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# Recently approved therapies in acute myeloid leukemia: A complex treatment landscape

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ABSTRACT

Acute myeloid leukemia (AML) is a heterogeneous disease. Until recently, treatment for patients with AML was limited to induction chemotherapy with cytarabine and anthracycline or hypomethylating agents, and, in some instances, allogeneic hematopoietic stem cell transplant. With the recent approval of new therapies—*i.e.*, CPX-351, enasidenib, ivosidenib, gemtuzumab ozogamicin, and midostaurin—a new era in AML treatment has emerged. Comprehensive diagnostic testing, such as cytogenetic and molecular testing, is necessary for establishing patient eligibility for these new agents and should be performed in a timely manner. However, choosing a therapy for patients who are eligible for multiple treatments may be a complex process, particularly for patients with newly diagnosed AML. This review discusses data, including associated safety profiles that supported these recent approvals, and provides insights to help clinicians navigate new therapy options for this devastating disease. Given the heterogeneity of AML, the treatment landscape will likely continue to grow and evolve as additional agents (and their combinations) are approved for the treatment of subpopulations of patients with AML. Physicians will need to remain abreast of the ever-changing treatment landscape.

## 1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease with multiple molecular pathways driving its progression [1,2]. It is a clonal hematopoietic disorder characterized by uncontrolled proliferation without differentiation of myeloid progenitors [3]. With an approximate 5-year survival rate of 27%, AML has a particularly poor prognosis and is rapidly fatal if left untreated [4].

After remaining stagnant for over 30 years, the AML treatment landscape has recently undergone significant changes [5–7]. Beginning with midostaurin and followed swiftly by CPX-351, gemtuzumab ozogamicin (GO), enasidenib, and ivosidenib, these desperately needed treatments for certain subsets of patients with AML were approved by the US Food and Drug Administration (FDA) in 2017 and 2018 [8–12]. Because of these approvals, the standard of care for management of patients with AML is rapidly changing. However, the inherent complexity of the disease and its diagnosis necessitates careful consideration to select the most appropriate treatment for each patient.

## 2. Disease overview

An estimated 19,520 new cases of AML will be diagnosed in the United States in 2018, accounting for approximately one-third of all new leukemia cases [4,13]. AML is typically considered a disease of older adults, with a median age at diagnosis of 68 years, but it can be seen in any age group [4,14]. Following the diagnosis of AML, additional testing aids in risk stratification and treatment decision making [15,16]. Testing involves karyotyping of the bone marrow to identify

*Abbreviations:* 7 + 3, cytarabine 7 days and daunorubicin (3 days); AE, adverse event; alloHSCT, allogeneic hematopoietic stem cell transplant; AML, acute myeloid leukemia; AML-MRC, AML with myelodysplasia-related changes; AR, allelic ratio; BSC, best supportive care; CAP-ASH, College of American Pathologists and American Society of Hematology; CEBPA, CCAAT/enhancer-binding protein alpha; CR, complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet count recovery; DNMT3 A, DNA methyltransferase 3; EFS, event-free survival; ELN, European LeukemiaNet; FDA, United States Food and Drug Administration; FISH, fluorescence in situ hybridization; FLT3, fms-like tyrosine kinase 3; GO, gemtuzumab ozogamicin; IDH, isocitrate dehydrogenase; IDH-DS, IDH inhibitor–associated differentiation syndrome; ITD, internal tandem duplication; IV, intravenous; MDS, myelodysplastic syndromes; MRC, United Kingdom Medical Research Council; NCCN, National Comprehensive Cancer Network; NPM1, nucleophosmin 1; OS, overall survival; q12h, every 12 h; R/R, relapsed or refractory; sAML, secondary AML; tAML, therapy-related AML; TKD, , tyrosine kinase domain; TP53, tumor protein 53; VOD, veno-occlusive disease; WHO, World Health Organization

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**Table 1**
WHO 2016 classification of AML with recurrent genetic abnormalities [15].

| |
|---|
| AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* |
| AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* |
| AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* |
| AML with t(6;9)(p23;q34.1); *DEK-NUP214* |
| AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM* |
| AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1* |
| Provisional entity: AML with *BCR-ABL1* |
| AML with mutated *NPM1* |
| AML with biallelic mutations of *CEBPA* |
| Provisional entity: AML with mutated *RUNX1* |

AML, acute myeloid leukemia; *CEBPA*, CCAAT/enhancer-binding protein alpha; inv, inversion; *NPM1*, nucleophosmin 1; t, translocation.

cytogenetic abnormalities (occurring in ≈50%–60% of adults with AML) [7,16,17] and molecular testing, including next-generation sequencing [18].

Although more than 1 factor likely drives the disease, certain abnormalities are more common than others [2]. For example, mutations in nucleophosmin 1 (*NPM1*; occurring in ≈30% of all AML cases and in 50%–60% of cytogenetically normal AML cases) and fms-like tyrosine kinase 3 (*FLT3*; occurring in ≈30% of patients with *de novo* AML) are among the most common genetic mutations in AML [2,19–21]. Mutations and chromosomal abnormalities can co-occur in a variety of combinations, which can alter their prognostic impact [2].

### 2.1. Cytogenetic abnormalities and genetic mutations

Nearly all patients with AML (97%) carry at least 1 somatic mutation [22]. The World Health Organization (WHO) guidelines use cytogenetic alterations and recurrent genetic mutations, first described in 2008 and updated in 2016 (Table 1), for the classification of AML [15,23]. Cytogenetic alterations and genetic abnormalities are helpful for risk stratification and can also guide treatment choice [7,16].

In the most recent versions of the European LeukemiaNet (ELN) recommendations and National Comprehensive Cancer Network (NCCN) Guidelines, patients with AML are stratified into 3 risk categories: favorable, intermediate, and adverse (Table 2) [7,16]. Patients in the adverse-risk group typically have higher rates of relapse and worse overall survival (OS) [24,25]. Unlike previous risk stratification groupings (*e.g.*, United Kingdom Medical Research Council [MRC]), which took into account only cytogenetics [26], the new risk categories consider both cytogenetic abnormalities and genetic mutations—including gene-gene interactions—to further refine prognostic groups. This is important, because the presence of a mutation does not automatically confer a worse prognosis, and some genetic interactions can affect prognosis. For example, internal tandem duplications (ITDs) are the most common mutations in *FLT3* and their prognostic impact can vary based on mutant burden and co-occurrence of other mutations. The allelic ratio (AR) of *FLT3*-ITD mutant to *FLT3* wild-type can impact survival outcomes, with a high *FLT3*-ITD AR (≥0.5) generally associated with shorter OS and disease-free survival than a low AR [27–29]. Likewise, a triple combination of *FLT3*-ITD, *NPM1*, and DNA methyltransferase 3A (*DNMT3A*) mutations confers a worse prognosis than the individual mutations or any combination of 2 mutations [2]. Lastly, as additional correlative studies are performed and new treatments become available, risk stratification categories are likely to be revised. For example, isocitrate dehydrogenase 2-R172 (*IDH2*-R172)–mutated AML is not currently a category in the ELN recommendations or NCCN Guidelines, but it was identified as a separate category in a recent whole-genome sequencing study [2]. With the approval of enasidenib and ivosidenib, the identification of patients with *IDH* mutations will become more relevant for treatment decisions.

The ELN recommendations, NCCN Clinical Practice Guidelines in Oncology, and College of American Pathologists and American Society of Hematology (CAP-ASH) guidelines recommend testing for certain genetic abnormalities following a diagnosis of AML; however, recommendations can differ between these groups and are rapidly changing [7,16,18]. For example, all groups recommend testing for CCAAT/enhancer-binding protein alpha (*CEBPA*), *FLT3, NPM1*, and *TP53*. Testing for *IDH1/2* is not currently recommended by the ELN but is recommended in the NCCN Guidelines and CAP-ASH guidelines, although this will likely change in the future given the recent approvals of enasidenib and ivosidenib. Testing for *ASXL1*, *RUNX1*, and *KIT* are recommended by both the ELN recommendations and the NCCN Guidelines.

AML subtypes, including *de novo* AML (not related to prior hematologic disease), secondary AML (sAML; arising from an antecedent hematologic disorder), and therapy-related AML (tAML; due to prior antineoplastic therapy), further help to define prognosis and treatment options [30].

### 2.2. De novo AML

*De novo* AML often has a better prognosis than sAML and tAML [30]. Variables such as mutation status and cytogenetics have the greatest prognostic significance. Approximately 40%–50% of patients with *de novo* AML have a normal karyotype [25,31]. *FLT3*-ITD and *RUNX1* mutations have been associated with a poor prognosis in patients with *de novo* AML with a normal karyotype, whereas *NPM1* and biallelic *CEBPA* mutations confer a better prognosis [32]. AML is a polyclonal disease; the clones and associated mutations present at the time of diagnosis, and relapse can vary [1]. In addition, sensitivity to targeted agents can vary between newly diagnosed and relapsed AML. For example, in *FLT3*-mutated AML, samples obtained at diagnosis are often less sensitive to inhibition of FLT3 alone than samples obtained at relapse [33]. Therefore, it has been speculated that less-specific targeted treatments might be more efficacious in early disease while more-specific agents might be better suited to relapsed or refractory (R/R) disease [34].

### 2.3. sAML and tAML

Mutations found in *de novo* AML only partially overlap with those found in sAML and tAML [16]. Patients with sAML typically have worse outcomes than those with *de novo* AML, and sAML is not commonly considered curable without an allogeneic hematopoietic stem cell transplant (alloHSCT) [35]. Because sAML evolves from antecedent hematologic disorders [36,37], the spectrum of genetic abnormalities is distinct from that found in *de novo* AML [37]. Lindsley and colleagues showed that 8 genes (*SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR*, and *STAG2*) were identified with > 95% specificity in sAML but not in *de novo* AML [37], whereas mutations in *NPM1*, MLL/11q23 rearrangements, and core-binding factor rearrangements were found at a significantly higher frequency in *de novo* AML than in sAML [37]. Thus, the mutation spectrum can perhaps identify a portion of clinically defined *de novo* AML cases (≤30%) that may have arisen from an undiagnosed antecedent myelodysplastic syndrome (MDS) [37].

As noted earlier, tAML emerges as a result of previous exposure to cytotoxic therapy [16,37]. The incidence of tAML may have increased in recent years due to increased use of adjuvant cancer treatments for solid tumors and an increased number of cancer survivors [30]. Genetic aberrations present in patients with tAML are heterogeneous and can include mutations commonly seen in *de novo* AML or sAML [37]. However, in general, tAML harbors more adverse genetic lesions, including a complex karyotype and aberrations in chromosomes 5, 7, and/or 17, which are usually associated with inferior survival outcomes [16]. Moreover, molecular abnormalities in *TP53* are more frequent in tAML and typically result in poor responses with conventional chemotherapy and alloHSCT [16,30,38].