Focus on Advancing Treatment for Acute Myeloid Leukemia

Bruno Medieros, MD, and Farhad Ravandi-Kashini, MD

Overview: Bruno Medieros, MD, and Farhad Ravandi-Kashini, MD, discuss recent advances in the treatment of acute myeloid leukemia (AML) and how new approvals have changed the paradigm for how AML is treated. A central topic in this program is how a better understanding of the molecular genetics of AML has led to new treatments. Dr. Medieros and Dr. Ravandi-Kashini also discuss the pathology and genetics that support the use of new targeted therapies, and the implications of findings from recent clinical trials.

Content Areas

- Daunorubicin-cytarabine
- Targeted treatment
- FLT3 Tyrosine Kinase Inhibitors
- Isocitrate Dehydrogenase Mutations
- Apoptosis
- CD33 monoclonal antibodies
- Bispecific antibodies

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Target Audience

This activity is intended for hematologist-oncologists; oncology nurse practitioners, nurses, physician assistants, and other healthcare providers who treat patients with AML.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Apply NCCN practice guidelines, expert recommendations, and/or the outcomes of clinical trials to AML treatment protocols
- Discuss the clinical significance of FLT3, IDH, CD33, and BCL-2
- Associate specific tumor genetic and molecular profiles with treatment mechanisms of action
- Recognize adverse events and potential drug-drug interactions associated with newly-approved treatments

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Abbreviations

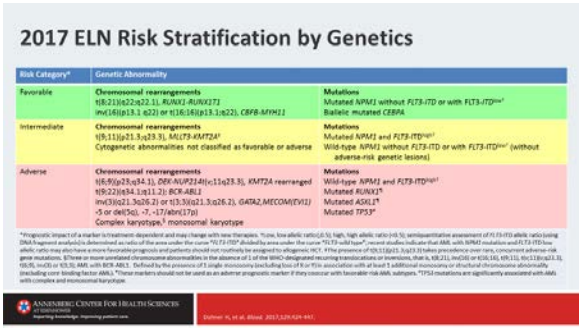
AML, acute myeloid leukemia
BiTE, bispecific T-cell-engaging
CI, confidence interval
CRc, composite complete remission (includes CR, CRi, and CRp)
CRh, CR with partial hematologic recovery
CRi, CR with incomplete hematologic recovery
CRp, CR with incomplete platelet counts
DART, dual-affinity retargeting
DFS, disease-free survival
EFS, event-free survival
ELN, European LeukemiaNet
GO, gemtuzumab ozogamicin
HR, hazard ratio
HSCT, hematopoietic stem cell transplant
MDS, myelodysplastic syndrome
OR, odds ratio
OS, overall survival
RFS, relapse-free survival
R/R AML, relapsed or refractory AML

Focus on Advancing Treatment for Acute Myeloid Leukemia

Standard chemotherapy for acute myeloid leukemia (AML) has remained essentially unchanged for the past 3 decades, but since 2017, the FDA has approved 7 new treatments. In addition to a change in the standard daunorubicin/cytarabine regimen, an understanding of the biology of AML has led to the introduction of new targeted treatments, and a new standard of care.

Genetic and Molecular Changes in AML

Cytogenetics and mutational analysis have been important in defining hematopoietic disorders, and are becoming an increasingly powerful prognostic tool and for guiding clinical decision making.[1,2] In addition to cytogenetic analysis, mutational analyses for *NPM1, FLT3, CEBPA, IDH1 and IDH2, DNMT3a,* and *KIT* mutations can help define patient prognosis, and in the cases of *FLT3* and *IDH*, can guide treatment. The European LeukemiaNet (ELN) has proposed a 3-group classification system for genetic risk that uses cytogenetic features, mutational analyses, and interactions between lesions, to define patients with a favorable, adverse, or intermediate prognosis (**see Figure 1**).



Daunorubicin-Cytarabine Liposome (CPX-351)

Daunorubicin-cytarabine liposome (CPX-351) is a 1:5 molar ratio of daunorubicin to cytarabine.[3] Liposomal encapsulation improves the half-life of daunorubicin-cytarabine, and also maintains the synergistic 1:5 ratio. In preclinical studies, this daunorubicin-cytarabine ratio had the greatest cytotoxic effect, and encapsulation in liposomes maintains this ratio. Consequently, CPX-351 has a greater antineoplastic effect than coadministration of unencapsulated chemotherapy.[4,5] Preclinical studies also suggest that CPX-351 is preferentially taken up in the bone marrow and by leukemic cells.[6]

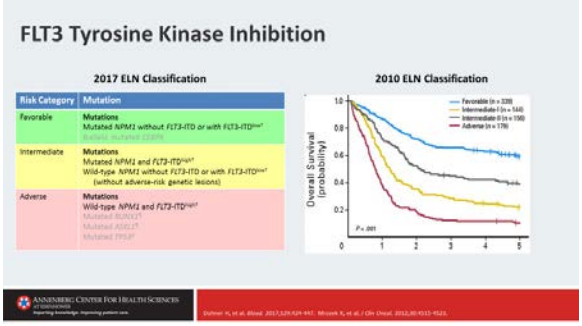
Pharmacokinetic studies in humans showed that the daunorubicin-cytarabine ratio was maintained in plasma and bone marrow for at least 24 hours.[6] CPX-351 was tested in a randomized, open-label, parallel-arm trial of treatment-naïve patients between 60-75 years old (N=309). Patients had to be able to tolerate intensive chemotherapy, and had a performance status of 0-2.[3] Randomization was either to treatment with CPX-351 (n=153) or standard 7+3 chemotherapy (n=156); both arms received 1-2 cycles of induction therapy, followed by 1-2 cycles of consolidation for patients in CR or CRi. Patients were followed for 5 years or until death. CPX-351 was superior to conventional 7+3 chemotherapy on several measures, and the benefit for CPX-351 treatment was independent of patient age and AML subtype. Overall survival was 9.56 months (CI 6.60-11.86) for patients receiving CPX-351, compared to 5.95 months (CI 4.99-7.75, *P*=0.005) in the 7+3 arm, and more patients responded to CPX-351 (37%, compared to 26%, had complete responses, *P*=0.04). Other endpoints were improved in the CPX-351 group, including all-cause mortality at 30 and 60 days, the number of patients going on to receive hematopoietic stem cell transplant (HSCT), and median survival after HSCT (not reached in CPX-351 group, vs 10.25 months for 7+3).

In a separate analysis of the phase 3 data, Kolitz and colleagues presented data suggesting that CPX-351 could be administered in the outpatient setting without a loss of efficacy.[7] Median survival for patients who received their first course of consolidation therapy as inpatients

(n=24/49) had a median OS of 14.7 months, and this was similar to the OS in those who were treated as outpatients (n=25/49, 25.4 months). While median OS had not been reached in patients who received CPX-351 as inpatients during the second consolidation cycle, median survival was 26.3 months in outpatients. Based on these studies, CPX-351 has become the new standard of care in patients with therapy-related AML and AML with myelodysplasia-related changes. To date, it remains unclear whether CPX-351 will provide the same level of benefit in patients under 60 years of age.

FLT3 Tyrosine Kinase Inhibitors

The FMS-like tyrosine kinase 3 (*FLT3*) receptor has a role in the survival, proliferation, and differentiation of hematopoietic stem cells, and is overexpressed in >70% of AML cases.[8-10] Mutations in *FLT3* constitutively activate the FLT3 pathway, driving the survival and proliferation of leukemic cells. The most common mutation is an internal tandem duplication (*FLT*-ITD) of the juxtamembrane domain; up to 30% of patients with AML have the *FLT3*-ITD mutation, and *FLT3*-ITD is associated with shorter remissions and overall survival.[1,2,10,11] Mutations to the tyrosine kinase domain also occur (*FLT3*-TKD), but are less common (10% or less of cases) and are not as clearly linked to prognosis.[1,10] The prognostic effect of mutations to the *FLT3* gene is modified by other, nonlinked loci, the presence of a wild-type *FLT3* allele, and the ratio of FLT3-ITD to FLT3 wild-type expression (**see Figure 2**).



Small-molecule tyrosine kinase inhibitors that bind FLT3 and competitively inhibit protein phosphorylation have been identified.[10] These inhibitors differ in their specificity for FLT3 vs other tyrosine kinases (eg, c-Kit and VEGF) and mechanisms of action. Midostaurin and gilteritinib bind to the active conformation of FLT3 in the gatekeeper domain (type I inhibitors), while sorafenib, ponatinib, and quizartinib bind the inactive conformation near the ATP-binding domain (type II inhibitors). These differing mechanisms are clinically significant since mutations in the gatekeeper or ATP-binding domains affect the effectiveness of the inhibitor, or can lead to resistance. In general, type I inhibitors are effective against ITD and TKD mutants, while type II inhibitors only target *FLT3*-TKD mutants.

Midostaurin is a FLT3-protein kinase C inhibitor that had activity as a single agent in *FLT3*-mutant AML.[10] However, the real value of midostaurin was demonstrated in a phase 3 trial of treatment-naïve patients, under 60 years of age, who received conventional daunorubicin-cytarabine induction chemotherapy, with or without midostaurin (50 mg twice daily for days 8-22).[12] Patients went on to receive 4 cycles of cytarabine consolidation treatment and 12 cycles of maintenance therapy with midostaurin or placebo. Those treated with midostaurin had a significant improvement in OS compared to patients who only received placebo (75 months vs 26 months, respectively). This benefit was independent of the type of *FLT3* mutation—OS was similar in patients with *FLT3*-ITD and *FLT3*-TKD mutations. In a post-hoc analysis, *NPM* mutation status may have had an effect, however, with midostaurin having the most pronounced effect on OS and event-free survival (EFS) in patients who had *NPM*-wild-type/*FLT3*-ITD^{high} AML.[13] In these patients, midostaurin improved the OS over placebo from 14 to 26 months (P=0.025) and EFS from 3 to 8 months (P=0.016). Results after 5 years of follow-up also

indicated significant benefits for midostaurin, with improvements in 5-year OS and EFS. The incidence of grade ≥3 adverse events was similar between the groups.

While midostaurin is a multikinase inhibitor, gilteritinib has activity preferentially against wild-type FLT3, FLT3-ITD, and several FLT3 mutants (FLT3-D835, a common source of resistance, and the gatekeeper F691L mutation).[14] Gilteritinib also has some activity against the Axl kinase, but not c-Kit, which is important for normal hematopoiesis. A phase 1/2 trial showed that 49% of patients with a *FLT3* mutation had a CRc to gilteritinib, but only 12% with *FLT3*$^{\text{wild-type}}$ responded.[15] Responses were still seen in patients who were treatment naïve (CRc=44%) or who had failed previous *FLT3* inhibitor treatment (CRc=31%). Gilteritinib was approved in November 2018 based on an interim analysis of the ADMIRAL trial.[16] Patients (N=138) with relapsed or refractory AML and a *FLT3*-ITD, *FLT3*-D835, or *FLT3*-I836 mutation were treated with 120 mg gilteritinib daily. After a median follow-up of 4.6 months, 21% of patients had a CR or CRh (21%, 95% CI: 14.5, 28.8). For patients relapsed or refractory AML (R/R AML) with a *FLT3* mutation, gilteritinib may be an option.

Results for a phase 3 study of quizartinib monotherapy were recently presented, leading to FDA submission of a new drug application.[17] In the QuANUTM study, patients with *FLT3*-ITD AML that was refractory to treatment, or who had relapsed within 6 months of remission after initial treatment, were randomized to treatment with quizartinib (60 mg/day) or conventional salvage chemotherapy. The CRc was 48% for patients who received quizartinib (compared to 30% for standard chemotherapy), and the overall response rate was 69% (compared to 30% with chemotherapy). Quizartinib met the primary endpoint of improved OS, with quizartinib-treated patients surviving a median of 6.2 months, vs 4.7 months in the chemotherapy group (HR=0.76, *P*=0.02). The benefit was independent of subsequent transplant, the use of another FLT3 inhibitor, and protocol deviations. Patients who had prior allogeneic HSCT also had a better overall survival with quizartinib, and the benefit was independent of karyotype risk category.

In patients with untreated, *FLT3*-mutant AML, FLT3 inhibitors are the standard of care given the improvement in outcomes when combined with chemotherapy, or when used as a monotherapy in patients with relapsed and refractory AML. Ongoing clinical trials will clarify whether adding the next generation of more potent and specific FLT3 inhibitors to chemotherapy will lead to better outcomes.

Isocitrate Dehydrogenase Mutations as Treatment Targets

The isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) enzymes are components of the citric acid cycle (aka, tricarboxylic acid or Krebs cycle); in addition to its metabolic role, α-ketoglutarate (the product of isocitrate oxidative decarboxylation by IDH1 and IDH2) has a role in cell-cycle regulation and gene expression though its effect on DNA methylation.[18] Mutant forms of IDH enzymes also produce the oncometabolite, (R)-2-hydroxyglutarate, which appears to promote cell proliferation and block differentiation in hematopoietic cells.[18] *IDH1* mutations are present in 7-14% of patients with AML, while *IDH2* mutations are found in 8%-19%.[19] Mutations in the *IDH* genes rarely occur together, and are usually found in patients without *FLT3* abnormalities.[20] The prognostic value for either *IDH* mutation is not clear.

Enasidenib was approved in 2017 for patients with an *IDH2* mutation, and in July 2018, the IDH1 inhibitor ivosidenib was approved. The approval for enasidenib was based on an open-label, single-arm trial of patients with an *IDH2* mutation; most patients had R/R AML (n=159),

but the trial also included treatment-naïve patients (n=24) and patients with MDS (n=14).[21] In this trial, enasidenib led to a response in 37% of patients with relapsed or refractory disease, including 18% who had a CR. The median OS in this group was 9.3 months, with 39% surviving to 1 year after a median follow-up of 7.7 months. The response rates for patients with R140Q and R172K mutations were similar (OR 36% and 42%, respectively), even though mutations at these positions may have disparate prognoses.[22]

Ivosidenib was tested in a phase 1, open-label, dose-escalation trial of patients with an *IDH1* mutation, most of whom had had at least 2 relapses, had relapsed after stem-cell transplant, were refractory after induction or reinduction, or had relapsed within 1 year.[23] The trial was conducted in 2 stages: the dose escalation phase included 78 patients, while the dose expansion phase enrolled 180 patients who were treated with 500 mg ivosidenib once daily on a continuous 28-day cycle. The CR/CRh rate for this study was 30%, with 22% of patients having a CR; CR occurred after a median of 2.7 months (range 0.9-5.6). Patients with a CR/CRh had a median response duration of 11.1 months, with 50.1% surviving to 18 months.

Both IDH inhibitors are associated with significant clinical benefit in patients with R/R AML, and ongoing clinical trials will determine whether there will be an improvement for patients with *IDH1* or *IDH2* mutations when combined with induction chemotherapy and/or hypomethylating agents.

Targeting Apoptosis

The BCL2 protein inhibits apoptosis (programmed cell death), and overexpression of BCL2 in AML has been associated with poor survival and chemotherapy resistance.[24] Venetoclax inhibits the antiapoptotic activity of BCL2 by disrupting its sequestration of proapoptotic proteins (eg, the BH3-only proteins, BIM and BAX), leading to p53-independent apoptosis.[25,26] The patients enrolled in the 2 open-label trials leading to the approval of venetoclax had newly-diagnosed AML (ie, were treatment naïve), were generally older (median age >74 years old), and were not otherwise eligible for intensive chemotherapy.[27,28] In the first study, patients (N=145) received decitabine or azacitidine with venetoclax 400 mg or 800 mg after a 3-day ramp-up phase (5 patients also received venetoclax 1200 mg). In the overall study population, 66% of patients achieved a CR/CRi with a median duration of 11.3 months after 15.1 months of follow-up. Median OS was 17.5 months, and no cases of tumor lysis syndrome were observed. Patients in the second study (N=61) reached a target dose of 600 mg after a 5-day ramp-up phase, and were also treated with cytarabine. The CR/CRi rate was (62%), and median duration of response was 13.2 months. OS was 11.4 months, with 45% of patients surviving 12 months, and was highly correlated with response: all patients who had a CR survived at least 12 months, compared to 49% for patients with a CRi and 5% for patients without a response. The authors also compared responses among several patient subsets. In general, responses were better in patients with intermediate genotypic features or without a history of hypomethylating treatment for an antecedent hematologic disorder, compared to patients with adverse genotypic features or with prior hypomethylating agent treatment. Patients in the intermediate risk category (n=37) had a response rate of 76%, compared to those in the adverse risk category (47%, n=19), and patients who had been treated with a hypomethylating agent had a CR/CRi of 53% (n=17) vs 66% (n=44) in those who had not; this was similar to the response rate in the 27 patients who had secondary AML (CR/CRi=52%). These findings are being confirmed in 2 ongoing, placebo-controlled, phase 3 trials of treatment-naïve patients who will receive venetoclax in

combination with azacitidine (NCT02993523) or low-dose cytarabine (NCT03069352).

For older patients who are unable to undergo induction chemotherapy, the combination of venetoclax plus a hypomethylating agent or low-dose cytarabine provides significant clinical benefit. These combinations are being tested and will clarify whether they should be the standard of care for previously untreated patients with AML who cannot tolerate induction chemotherapy.

Target Antigens and Novel Antibodies in AML

Tumor-associated antigens are one mechanism for targeting treatment to tumor cells. CD33 is a cell-surface receptor expressed primarily in the myeloid lineage, and, because of its nearly ubiquitous presence in patient AML samples, has become a target for antibody-mediated treatments.[29] One means of antibody-directed treatment is by using a monoclonal antibody to deliver a cytotoxic agent to tumor cells. Gemtuzumab ozogamicin (GO) is one example where this mechanism has been successfully applied. On binding to a tumor cell via the CD33 receptor, GO is internalized into the lysosome where calicheamicin is hydrolyzed and released into the cell.[30] GO was initially approved in 2000 for patients with $CD33^+$ AML who were not eligible for chemotherapy, but was withdrawn in 2010 when a confirmatory trial did not demonstrate an improvement in overall survival and raised the concern of treatment-related early mortality.[30,31]

The phase 3 ALFA-0701 was initiated after the withdrawal of GO to reevaluate its potential benefits.[32] Patients in this trial (N=278) were 50-70 years of age with de novo, treatment-naïve AML, and were randomized to standard treatment with daunorubicin/cytarabine, with or without GO 3 mg/m^2 on days 1, 4, and 7 during induction, and on day 1 during consolidation therapy. EFS was the primary endpoint. Treatment-related mortality was similar between the GO and control groups (n=6 without GO, vs 9 in the GO group, *P*=0.41), as was the CR/CRi (74%-81%, *P*=0.25). GO, however, had a significant benefit on both EFS and relapse-free survival (RFS): patients who were treated with GO had an estimated 3-year EFS of 31%, compared to 19% in the control group (*P*<0.05), and a 3-year RFS of 38%, compared to 25% in the control group (*P*<0.05). There was no significant difference in 3-year OS.

Hills et al also conducted a meta-analysis of individual patient data from 5 randomized trials of GO, including data from 3325 patients. Again, this meta-analysis showed that there was no difference in CR/CRi with GO treatment. Patients treated with GO, however, had a lower risk of relapse (OR 0.91, 0.73-0.90; *P*=0.0001) and improved 5-year survival (OR 0.90, 0.82-0.98; *P*=0·01). As part of this study, the authors also compared patients based on their cytogenetic risk.[31] GO led to a 20.7% difference in OS at 6 years in patients with a favorable cytogenetic profile (compared to patients who were only treated with standard therapy, *P*=0.006), with a 6-year survival of 77.5% in patients who received GO (compared to 54.8% in patients in the control group). A smaller, but still significant, difference of 5.7% was seen in patients with an intermediate cytogenetic profile (6-year survival=39.6% in the GO group, 33.9% in the control group; *P*=0.005). Patients with an adverse cytogenetic profile did not benefit from the addition of GO (6-year survival=2.2%). Finally, the authors found that doses of 3 mg/m^2 were associated with a lower risk of early death than 6 mg/m^2, and that the higher dose did not confer an advantage.

These studies led to the approval of GO for adults with newly-diagnosed, CD33-positive, and for patients with CD33-positive R/R AML in September 2017. The addition of GO to conventional induction chemotherapy improves

survival for AML patients with favorable- and intermediate-risk cytogenetics, but does not improve the outcomes for patients with an adverse-risk karyotype.

An alternative to monoclonal antibodies is a bispecific antibody that recruits an immune effector cell to a tumor cell via a tumor antigen, leading to the cell-mediated killing of the targeted cell. Bispecific T-cell-engaging (BiTE) antibodies are one example of this method, and dual-affinity retargeting (DART) antibodies are another variation, both of which are being tested in AML. One advantage of these methods is that, compared to antibodies that delivery a chemotherapeutic, fewer bispecific antibodies are needed to effect cell death—an important consideration when the target antigen is expressed at low levels. AMG-330 is a bispecific antibody that binds the CD33 tumor cell antigen, and then recruits a T-cell via the CD3 receptor.[32] In a phase 1 dose escalation trial, patients (N=35) with R/R AML were treated with AMG-330, and 4 patients attained a CR/CRi at doses between 120-240 µg/day.[33] XmAB14045 utilizes a similar approach, but targets the CD123 antigen or interleukin-3 receptor (IL-3R).[34] Expression of IL-3R is highest on B lymphoid and myeloid progenitors, and it is either not present or expressed at low levels on other hematopoietic precursor cells; CD123 expression has also been associated with poor prognosis.[35] As of February 2019, the phase 1 trial of XmAb14045 is on clinical hold and not enrolling additional patients, pending a review of 2 patient deaths possibly related to treatment.[36] Flotetuzumab utilizes the same target but is based on the DART platform rather than the immunoglobulin scaffold of BiTEs. This compound is currently undergoing phase 1 testing.[37]

Conclusion

The recent approvals have improved overall outcomes for several subsets of AML patients, but we still have the challenge of treating patients who do not have a targetable genotype or karyotype. The risk of resistance and managing patients who develop resistance are other areas that will be of increasing concern as well.

Figure 1

2017 ELN Risk Stratification by Genetics

Risk Category*	Genetic Abnormality	
Favorable	**Chromosomal rearrangements** t(8;21)(q22;q22.1), *RUNX1-RUNX1T1* inv(16)(p13.1 q22) or t(16;16)(p13.1;q22), *CBFB-MYH11*	**Mutations** Mutated *NPM1* without *FLT3-ITD* or with FLT3-*ITD*^{low†} Biallelic mutated *CEBPA*
Intermediate	**Chromosomal rearrangements** t(9;11)(p21.3;q23.3), *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse	**Mutations** Mutated *NPM1* and *FLT3*-ITD^{high†} Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low†} (without adverse-risk genetic lesions)
Adverse	**Chromosomal rearrangements** t(6;9)(p23;q34.1), *DEK-NUP214*t(v;11q23.3), *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2), *GATA2,MECOM(EVI1)* -5 or del(5q), -7, -17/abn(17p) Complex karyotype,§ monosomal karyotype	**Mutations** Wild-type *NPM1* and *FLT3*-ITD^{high†} Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*#

*Prognostic impact of a marker is treatment-dependent and may change with new therapies. †Low, low allelic ratio (,0.5); high, high allelic ratio (<0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT. ‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations. §Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCR-ABL1. Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML). ¶These markers should not be used as an adverse prognostic marker if they cooccur with favorable-risk AML subtypes. #TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

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Dohner H, et al. *Blood*. 2017;129:424-447.

Figure 2

2017 ELN Risk Stratification by Genetics

Risk Category*	Genetic Abnormality	
Favorable	**Chromosomal rearrangements** t(8;21)(q22;q22.1), *RUNX1-RUNX1T1* inv(16)(p13.1 q22) or t(16;16)(p13.1;q22), *CBFB-MYH11*	**Mutations** Mutated *NPM1* without *FLT3-ITD* or with FLT3-*ITD*^{low†} Biallelic mutated *CEBPA*
Intermediate	**Chromosomal rearrangements** t(9;11)(p21.3;q23.3), *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse	**Mutations** Mutated *NPM1* and *FLT3*-ITD^{high†} Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low†} (without adverse-risk genetic lesions)
Adverse	**Chromosomal rearrangements** t(6;9)(p23;q34.1), *DEK-NUP214*t(v;11q23.3), *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2), *GATA2,MECOM(EVI1)* -5 or del(5q), -7, -17/abn(17p) Complex karyotype,§ monosomal karyotype	**Mutations** Wild-type *NPM1* and *FLT3*-ITD^{high†} Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*#

*Prognostic impact of a marker is treatment-dependent and may change with new therapies. †Low, low allelic ratio (,0.5); high, high allelic ratio (<0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT. ‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations. §Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCR-ABL1. Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML). ¶These markers should not be used as an adverse prognostic marker if they cooccur with favorable-risk AML subtypes. #TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

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