understanding of AML biology have been translated into novel therapies and more complex clinical treatment guidelines. Somatic genetic abnormalities and germ line predispositions now define and guide treatment and counseling for the subtypes of this hematologic malignancy. In this How I Treat article, we discuss how we approach AML in daily clinical practice, considering the recent updates in the context of new treatments and discoveries over the past decade.

Introduction

The World Health Organization (WHO) Blue Books classifying cancers were first published in 1967. Later, the Society for Hematopathology and the European Association for Haematopathology joined this effort and contributed to the development of the third, fourth, and revised fourth editions of the WHO classification of the tumors of hematopoietic and lymphoid tissues. In 2022, the framework of the fifth edition of the WHO classification for myeloid neoplasms was published.[1] In a parallel, a large group of hematopathologists and clinical specialists, many of whom were also involved in the development of earlier editions of the WHO classifications, developed another classification that focused on integrating cytogenetic, molecular, and clinical data and published their work as 2022 International Consensus Classification (ICC).[2] For clinical practice, in 2010, an international expert working group published the first edition of the European LeukemiaNet (ELN) for the diagnosis and management of acute myeloid leukemia (AML) in adults.[3] After the advances in diagnostics and therapeutics, these ELN recommendations were revised in 2017[4] and, more recently, in 2022.[5] Because the impact of measurable residual disease (MRD) in AML has become increasingly apparent, an ELN working group issued the first consensus document on MRD testing in AML clinical practice in 2017,[6] which was updated in 2021.[7]

Together, the updated 2022 ELN and 2021 MRD guidelines, in addition to the fifth edition of the WHO and ICC classifications of myeloid neoplasms[1,2,5,7] (Tables 1 and 2), refine the latest recommendations for the classification, risk stratification, prognostication, monitoring, and response assessment for the treatment of AML. In this article, we discuss how we incorporate these updates in our daily clinical practice, considering the multitude of new treatments (Figure 1) and discoveries in AML over the past decade. Notably, whenever available, clinical trials constitute the preferred therapy for patients with nonacute promyelocytic AML, particularly in light of these newly revised classifications, highlighting the main changes and modifications with a potentially major impact on AML treatment modalities. The proposed approaches to diagnosis and treatment in the following cases are based on evidence, whenever available, recently published guidelines, and our collective experience and opinion when no high-quality evidence exists.

Case 1

A 45-year-old man was diagnosed with de novo AML. Metaphase cytogenetics at diagnosis were interpreted as a normal karyotype. Molecular testing revealed an fms-related receptor tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD) mutation with a mutant allelic ratio (AR) of 0.25, a nucleophosmin 1 (*NPM1*) mutation (c.862_863insCATG) with a 30% variant allelic frequency (VAF), and a DNA methyltransferase 3 alpha (*DNMT3A*) mutation (R882C) with a 40% VAF. He achieved complete remission (CR) after initial induction therapy with 7 + 3 + midostaurin and went on to receive a consolidation cycle with high-dose cytarabine and midostaurin. After the first consolidation cycle, MRD was detected via multiparameter flow cytometry (MFC). At the same time, molecular MRD assessment

Table 1. Major clinically relevant differences among ELN 2022, fifth edition of the WHO, and the ICC 2022 of myeloid neoplasms

	ELN 2022 & ICC 2022	WHO fifth edition
MDS/AML (without AML-defining genetic alterations)	10%-19% blasts	Designated as MDS-IB2 (10%-19% bone marrow or 5%-19% peripheral blood or Auer rods)
AML with antecedent MDS, MDS/MPN, or prior exposure to therapy	Myelodysplasia added as a diagnostic qualifier	Included as a separate entity, AML-MR
AML with NPM1 mutations, KMT2A rearrangement, MECOM rearrangement, and NUP98 rearrangement	Requires ≥10% blasts in bone marrow or peripheral blood	Can be diagnosed irrespective of blast count
AML with CEBPA mutation	Requires ≥10% blasts in bone marrow or peripheral blood Includes only bzip mutations	Requires ≥20% blasts in bone marrow or peripheral blood Includes biallelic and bzip mutations
TP53 mutation	Included separately in the hierarchical classification	Not included as a separate entity for AML
Therapy-related	Added as a diagnostic qualifier	Included as separate entity AML-pCT

bzip, basic leucine zipper; MDS, myelodysplasia; MDS-IB2, MDS with increased blasts; MPN, myeloproliferative neoplasm; pCT, post cytotoxic therapy.

using quantitative reverse transcription polymerase chain reaction showed the presence of residual *NPM1* mutations in the blood. Next-generation sequencing (NGS) was not performed. The patient then underwent matched unrelated allogeneic hematopoietic cell transplantation (allo-HCT) with a myeloablative conditioning (MAC) regimen. Given the presence of an *FLT3*-ITD mutation at the time of the initial diagnosis, posttransplantation maintenance therapy with sorafenib was initiated. One hundred days after transplantation, repeat bone marrow biopsy and aspiration showed continued CR without evidence of MRD via flow cytometry or molecular methods, except for the detection of a different *DNMT3A* mutation with 42% VAF using the same NGS panel used at the initial diagnosis.

The 2017 ELN recommendations considered AML with *NPM1* mutation and low (<0.5) *FLT3*-ITD mutation AR as part of the favorable-risk category.[4] This recommendation was based on studies showing that *NPM1*-mutated disease with an *FLT3*-ITD AR ≥0.5, was associated with worse survival rates, contrary to a low AR ratio (<0.5), which had similar survival to the *FLT3* wild-type subgroups.[8-10] However, the 2022 ELN updated recommendations no longer consider the *FLT3*-ITD AR in the risk classification, and now, *FLT3*-ITD is classified as intermediate-risk, regardless of *NPM1* mutation status. This change was prompted by the lack of standardization of *FLT3*-ITD quantification, the impact of midostaurin therapy, and the incorporation of MRD status in the treatment schema.[11]

MRD monitoring in AML is increasingly performed using molecular testing for those with suitable leukemia-associated genomic alterations (such as *NPM1* mutations or core binding factor translocations) or otherwise using MFC. For patients with favorable and intermediate-risk AML, persistence of MRD after treatment may lead to upstaging of the initial ELN risk classification from favorable to intermediate and from intermediate to adverse, respectively, and affect decisions regarding the benefit of allo-HCT.[5] Our patient achieved CR but with the persistence of MRD (now denoted CR_{MRD+} by ELN 2022 guidelines) after 2 cycles of chemotherapy, which did not justify a change to our initial decision to recommend to him an allo-HCT in an effort to reduce the risk of disease relapse.

Although centralized MRD assessment is common in clinical trials, standardized AML MRD assessment using MFC is still not available in many centers.[12] For patients with *NPM1*-mutated AML, the use of molecular testing for MRD is recommended instead of MFC, per the 2021 ELN MRD guidelines.[7] Currently, commercial NGS testing is not recommended for use in AML MRD and should not be used as the sole method for MRD assessment, although large-scale efforts to generate supportive evidence for this approach are being undertaken.[13] Recent evidence strongly supports the use of residual *FLT3*-ITD detection in CR, using NGS for MRD assessment,[13-15] with persistence during remission associated with an increased risk of relapse and death; however, this approach has not yet been recommended by the ELN, largely because *FLT3* mutations are often subclonal, suggesting that although persistence of *FLT3*-ITD may have a significant positive predictive value, its absence may not have sufficient negative predictive value for MRD assessment. Given that patients treated with *FLT3*-inhibitors may experience high rates of *FLT3*-ITD–negative relapse, it is necessary to assess for MRD using alternative molecular targets and/or MFC during serial surveillance to limit false negative results.[16] Furthermore, the persistence of *DTA* clonal hematopoiesis mutations (*DNMT3A, TET2,* and *ASXL1*) may not be prognostically impactful and should generally not be considered to represent MRD when detected in isolation. As in our patient's case, there is evidence that *DNMT3A* mutations after induction,[17] before transplantation,[18] or after transplantation,[19] when detected in isolation, are not necessarily associated with relapse. Clonal hematopoiesis may be present in up to 16% of donors older than 55 years and are capable of engrafting in allo-HCT recipients, and *DNMT3A*-mutated clones have been shown to be associated with an increased risk of chronic graft-versus-host-disease (GVHD) but a lower risk of

Table 2. Major clinically relevant changes introduced to the ELN 2022 recommendations for the diagnosis and management of AML

Updates pertinent to the disease classification
Genetic aberrations are prioritized for defining AML disease classification that are now hierarchical in nature
Blast threshold ≥10% with recurrent genetic abnormality is sufficient to diagnose AML [with the exception of AML with t(9;22)(q34.1;q11.2)]*
Introduction of a new category MDS/AML with 10%-19% blasts with defined genomic abnormalities
Removal of therapy-related myeloid neoplasms
Dysplastic morphology and prior history of MDS or MDS/MPN are now diagnostic qualifiers rather than separate clinical entities
AML with MDS-related gene mutations is considered adverse-risk (unless co-occurring with *NPM1*, *CEBPA*, or core binding factor AML) and defined based on specific gene mutations (these cases should lack *TP53*), irrespective of a history of MDS or evidence of dysplastic morphology
Additional recurrent genetic abnormalities variants added as AML-defining entities
Both monoallelic and biallelic in-frame bZIP mutations of *CEBPA* are now considered favorable-risk AMLs
TP53 mutations at an allelic fraction of at least 10% define a novel class of AML and MDS
Considering germ line predisposition risk for all patients with hematologic malignancies, regardless of age, testing should be performed as early as possible, using a tissue source not likely to undergo somatic mutations (ie, cultured skin fibroblasts or hair follicles), and when identified, germ line variants should be applied as diagnostic qualifiers to the AML category†
FLT3-ITD AR is no longer relevant for risk classification; therefore, *FLT3*-ITD–mutated AMLs are considered in the intermediate-risk category, regardless of the *NPM1* mutation status
NPM1 mutated AML is considered favorable-risk disease; however, if adverse-risk cytogenetics abnormalities are present, it would be considered an adverse-risk disease
AML with hyperdiploid karyotype is no longer considered adverse risk
Updates pertinent to the diagnostic procedures and MRD monitoring
Identification of LAIP, in addition to the DfN aberrant phenotype, should be performed at diagnosis for subsequent MRD monitoring via MFC
Conventional cytogenetics analysis and molecular testing are imperative
Risk stratification and management of favorable- and intermediate-risk AML can be modified via MRD testing
Isolated detection of a *DTA* mutation (*DNMT3A, TET2,* and *ASXL1*) should not be considered MRD
NGS-based MRD lacks standardization and, currently, should not be used alone for MRD assessment; MFC remains the gold standard for AML, except for those with alterations in *NPM1*, acute promyelocytic, or core binding factor AML
General updates pertinent to clinical management
Pre-allo-HCT MRD positivity is an independent adverse-risk factor for pos-tallo-HCT outcomes; however, no randomized evidence regarding the positive impact of additional intensive chemotherapy or other interventions used for pre-allo-HCT MRD eradication is available yet
MAC regimen is generally preferred for fit patients with pre-allo-HCT MRD positivity
Introduction of additional response criteria, that is, CRh_{MRD-} or CRi_{MRD-}

AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; bZIP, basic leucine zipper; CRh, complete remission with partial hematological recovery; CRi, complete remission with incomplete count recovery; DfN, different from normal; LAIP, leukemia-associated immunophenotypes; MDS, myelodysplasia; MPN, myeloproliferative neoplasm.

*for detailed genetic abnormalities, refer to Table 1 in the article by Döhner H. et al[5]

†for detailed germ line disorders, refer to Table 2 in the article by Döhner H. et al[5]

relapse.[20] In our patient's case, it is likely that the *DNMT3A* mutation detected after allo-HCT is donor-derived, given that this specific mutation was not identified in this patient's pretransplantation sample for which chimerism studies showed that the patient's myeloid cells were 100% of donor origin. As often is the case, the donor did not undergo molecular testing before donation. Given all the aforementioned information, this patient's condition is still considered to be in CR_{MRD-} status even on day 100 of his post-transplantation assessment.

Maintenance therapy with sorafenib, an *FLT3* inhibitor, is now commonly used in this patient population, with supportive evidence from 2 randomized controlled trials,[21,22] albeit this has not yet been approved by the Food and Drug Administration or the European Medicines Agency, and there are difficulties in the long-term tolerance of this drug. A recent 202-patient phase 3 clinical trial showed that post-allo-HCT sorafenib maintenance therapy in patients aged from 18 to 60 years with *FLT3*-ITD–mutated AML in CR reduced the risk of relapse at 1 year compared with no maintenance (1-year cumulative incidence of relapse 7% vs 24.5%; hazard ratio [HR] 0.25; 95% confidence interval [CI], 0.11–0.57; $P = .001$).[21] It is important to note that depending on the patient's preference and the treating physician, sorafenib was administered as a component of the induction or consolidation treatment before transplantation to 59% and 57% of the patients in the sorafenib and control arms, respectively. Compared with the SORMAIN clinical trial,[22] the first randomized study to show an overall survival (OS) advantage with posttransplantation maintenance with sorafenib; despite a small sample size, this phase 3 study's maintenance time was cut in half, but the rates of relapse in both studies appeared to be comparable. Furthermore, in both trials, patients with relapsed or refractory disease were treated

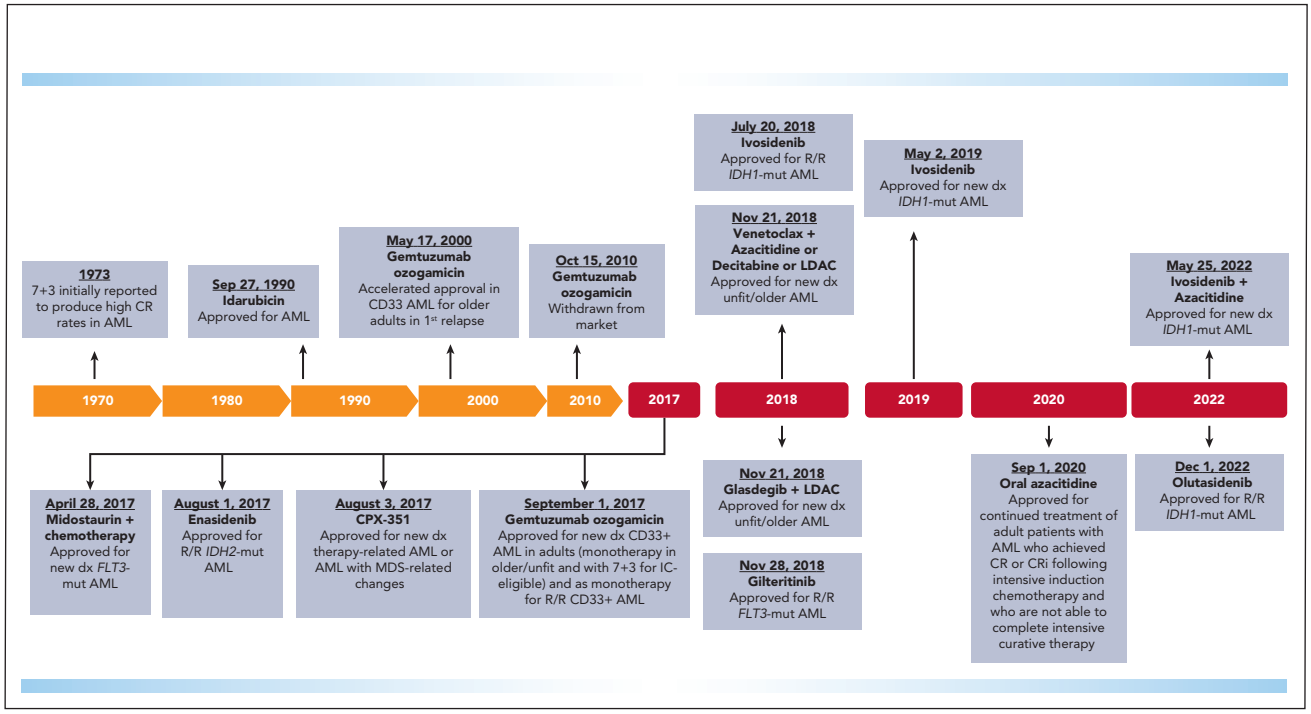

Figure 1. Timeline of FDA approvals for the treatment of AML. CRi, complete remission with incomplete count recovery; dx, diagnosed; FDA, Food and Drug Administration; IC, intensive chemotherapy; LDAC, low dose cytarabine; MDS, myelodysplasia; Mut, mutated; R/R, relapsed and refractory.

with sorafenib-containing salvage chemotherapy (11% in the sorafenib group and 10% in the control group,[21] and 18 of the 25 patients enrolled in the SORMAIN trial whose disease relapsed were treated with sorafenib[22]). Moreover, none of the patients in those trials received midostaurin for the treatment of AML; therefore, the benefit of sorafenib for post-allo-HCT maintenance remains unclear in the setting of prior midostaurin use. Post-allo-HCT maintenance therapy for 1 year with midostaurin for patients with AML in CR1 harboring an *FLT3* mutation was evaluated in RADIUS, a randomized phase 2 clinical trial, but was inadequately powered and unable to detect an improvement in relapse free survival or OS associated with the addition of midostaurin.[23]

The use of quizartinib for maintenance therapy was also evaluated in a QuANTUM-First global, randomized, double-blind, placebo-controlled phase 3 clinical trial.[24] After the induction with cytarabine and anthracycline, patients who achieved CR received up to 4 cycles of high-dose cytarabine with quizartinib or placebo. Allo-HCT was performed with the treating physician's discretion, followed by up to 3 years of continuation with quizartinib or placebo. OS was significantly longer in the quizartinib than the placebo arm (HR, 0.776; 95% CI, 0.615-0.979; two-sided P = .0324); however, when censored for allo-HCT, OS trended longer with quizartinib but was not statistically significant (HR, 0.752; 95% CI, 0.562-1.008; two-sided P = .055). In a phase 3 randomized trial, gilteritinib is also being studied for maintenance after transplantation among patients with *FLT3*-ITD AML (BMT CTN 1506, NCT02997202). This clinical trial will probably be the most informative for current clinical practice because it is being conducted in an era in which pre-HCT midostaurin therapy is the standard of care.[25] The ideal FLT3-inhibitor duration will require more research to be determined, but quizartinib, crenolanib, and gilteritinib may have improved tolerabilities and make FLT3-inhibitor treatment after allo-HCT possible for a longer than usual duration. The optimal timing to initiate post-allo-HCT maintenance with an *FLT3* inhibitor remains to be determined; however, most experts suggest starting treatments as soon as possible after allo-HCT if there is evidence of count recovery without GVHD.[26]

In a patient with AML with mutated *NPM1* but without *FLT3*-ITD and achieving *NPM1* MRD negativity in the blood after 2 cycles of intensive therapy, it would be reasonable to defer allo-HCT in favor of continued consolidative chemotherapy. In such instances, MRD monitoring at the end of treatment and every 3 months thereafter from a bone marrow sample or every 4 to 6 weeks from peripheral blood would be recommended for at least 24 months. At any time point, evidence of MRD relapse, if confirmed in a subsequent sample, would trigger the decision to consider allo-HCT.[7] MRD relapse is defined as conversion from MRD negativity to MRD positivity, or a 10-fold increase in MRD copy number variations between any 2 positive samples measured in the same tissue.[7]

However, for an eligible patient, such as ours, with AML with *FLT3*-ITD–mutated AML at diagnosis, we currently offer allo-HCT regardless of MRD status. AML with concurrent *DNMT3A, NPM1,* and *FLT3*-ITD mutations may represent a particularly poor-risk disease subset.[27,28] If allo-HCT is not possible or is declined, 1 could consider completing consolidation therapy cycles with midostaurin maintenance, although the value of this maintenance therapy remains inconclusive.[25,29] The GIMEMA AML1310 clinical trial assigned ELN2017 patients at intermediate-risk to allo-HCT if they had evidence of

sustained MRD, providing suggestive evidence that this poor prognostic indicator could be mitigated by intensification.[30] No high-quality randomized controlled trial evidence is currently available to support deferring allo-HCT among patients with *FLT3*-ITD–mutated AML who achieved MRD negativity after induction therapy.

The detection of MRD before allo-HCT is a well-established risk factor in determining the risk of relapse.[31,32] The intensity of an allo-HCT preparative regimen has been shown to affect survival in AML; whenever possible, MAC is preferred over reduced-intensity conditioning regimens,[33] particularly in those with evidence of MRD positivity before allo-HCT.[18,34] However, in many patients with AML, administering a MAC regimen is not feasible, and it is currently unproven whether particular reduced-intensity conditioning regimens (eg, those containing melphalan) can decrease relapse and improve survival[35] particularly in patients with evidence of MRD positivity before allo-HCT.[13]

Finally, multiple agents have shown therapeutic promise for patients with *NPM1*-mutated AML. High antileukemic efficacy has been reported in patients with *NPM1*-mutated AML treated with either gemtuzumab ozogamicin or venetoclax-containing combination regimens as well as novel targeted therapies, such as menin inhibitors.[36-40] It is currently unknown how these drugs will be optimally used in combination therapies for future treatment, and whether they would be used alone or in combination for maintenance.

Case 1 summary points

1. *FLT3*-ITD AR is no longer incorporated into ELN risk stratification.
2. AML with *FLT3*-ITD is considered intermediate-risk, regardless of the *NPM1* mutation status.
3. Quantitative polymerase chain reaction–based and error-corrected NGS-MRD testing in patients with *NPM1*-mutated AML may be useful for risk-stratification, therapy selection, and early detection of relapse.
4. NGS testing for AML MRD currently requires standardization; however, large-scale efforts to establish the clinical use of this methodology for *FLT3*-ITD and *NPM1* mutations have recently been reported and are underway for other recurrent mutations.
5. Preleukemic *DTA* mutations (*DNMT3A*, *tet methylcytosine dioxygenase 2*, and *additional sex combs like-1*), commonly associated with clonal hematopoiesis of indeterminate potential, when detected in isolation at CR, should not be considered evidence of AML MRD.
6. MAC rather than a reduced-intensity conditioning may improve survival in patients with AML in CR undergoing allo-HCT and should be considered whenever possible, particularly for those with evidence of MRD positivity before allo-HCT.
7. Post-HCT *FLT3*-ITD–directed therapy should be considered in the absence of significant toxicities.
8. Randomized clinical trials are required to generate evidence to support allo-HCT assignment among patients who are at intermediate risk based on MRD status and the role of pre, peri, and posttransplantation interventions in those tested positive for MRD.

Case 2

A 62-year-old woman was diagnosed with myelodysplastic syndrome/neoplasm (MDS) with a bone marrow evaluation showing 13% myeloblasts, a complex karyotype with deleted 17p, and mutated tumor protein 53 (*TP53),* detected by NGS, with a VAF of 35%. The patient underwent treatment with 4 cycles of azacitidine. A repeat bone marrow biopsy at that point showed only 4% myeloblasts with persistence of deletion 17p along with the rest of the cytogenetic abnormalities and *TP53* mutation with VAF decreased to 12%. She then underwent matched-related donor allo-HCT with fludarabine and melphalan reduced-intensity conditioning. After allo-HCT, her disease remained in remission for 7 months, after which she developed worsening cytopenias. A repeat bone marrow biopsy and aspiration showed relapsed AML with 65% myeloblasts. Her clinical status rapidly deteriorated before receiving salvage chemotherapy, and she passed away.

The new 2022 ELN and the ICC introduced numerous new hierarchical categories for the classification of AML based on cytogenetic and mutation profiles.[2,5] Despite softening the boundaries between MDS and AML, particularly the boundaries defining MDS with increased blasts (MDS-IB2) and AML, the revised fifth edition WHO classification retained the 20% cutoff to delineate MDS from AML for cases not classified as AML with recurrent genetic abnormalities, such as *NPM1*-m or *KMT2A-r*.[1] Because blast cutoffs are arbitrary because of the inherent biologic continuity in myeloid malignancies, a new category denoted as MDS/AML was introduced in the ICC classification to reflect the clinical behavior of these cancers based on their biology and genetics rather than a specific blast cutoff.[5] Therefore, based on this new 2022 ELN classification and in the absence of AML-associated gene mutations, our patient's disease at initial presentation would be classified as MDS/AML with mutated *TP53*, because the *TP53* VAF upon diagnosis was ≥10%. According to the WHO 2022 classification, the patient's disease would be diagnosed as MDS with biallelic *TP53* inactivation.

MDS and AML cases may have both mono and biallelic *TP53* alterations, which is consistent with *TP53*'s tumor-suppressive activity.[41] The *TP53* multihit condition, defined as having 2 or more *TP53* mutations, 1 mutation with loss of the other copy via deletion of 17p or 1 mutation with concurrent copy neutral loss of heterozygosity of the wild-type allele, predicted the probability of mortality and leukemic progression in MDS independently of the risk status of the revised international prognostic scoring system.[42] The subset of MDS cases with multihit *TP53* alterations have a complex karyotype, increased bone marrow blasts, higher risk of leukemic progression, and worse OS compared with monoallelic alterations, which have characteristics similar to those of MDS without *TP53* mutations.[43] *TP53*-mutated MDS, AML, or MDS/AML are usually chemotherapy-resistant with lower rates of CR and inferior survival compared with *TP53* wild-type cases.[28,44,45] Induction chemotherapy with cytotoxic agents, including anthracyclines and cytarabine, liposomal daunorubicin/cytarabine, and single hypomethylating agent for *TP*53-mutated MDS/AML, has consistently shown dismal outcomes.[46,47] Although liposomal daunorubicin/cytarabine is approved for what used to be called therapy-related AML or secondary AML, prior therapy with a hypomethylating agent and a

mutated *TP53* were shown to predict inferior outcomes with this therapy.[48,49] Preclinical studies identified preferential sensitivity of *TP53* mutated cells to drugs inhibiting DNA methylation, that is, hypomethylating agents.[50,51] A single institution prospective clinical trial showed a 100% response rate (n = 21; with only 19% CR, n = 4) with a 10-day decitabine regimen for *TP53*-mutated MDS and AML, although these responses were not durable.[52] However, in larger studies, patients with *TP53* mutated disease treated with decitabine had similar rates of responses to those with wild-type *TP53*.[53] Furthermore, a 5-day regimen of decitabine seems to have similar survival rates when compared with a 10-day regimen.[54] Although the VIALE-A trial has established azacitidine-venetoclax as the standard of care for older and/or unfit adults with newly diagnosed AML,[55] emerging evidence is casting doubt whether patients with *TP53* mutations benefit from this combination.[56] For example, in a pooled analysis including patients from the VIALE-A trial and a prior nonrandomized, single-arm phase 1b clinical trial,[57] patients with AML harboring poor-risk cytogenetics with *TP53* mutations, the combination of azacitidine and venetoclax was associated with higher rates of remission but not the duration of response or OS compared with azacitidine alone.[56] Interestingly, the combination of venetoclax with low-dose cytarabine did not result in increased rates of remission for *TP53* mutated AML.[58] Therefore, those patients should be strongly considered for innovative clinical trials. In some analyses, MDS patients with monoallelic *TP53* mutations did not vary in outcomes or disease responsiveness to therapy compared with patients with *TP53* wild-type disease.[43] Nevertheless, such findings were not confirmed in other studies in which molecular characteristics were not significantly associated with survival in mutant *TP53* AML and MDS.[59,60]

Although MDS-IB2 can now be considered AML-equivalent, this arbitrary cutoff of 10% carries the risk of overtreatment. The combination of azacitidine or decitabine with venetoclax demonstrated synergy and superior clinical activity compared with the single hypomethylating agent for treating AML in elderly patients or those ineligible to receive intensive chemotherapy.[55,57,61] In the *TP53*-mutated molecular subgroup analysis, the combination had higher rates of composite CR than the single-agent treatment.[55] However, in a phase 1b study (NCT02942290) evaluating azacitidine in combination with venetoclax for patients with higher-risk MDS, venetoclax was originally administered for 28 days in each cycle, similar to the treatment of AML, but treatment intolerance led to amend dosing for 14 days per treatment cycle. This 14-day shortened regimen of venetoclax therapy is being tested in phase 3 clinical trial, comparing azacitidine single-agent with the combination of azacitidine and venetoclax for the treatment of patients with newly diagnosed higher-risk MDS (NCT04401748). In addition, in an international open-label randomized phase 3 trial, older, fit patients (age ≥60 years and eligible for intensive chemotherapy; ECOG performance status, 0-2), when compared with intensive chemotherapy + cytarabine and daunorubicin, 10 days of decitabine resulted in a similar OS (HR = 1.04; 95% CI, 0.86-1.26; two-sided *P* = .68) and allo-HCT rates with a better safety profile.[62] Although patients with ~10% to 19% blasts now are included in ELN & ICC 2022 as having MDS/AML, randomized studies of azacitidine-venetoclax combinations have only been reported for patients with AML and 20% or higher blast count. Until we have results from the VERONA clinical trial (NCT04401748) for patients with MDS/AML (or patients with higher-risk MDS in general) with less than 20% blasts, the use of venetoclax should not currently be routinely recommended but can be considered on a case-by-case basis, especially for younger patients, as a bridge to transplantation.

Multiple clinical trials are ongoing for patients with *TP53*-mutated myeloid malignancies. Although appearing promising in early trials,[63,64] a recent phase 3 trial of eprenetapopt (APR-246) + azacitidine vs azacitidine alone in patients with *TP53*-mutated MDS failed to meet the primary end point. Magrolimab, an anti-CD47 immunoglobulin G4 monoclonal antibody that activates T-cell–mediated cytotoxicity and antibody-dependent cellular phagocytosis by blocking CD47/SIRP signaling pathway, has also shown promising rates of remission (13 of 22; 59%) in early single-arm trials, combined with azacitidine for *TP53*-mutated AML.[65] After allo-HCT, the main cause of mortality in individuals with *TP53* mutations is an early disease recurrence. In a phase 2, single-arm, multicenter, open-label clinical trial, eprenetapopt (APR-246), a small molecule p53 activator, combined with azacitidine as maintenance therapy after allo-HCT in patients with mutated *TP53* AML or MDS, showed a median OS of 20.6 months (95% CI, 14.2 to not estimable) and a 1-year OS probability was 78.8% (95% CI, 60.6-89.3).[66]

Case 2 summary points

1. Intensive chemotherapy for *TP53*-mutated MDS/AML has generally resulted in inferior outcomes, and alternative therapeutic strategies (hypomethylating agent based) should be considered even for fit patients.
2. Given the dire outcomes with standard of care therapy, the most appropriate treatment recommendation for a patient with *TP53*-mutated MDS/AML is enrollment in a clinical trial.

Case 3

A 27-year-old woman with de novo AML was found to have monosomy 7 in the conventional karyotype, and *ASXL1*, *KRAS*, *NRAS,* and *SETBP1* mutations were detected using a limited NGS panel. Upon performing diagnostic flow cytometry, it was noted that monocytes and natural killer cells were absent, which confirmed the diagnosis of AML. The patient underwent intensive induction chemotherapy. She achieved CR and then received 1 cycle of consolidation with intermediate-dose cytarabine consecutively on days 1, 2, and 3. A repeat bone marrow biopsy and aspiration confirmed continued remission with persistence of MRD, shown via MFC and NGS, and the patient was referred to our center. Upon further investigation, our patient had a history of recurrent infections with non-tuberculosis mycobacteria, recurrent genital and extragenital human papillomavirus infections, and unprovoked venous thromboembolism during adolescence. A skin biopsy was performed and cultured fibroblasts were sequenced to evaluate germ line DNA, which showed a deleterious germ line *GATA2* mutation (not included in the original NGS panel performed at the local hospital), commonly associated with pediatric and young adult patients with myeloid neoplasms and acquired monosomy 7.[67] As the matched sibling was also found to carry the same *GATA2* germ line mutation, he was not selected as a donor. She then underwent allo-HCT with a MAC from a matched unrelated donor. One hundred days after allo-HCT, bone marrow examination showed CR by cytomorphology;

however, persistent MRD was detected via MFC. An early immunosuppressive therapy taper was started. Her clinical course was complicated by gastrointestinal GVHD, from which she recovered with therapy. Two years after allo-HCT, the patient remained in CR.

GATA2-related malignancies often appear in adolescence or early adulthood. *GATA2* germ line mutations are responsible for ~7% of juvenile cases of childhood MDS and 15% of instances of childhood MDS with increased blasts.[67] In adult patients, the incidence is lower. In a study of 586 adult individuals with MDS, the incidence of germ line *GATA2* mutations was 0.5%.[67] Importantly, advanced MDS and monosomy 7 are significantly overrepresented in GATA2-related MDS.[67,68] Patients with genetically defined hereditary myeloid malignancy syndromes (HMMSs) constitute an increasingly recognized group that warrants further evaluation. A comprehensive practical outline was published focusing on diagnosing and managing HMMSs in clinical care.[69] The latest ELN recommendations advocate for screening for a germ line predisposition for HMMSs regardless of the age at diagnosis of the hematologic malignancy.[5] In all cases, a comprehensive family and personal medical history should always be obtained because they provide clues for further germ line testing.

Furthermore, as in our patient's case, 1 of us administered intermediate-dose cytarabine via a timed pump facilitated by home health, rather than high-dose cytarabine for AML consolidation, from days 1 to 3 instead of on alternate days, because that hastens blood count recovery, decreases toxicity, and potentially reduces health care cost.[70-72] Admittedly, the intermediate-dose cytarabine approach is not supported by randomized prospective clinical trials, and patients with favorable-risk AML might still benefit from high-dose cytarabine consolidation after standard 7 + 3 induction therapy.[73]

Case 3 summary points

1. Recognition and identification of myeloid neoplasms associated with germ line predisposition from a tissue source that is unlikely to undergo somatic mutation frequently (ie, cultured skin fibroblast) is imperative.
2. Germ line variations often have a VAF of ~50% if heterozygous, or ~100% if homozygous. However, the VAF must be interpreted in relation to germ line mosaicism, loss of heterozygosity, copy number variations in tumor cells, insertions/deletions, structural rearrangements, and sequencing artifacts, including statistical fluctuation, which is especially important for shallow sequencing depths.
3. Refrain from using family donors for patients with HMMSs, unless the donor is confirmed to not carry the pathogenic variant.

Case 4

A 77-year-old woman with a history of diabetes mellitus type 2, hypertension, and stage 3 chronic kidney diseases presented with hyperleukocytosis, a white blood cell count of 54 × 10^3/μL, and a uric acid level of 12 mg/dL. She was diagnosed with AML with a normal karyotype and *IDH1* and *FLT3*-ITD mutations. Hydroxyurea was started in conjunction with uric acid–lowering medication. After the white blood cell count was < 25 ×10^3/μL, chemotherapy with a combination of azacitidine and venetoclax was initiated. On day 21 of the first cycle, a bone marrow biopsy and aspiration showed disease in CR without MRD (CR_{MRD-}). She received 12 additional cycles of azacitidine and venetoclax, after which a repeat bone marrow biopsy and aspiration revealed relapsed disease with *IDH1* and *FLT3*-ITD mutations. Because she was not a candidate for a clinical trial, gilteritinib was started, and after 3 months the disease persisted. Ivosidenib was then initiated. Three months after this therapy, her disease remained uncontrolled; she then succumbed to AML after transitioning to hospice care.

The treatment of individuals deemed unsuitable for intensive chemotherapy has made significant progress. Particularly, the addition of venetoclax to azacitidine improved the rates of composite CR (66.4% vs 28.3%; $P < .001$) and the median OS (14.7 months; 95% CI, 11.9-18.7) in the azacitidine-venetoclax group and 9.6 months (95% CI, 7.4-12.7) in the control group $P < .001$).[55] Based on the results of a phase 2 study,[61] azacitidine could be substituted with decitabine, although the latter has not yet been evaluated in a randomized controlled trial. Low-dose cytarabine combined with venetoclax is an alternative therapy for individuals unable to receive a hypomethylating drug.[58] With the use of a hypomethylating agent combination with venetoclax, response assessment should be conducted early during the first cycle, usually between days 14 and 21, owing to the high rates of early responses [the median time to first response in the VIALE-A clinical trial was 1.3 months (range, 0.6-9.9)].[55] This will allow the delay or dose modification of subsequent cycles. Because the combination of a hypomethylating agent and venetoclax is a mutation-agnostic treatment approach, patients with AML and additional targetable mutations could be offered other alternatives. In the AGILE randomized, placebo-controlled, phase 3 trial, the combination of ivosidenib and azacitidine showed a significant OS survival benefit compared with azacitidine monotherapy but was not compared with the combination of azacitidine + venetoclax.[74]

Pooled subgroup analysis of patients with *IDH1/2*-mutant AML who did not receive any treatmnent, which included patients from the phase 3 VIALE-A study and the single-arm phase 1b study treated with azacitidine with or without venetoclax,[57] showed high response rates (79% composite CR), prolonged duration of remission (29.5 months), and improved median OS (24.5 months).[75] *IDH1/2* mutations were detected in 81 of 308 (26%) in the venetoclax + azacitidine groups (among those, 33 patients had an *IDH1* mutation, and 41 had an *IDH2* mutation) and 28 of 127 (22%) in the azacitidine group (among those, 11 patients had an *IDH1* mutation, and 18 had an *IDH2* mutation). Only a small number of patients had a comutation with *FLT3* (n = 14/81), among whom the median OS was inferior to that of the *FLT3* wild-type group. More recently, in a phase 3 open-label randomized clinical trial, the combination of gilteritinib with azacitidine compared with monotherapy azacitidine did not improve the OS of patients with *FLT3*-mutated AML, unfit for intensive chemotherapy.[76]

The current classification of AML does not address the risk stratification of patients treated with a combination of hypomethylating agents and venetoclax. Patients with AML harboring mutations involving genes such as *IDH1/2*, *FLT3* (particularly *FLT3*-TKD), and *NPM1* have relatively favorable outcomes when treated with a hypomethylating agent and

venetoclax. The role of MRD testing in patients treated with this combination has not been fully defined. It is possible that this could play an important role in decisions regarding treatment simplification, augmentation, or discontinuation. Moreover, triplet therapies (the addition of a third agent to the backbone of a hypomethylating agent and venetoclax) are currently being tested in a multitude of clinical trials; however, dose interruptions are frequently needed to mitigate myelosuppression.[77,78] In addition, in the future, oral alternatives to IV hypomethylating agents will be combined with targeted therapy as they have shown equivalent area-under-the-curve with similar safety profiles and preliminary clinical activity.[79] Furthermore, clinical outcomes with a hypomethylating agent, whether azacitidine or decitabine, seem comparable and could potentially be used interchangeably.[80] Lastly, the ELN risk groups, which are based on fit/younger patients with AML receiving intensive chemotherapy, are not prognostic in patients receiving lower-intensity–based chemotherapy, such as low-dose cytarabine- or hypomethylating agents–based combinations with venetoclax.[81] In an exploratory post hoc analysis of pooled treatment-naïve, intensive chemotherapy-ineligible patients treated with azacitidine and venetoclax, the median OS survivals were similar for patients with favorable- and intermediate-risk AML, based on the ELN 2017 classification criteria.[81] Furthermore, 2 distinct subgroups in the adverse-risk AML subtypes (those with a *TP53* and *RUNX1* mutations) had shorter median OS when compared with the rest of the patients having adverse-risk AML (5.42 months vs 22.9 months, respectively).[81] Therefore, a modified risk stratification system is needed for patients treated with lower-intensity therapies.

Case 4 summary points

1. Azacitidine could be substituted with decitabine, although the latter has not yet been evaluated in a randomized clinical trial. Low-dose cytarabine combined with venetoclax is an approved alternative therapy.
2. A modified risk stratification system is needed for patients with AML treated with lower-intensity therapies, and the role of MRD testing remains to be established.
3. Because of the high rates of early responses to venetoclax in combination with hypomethylating agents and the need to delay or modify dosing in the setting of persistent cytopenias in a leukemia-free marrow, the response to such therapy should be evaluated early during the first cycle, usually between days 14 and 21.
4. An increasingly popular clinical trial design for chemotherapy-ineligible patients involves evaluating triplet treatments, which require the study of a third drug added to the backbone of a hypomethylating agent and venetoclax.

Conclusions

To date, the classification of AML and hematologic malignancies has generally relied on experts in the field who meet every couple of years to produce consensus recommendations based on their interpretation of the best available evidence. As lower-intensity therapies are increasingly used for the treatment of AML, a dedicated risk stratification system is urgently needed. An increasingly scientific approach to genetic evaluation, both at diagnosis (for prognostication, treatment assignment-based predictive biomarkers for specific therapies, and homogenous interpretable clinical trials) and after treatment (for prognostication, treatment assignment, and personalization of therapy based on the risk of relapse) is positively influencing diagnostic classifications and clinical guidelines. In the future, hematologic neoplasm classification and clinical treatment guideline revisions will increasingly focus on improving prognostication and guiding personalized precision therapies. Experts in the field have called for the establishment of an international working group to encourage this cooperation and the unification of such classifications.[82,83] Ultimately, we need substantially better treatment options for all AML patients, with the hope that a new era of precision medicine will facilitate discovery by separating signals from noise, leading to new options and approaches for the treatment of patients with AML.

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Authorship

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Footnote

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REFERENCES

1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*. 2022;36(7):1703-1719.
2. Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemia: integrating morphological, clinical, and genomic data. *Blood*. 2022;140(11): 1200-1228.
3. Döhner H, Estey EH, Amadori S, et al; European LeukemiaNet. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115(3): 453-474.
4. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017; 129(4):424-447.
5. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 ELN recommendations from an international expert panel. *Blood*. 2022; 140(12):1345-1377.
6. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2018;131(12):1275-1291.
7. Heuser M, Freeman SD, Ossenkoppele GJ, et al. 2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2021;138(26):2753-2767.
8. Schlenk RF, Kayser S, Bullinger L, et al; German-Austrian AML Study Group. Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. *Blood*. 2014;124(23):3441-3449.
9. Pratcorona M, Brunet S, Nomdedéu J, et al; Grupo Cooperativo Para el Estudio y Tratamiento de las Leucemias Agudas Mieloblasticas. Favorable outcome of patients with acute myeloid leukemia harboring a low-allelic burden FLT3-ITD mutation and concomitant NPM1 mutation: relevance to post-remission therapy. *Blood*. 2013;121(14):2734-2738.
10. Gale RE, Green C, Allen C, et al; Medical Research Council Adult Leukaemia Working Party. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood*. 2008;111(5): 2776-2784.
11. Döhner K, Thiede C, Jahn N, et al. Impact of NPM1/FLT3-ITD genotypes defined by the 2017 European LeukemiaNet in patients with acute myeloid leukemia. *Blood*. 2020;135(5): 371-380.
12. Tettero JM, Freeman S, Buecklein V, et al. Technical aspects of flow cytometry-based measurable residual disease quantification in acute myeloid leukemia: experience of the European LeukemiaNet MRD Working Party. *Hemasphere*. 2022;6(1):e676.
13. Dillon LW, Gui G, Page KM, et al. DNA sequencing to detect residual disease in adults with acute myeloid leukemia prior to hematopoietic cell transplant. *JAMA*. 2023; 329(9):745-755.
14. Grob T, Sanders MA, Vonk CM, et al. Prognostic value of *LT3*-internal tandem duplication residual disease in acute myeloid leukemia. *J Clin Oncol*. 2023;41(4):756-765.
15. Loo S, Dillon R, Ivey A, et al. Pre-transplant FLT3-ITD MRD assessed by high-sensitivity PCR-NGS determines post-transplant clinical outcome. *Blood*. 2022;140(22):2407-2411.
16. Schmalbrock LK, Dolnik A, Cocciardi S, et al. Clonal evolution of acute myeloid leukemia with FLT3-ITD mutation under treatment with midostaurin. *Blood*. 2021;137(22):3093-3104.
17. Jongen-Lavrencic M, Grob T, Hanekamp D, et al. Molecular minimal residual disease in acute myeloid leukemia. *N Engl J Med*. 2018; 378(13):1189-1199.
18. Hourigan CS, Dillon LW, Gui G, et al. Impact of conditioning intensity of allogeneic transplantation for acute myeloid leukemia with genomic evidence of residual disease. *J Clin Oncol*. 2020;38(12):1273-1283.
19. Heuser M, Heida B, Büttner K, et al. Posttransplantation MRD monitoring in patients with AML by next-generation sequencing using DTA and non-DTA mutations. *Blood Adv*. 2021;5(9):2294-2304.
20. Frick M, Chan W, Arends CM, et al. Role of donor clonal hematopoiesis in allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol*. 2019;37(5):375-385.
21. Xuan L, Wang Y, Huang F, et al. Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. *Lancet Oncol*. 2020;21(9):1201-1212.
22. Burchert A, Bug G, Fritz LV, et al. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with. *J Clin Oncol*. 2020;38(26): 2993-3002.
23. Maziarz RT, Levis M, Patnaik MM, et al. Midostaurin after allogeneic stem cell transplant in patients with FLT3-internal tandem duplication-positive acute myeloid leukemia. *Bone Marrow Transplant*. 2021; 56(5):1180-1189.
24. Erba H, Montesinos P, Vrhovac R. Quizartinib prolonged survival vs. placebo plus intensive induction and consolidation therapy followed by single-agent continuation in patients aged 18-75 years with newly diagnosed FLT3-ITD+ AML. Presented at: European Hematology Association Meeting; 2022.
25. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-464.
26. DeFilipp Z, Chen YB. How I treat with maintenance therapy after allogeneic HCT. *Blood*. 2023;141(1):39-48.
27. Loghavi S, Zuo Z, Ravandi F, et al. Clinical features of de novo acute myeloid leukemia with concurrent DNMT3A, FLT3 and NPM1 mutations. *J Hematol Oncol*. 2014;7:74.
28. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016; 374(23):2209-2221.
29. Larson RA, Mandrekar SJ, Huebner LJ, et al. Midostaurin reduces relapse in FLT3-mutant acute myeloid leukemia: the Alliance CALGB 10603/RATIFY trial. *Leukemia*. 2021;35(9): 2539-2551.
30. Venditti A, Piciocchi A, Candoni A, et al. GIMEMA AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia. *Blood*. 2019;134(12):935-945.
31. Short NJ, Zhou S, Fu C, et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. *JAMA Oncol*. 2020;6(12):1890-1899.
32. Buckley SA, Wood BL, Othus M, et al. Minimal residual disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a meta-analysis. *Haematologica*. 2017;102(5):865-873.
33. Scott BL, Pasquini MC, Fei M, et al. Myeloablative versus reduced-intensity conditioning for hematopoietic cell transplantation in acute myelogenous leukemia and myelodysplastic syndromes-long-term follow-up of the BMT CTN 0901 clinical trial. *Transplant Cell Ther*. 2021;27(6): 483.e1-483.e6.
34. Gilleece MH, Labopin M, Yakoub-Agha I, et al. Measurable residual disease, conditioning regimen intensity, and age predict outcome of allogeneic hematopoietic cell transplantation for acute myeloid leukemia in first remission: a registry analysis of 2292 patients by the Acute Leukemia Working Party European Society of Blood and Marrow Transplantation. *Am J Hematol*. 2018;93(9):1142-1152.
35. Zhou Z, Nath R, Cerny J, et al. Reduced intensity conditioning for acute myeloid leukemia using melphalan- vs busulfan-based regimens: a CIBMTR report. *Blood Adv*. 2020;4(13):3180-3190.
36. Fiskus W, Daver N, Boettcher S, et al. Activity of menin inhibitor ziftomenib (KO-539) as monotherapy or in combinations against AML cells with MLL1 rearrangement or mutant NPM1. *Leukemia*. 2022;36(11):2729-2733.
37. Walker AR, Byrd JC, Blachly JS, et al. Entospletinib in combination with induction chemotherapy in previously untreated acute

myeloid leukemia: response and predictive significance of HOXA9 and MEIS1 expression. *Clin Cancer Res*. 2020;26(22):5852-5859.

38. Schlenk RF, Paschka P, Krzykalla J, et al. Gemtuzumab ozogamicin in NPM1-mutated acute myeloid leukemia: early results from the prospective randomized AMLSG 09-09 phase III study. *J Clin Oncol*. 2020;38(6):623-632.

39. Kapp-Schwoerer S, Weber D, Corbacioglu A, et al. Impact of gemtuzumab ozogamicin on MRD and relapse risk in patients with NPM1-mutated AML: results from the AMLSG 09-09 trial. *Blood*. 2020;136(26):3041-3050.

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

41. Kastenhuber ER, Lowe SW. Putting p53 in context. *Cell*. 2017;170(6):1062-1078.

42. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12):2454-2465.

43. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med*. 2020;26(10):1549-1556.

44. Haase D, Stevenson KE, Neuberg D, et al; International Working Group for MDS Molecular Prognostic Committee. TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. *Leukemia*. 2019;33(7):1747-1758.

45. Hunter AM, Sallman DA. Current status and new treatment approaches in TP53 mutated AML. *Best Pract Res Clin Haematol*. 2019;32(2):134-144.

46. Seifert H, Mohr B, Thiede C, et al; Study Alliance Leukemia SAL. The prognostic impact of 17p (p53) deletion in 2272 adults with acute myeloid leukemia. *Leukemia*. 2009;23(4):656-663.

47. Kadia TM, Jain P, Ravandi F, et al. TP53 mutations in newly diagnosed acute myeloid leukemia: Clinicomolecular characteristics, response to therapy, and outcomes. *Cancer*. 2016;122(22):3484-3491.

48. Goldberg AD, Talati C, Desai P, et al. TP53 mutations predict poorer responses to CPX-351 in acute myeloid leukemia [abstract]. *Blood*. 2018;132(suppl 1). Abstract 1433.

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

50. Yi L, Sun Y, Levine A. Selected drugs that inhibit DNA methylation can preferentially kill p53 deficient cells. *Oncotarget*. 2014;5(19):8924-8936.

51. Nieto M, Samper E, Fraga MF, González de Buitrago G, Esteller M, Serrano M. The absence of p53 is critical for the induction of apoptosis by 5-aza-2′-deoxycytidine. *Oncogene*. 2004;23(3):735-743.

52. Welch JS, Petti AA, Miller CA, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med*. 2016;375(21):2023-2036.

53. Montalban-Bravo G, Takahashi K, Garcia-Manero G. Decitabine in TP53-mutated AML. *N Engl J Med*. 2017;376(8):796-797.

54. Short NJ, Kantarjian HM, Loghavi S, et al. Treatment with a 5-day versus a 10-day schedule of decitabine in older patients with newly diagnosed acute myeloid leukaemia: a randomised phase 2 trial. *Lancet Haematol*. 2019;6(1):e29-e37.

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

56. Pollyea DA, Pratz KW, Wei AH, et al. Outcomes in patients with poor-risk cytogenetics with or without TP53 mutations treated with venetoclax and azacitidine. *Clin Cancer Res*. 2022;28(24):5272-5279.

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

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

59. Grob T, Al Hinai ASA, Sanders MA, et al. Molecular characterization of mutant TP53 acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood*. 2022;139(15):2347-2354.

60. Zeidan AM, Bewersdorf JP, Hasle V, et al. Prognostic implications of mono-hit and multi-hit TP53 alterations in patients with acute myeloid leukemia and higher risk myelodysplastic syndromes treated with azacitidine-based therapy. *Leukemia*. 2023;37(1):240-243.

61. DiNardo CD, Maiti A, Rausch CR, et al. 10-day decitabine with venetoclax for newly diagnosed intensive chemotherapy ineligible, and relapsed or refractory acute myeloid leukaemia: a single-centre, phase 2 trial. *Lancet Haematol*. 2020;7(10):e724-e736.

62. Lübbert M, Wijermans P, Kicinski M. 10-day decitabine vs. conventional chemotherapy ("3 + 7") followed by allografting (HSCT) in AML patients ≥60 years: a randomized phase III study of the EORTC leukemia group, GIMEMA, CELG, and GMDS-SG. Presented at: European Hematology Association Meeting; 2022.

63. Mishra A, Tamari R, DeZern AE, et al. Phase II trial of eprenetapopt (APR-246) in combination with azacitidine (AZA) as maintenance therapy for TP53 mutated AML or MDS following allogeneic stem cell transplantation (SCT) [abstract]. *Blood*. 2021;138(suppl 1). Abstract 409.

64. Garcia-Manero G, Goldberg AD, Winer ES, et al. Phase I and expansion study of eprenetapopt (APR-246) in combination with venetoclax (VEN) and azacitidine (AZA) in TP53-mutant acute myeloid leukemia (AML) [abstract]. *Blood*. 2021;138(suppl 1). Abstract 3409.

65. Johnson L, Zhang Y, Li B, et al. Nature of clinical response and depth of molecular response in patients with TP53 mutant myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) treated with magrolimab with azacitidine [abstract]. *Blood*. 2022;140(suppl 1):6934-6935.

66. Mishra A, Tamari R, DeZern AE, et al. Eprenetapopt plus azacitidine after allogeneic hematopoietic stem-cell transplantation for TP53-mutant acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2022;40(34):3985-3993.

67. Wlodarski MW, Hirabayashi S, Pastor V, et al; EWOG-MDS. Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents. *Blood*. 2016;127(11):1387-1397; quiz 518.

68. Micol JB, Abdel-Wahab O. Collaborating constitutive and somatic genetic events in myeloid malignancies: ASXL1 mutations in patients with germline GATA2 mutations. *Haematologica*. 2014;99(2):201-203.

69. The University of Chicago Hematopoietic Malignancies Cancer Risk Team. How I diagnose and manage individuals at risk for inherited myeloid malignancies. *Blood*. 2016;128(14):1800-1813.

70. Löwenberg B. Sense and nonsense of high-dose cytarabine for acute myeloid leukemia. *Blood*. 2013;121(1):26-28.

71. Jaramillo S, Benner A, Krauter J, et al. Condensed versus standard schedule of high-dose cytarabine consolidation therapy with pegfilgrastim growth factor support in acute myeloid leukemia. *Blood Cancer J*. 2017;7(5):e564.

72. Dumas PY, Bertoli S, Bérard E, et al. Delivering HDAC over 3 or 5 days as consolidation in AML impacts health care resource consumption but not outcome. *Blood Adv*. 2020;4(16):3840-3849.

73. Kolla BC, Halim NAA, Cao Q, et al. High risk of relapse with intermediate dose cytarabine for consolidation in young favourable-risk acute myeloid leukaemia patients following induction with 7+3: a retrospective multicentre analysis and critical review of the literature. *Br J Haematol*. 2021;194(1):140-144.

74. Montesinos P, Recher C, Vives S, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. *N Engl J Med*. 2022;386(16):1519-1531.

75. Pollyea DA, DiNardo CD, Arellano ML, et al. Impact of venetoclax and azacitidine in treatment-naïve patients with acute myeloid leukemia and IDH1/2 mutations. *Clin Cancer Res*. 2022;28(13):2753-2761.

76. Wang ES, Montesinos P, Minden MD, et al. Phase 3 trial of gilteritinib plus azacitidine vs azacitidine for newly diagnosed FLT3mut+ AML ineligible for intensive chemotherapy. *Blood*. 2022;140(17):1845-1857.

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

78. Yilmaz M, Kantarjian H, Short NJ, et al. Hypomethylating agent and venetoclax with FLT3 inhibitor "triplet" therapy in older/unfit patients with FLT3 mutated AML. *Blood Cancer J*. 2022;12(5):77.

79. Kim N, Norsworthy KJ, Subramaniam S, et al. FDA approval summary: decitabine and cedazuridine tablets for myelodysplastic syndromes. *Clin Cancer Res*. 2022;28(16):3411-3416.

80. Zeidan AM, Fenaux P, Gobbi M, et al. Prospective comparison of outcomes with azacitidine and decitabine in patients with AML ineligible for intensive chemotherapy. *Blood*. 2022;140(3):285-289.

81. Döhner H, Pratz KW, DiNardo CD, et al. ELN risk stratification is not predictive of outcomes for treatment-naïve patients with acute myeloid leukemia treated with venetoclax and azacitidin [abstract]. *Blood*. 2022;140(suppl 1):1441-1444.

82. Cazzola M, Sehn LH. Developing a classification of hematologic neoplasms in the era of precision medicine. *Blood*. 2022;140(11):1193-1199.

83. Patnaik MM, Zeidan AM, Padron E, et al. Differences in classification schemata for myelodysplastic/myeloproliferative overlap neoplasms. *Leukemia*. 2022;36(12):2934-2938.