Diagnosis and Treatment of Patients With Acute Myeloid Leukemia With Myelodysplasia-Related Changes (AML-MRC)

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ABSTRACT

Objectives: *Acute myeloid leukemia (AML) with myelodysplasia-related changes (AML-MRC) represents a high-risk and somewhat diverse subtype of AML, and substantial confusion exists about the pathologic evaluation needed for diagnosis, which can include the patient's clinical history, cytogenetic analysis, mutational analysis, and/or morphologic evaluation. Treatment decisions based on incomplete or untimely pathology reports may result in the suboptimal treatment of patients with AML-MRC.*

Methods: *Using a PubMed search, diagnosis of and treatment options for AML-MRC were investigated.*

Results: *This article reviews the current diagnostic criteria for AML-MRC, provides guidance on assessments necessary for an AML-MRC diagnosis, summarizes clinical and prognostic features of AML-MRC, and discusses potential therapies for patients with AML-MRC. In addition to conventional chemotherapy, treatment options include CPX-351, a liposomal encapsulation of daunorubicin/cytarabine approved for treatment of adults with AML-MRC; targeted agents for patients with certain mutations/disease characteristics; and lower-intensity therapies for less fit patients.*

Conclusions: *Given the evolving and complex treatment landscape and the high-risk nature of the AML-MRC population, a clear understanding of the pathology information necessary for AML-MRC diagnosis has become increasingly important to help guide treatment decisions and thereby improve patient outcomes.*

Key Points

- Substantial confusion exists about the pathologic evaluation needed to diagnose acute myeloid leukemia with myelodysplasia-related changes (AML-MRC), and treatment decisions based on incomplete or untimely pathology reports may lead to suboptimal treatment.
- The patient's clinical history, cytogenetic analysis, mutational analysis, and morphologic evaluation are all important for the diagnosis, prognosis, and subsequent treatment plan for AML-MRC.
- Treatments for AML-MRC are conventional chemotherapy, CPX-351 (liposomal daunorubicin/cytarabine), targeted agents based on certain mutations/disease characteristics, and lower-intensity therapies.

The classification of acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) in general includes patients with acute myeloid leukemia (AML) that develops after myelodysplastic syndromes (MDSs) or MDS/myeloproliferative neoplasms (MPNs), AML with multilineage dysplasia, and de novo AML with certain MDS-related cytogenetic abnormalities.[1] The classification of AML-MRC overlaps somewhat with the traditional term "secondary AML," which includes patients with AML that develops from an antecedent hematologic disorder (including MDS and MDS/MPN), as well as those with therapy-related AML that develops after prior cytotoxic therapy, radiotherapy, or immunosuppressive therapy[2]; however, therapy-related AML is not included in the AML-MRC category.

It has been estimated that AML-MRC represents up to 48% of all adult AML cases.[3,4] Outcomes for patients with AML-MRC, or more generally those with secondary AML, following conventional combination chemotherapy, are poor compared with many other AML subtypes, with lower remission rates and shorter overall

survival (OS).[2,5-8] Several new agents have been approved over the past few years for the treatment of various AML subgroups, driving an evolving and complex treatment landscape. Given the high-risk nature of AML-MRC, a clear understanding of the AML-MRC diagnosis and appropriate treatment options is important to help improve outcomes.

Identification and Diagnosis of AML-MRC

Diagnostic Criteria for AML-MRC

The prognostic significance of dysplastic changes in the nonblast cells of patients with AML was first described by Gahn et al[9] in 1996. In 2002, the World Health Organization (WHO) introduced the category of "AML with multilineage dysplasia," which applied to patients who had 20% or more blasts in the blood or bone marrow and dysplasia in 50% or more of cells in two or more hematopoietic cell lineages.[10] In 2008, the WHO expanded the category to include patients with a history of MDS or MDS/MPN and those with certain myelodysplasia-related cytogenetic abnormalities, thus creating the AML-MRC category.[11]

According to the 2016 WHO Classification ▮Table 1▮, the current AML-MRC designation applies to patients with AML who have 20% or more blasts in the blood or bone marrow and who meet any of the following criteria: a history of MDS or MDS/MPN, such as chronic myelomonocytic leukemia (CMML); an MDS-related cytogenetic abnormality; or multilineage dysplasia in 50% or more of two or more cell lineages (ie, dysgranulopoiesis, dyserythropoiesis, or dysmegakaryopoiesis; ▮Image 1▮) in the absence of *NPM1* or biallelic *CEBPA* mutations (if the diagnosis is based on multilineage dysplasia alone).[1] AML-MRC includes a variety of cytogenetic abnormalities, including complex karyotypes (defined as three or more unrelated abnormalities, not including core binding factor rearrangements and the *PML/RARA* rearrangement) and other specified unbalanced and balanced abnormalities[1] (Table 1). Dysgranulopoiesis includes hypogranularity, nuclear hyposegmentation of granulocytes (ie, Pelger-Huët–like anomaly), abnormal granularity (pseudo–Chédiak-Higashi granules), and abnormally segmented nuclei.[3,4] Dyserythropoiesis includes megaloblastosis, nuclear budding, irregular nuclear contours, nuclear fragmentation, multinucleation, karyorrhexis, nuclear bridging, ring sideroblasts, and cytoplasmic vacuolization.[3,4] Dysmegakaryopoiesis includes small size, nuclear hypolobation, nuclear hypersegmentation, and separated nuclear lobes.[3,4]

The AML-MRC diagnosis excludes cases of therapy-related AML and AML with cytogenetic abnormalities qualifying for a diagnosis of AML with recurrent genetic abnormalities, such as t(8;21), inv(3), and t(6;9), the latter two of which may have multilineage dysplasia.[1,12] Although not part of the disease definition, various gene mutations are more commonly associated with AML-MRC, including mutations of *ASXL1*, *TP53*, and *U2AF1*, and may have prognostic significance within this group.[13-15]

The patient's clinical history, cytogenetic analysis, mutational analysis, and morphologic evaluation are all important for the diagnosis and prognosis of AML-MRC, as well as for informing treatment decisions. Since there are now newer initial treatment options for this subset of patients, it is critical for the pathologist to offer

▮Table 1▮
2016 World Health Organization Criteria for AML-MRC[1]

Patients with ≥20% blasts in peripheral blood or bone marrow who meet any of the following criteria[a]:			
Clinical history	A history of MDS or MDS/MPN, such as CMML and aCML		
Morphologic features	Multilineage dysplasia in ≥50% of ≥2 cell lineages (ie, dysgranulopoiesis, dyserythropoiesis, or dysmegakaryopoiesis) in the absence of *NPM1* or biallelic *CEBPA* mutations		
Cytogenetic abnormalities	An MDS-related cytogenetic abnormality, as indicated below		
	Complex karyotype:	Unbalanced abnormalities:	Balanced abnormalities:
	≥3 unrelated abnormalities, not including the recurrent cytogenetic abnormalities encountered in AML	−7/del(7q)	t(11;16)(q23.3;p13.3)
		del(5q)/t(5q)	t(3;21)(q26.2;q22.1)
		i(17q)/t(17p)	t(1;3)(p36.3;q21.2)
		−13/del(13q)	t(2;11)(p21;q23.3)
		del(11q)	t(5;12)(q32;p13.2)
		del(12p)/t(12p)	t(5;7)(q32;q11.2)
		idic(X)(q13)	t(5;17)(q32;p13.2)
			t(5;10)(q32;q21.2)
			t(3;5)(q25.3;q35.1)

aCML, atypical chronic myeloid leukemia, *BCR-ABL1* negative; AML, acute myeloid leukemia; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.
[a]Excludes patients with therapy-related AML (ie, arising after cytotoxic chemotherapy, radiotherapy, or immunotherapy) or a cytogenetic abnormality qualifying for a diagnosis of AML with recurrent genetic abnormalities.

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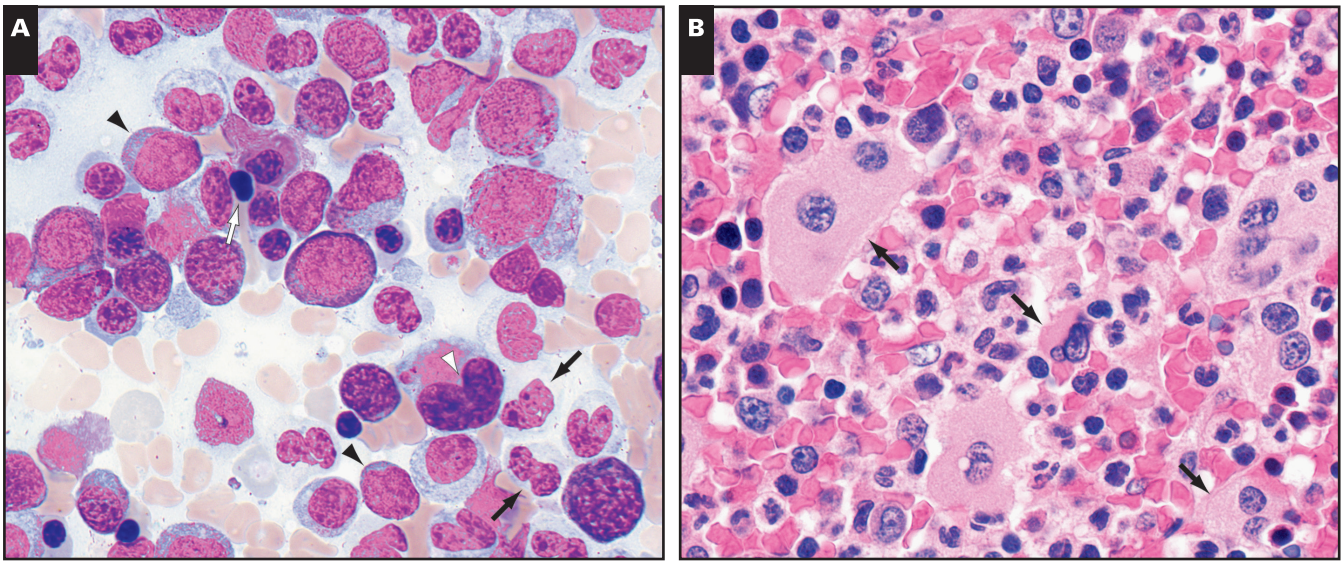

Image 1 Morphologic features of multilineage dysplasia. **A**, Dysplastic changes are usually most prominent on the bone marrow aspirate or peripheral blood smear. In this case, erythroid precursors show irregular nuclear contours (white arrow), granulocytes demonstrate clumped nuclear chromatin without complete segmentation and hypogranular cytoplasm (black arrows), and a small, hypolobated megakaryocyte is present (white arrowhead). Some blast cells are small (black arrowheads) and may be mistaken for lymphocytes (Wright-Giemsa, ×600). **B**, The bone marrow biopsy specimen is hypercellular with a heterogenous cellular composition. Dysplastic small and large megakaryocytes, with detached nuclear lobes, are easily identified on the biopsy specimen (some marked with arrows) (H&E, ×400).

the diagnosis of AML-MRC as soon as possible, which may require amending reports after receipt of cytogenetic and molecular genetic results. Patients with a known history of MDS or MDS/MPN are the easiest to diagnose, as they can be diagnosed based on clinical history. However, diagnosis on the basis of karyotype requires a longer period of time to complete the necessary assessments. Assessment of multilineage dysplasia requires a skilled hematopathologist comfortable with evaluation of dysplastic features, as well as adequate aspirate samples to judge morphologic changes and sufficient residual hematopoietic precursors to confidently comment on dysplastic features in 50% or more of the cells. If AML-MRC is diagnosed based on only multilineage dysplasia, then mutational analysis is also required to exclude patients with *NPM1* and biallelic *CEBPA* mutations, and this information is typically not immediately available. Some,[16] but not all,[17,18] early studies suggested that multilineage dysplasia alone was not predictive of a worse prognosis in patients with intermediate-risk cytogenetics who lacked a history of MDS or MDS/MPN. However, subsequent studies have shown this is only the case in the presence of *NPM1* and *CEBPA* mutations. AML cases with these mutations may have multilineage dysplasia, which is not prognostically significant. In the absence of such mutations, however, multilineage dysplasia remains a predictor of poor prognosis[19] and a criterion for the diagnosis of AML-MRC.[1]

The pathologist must integrate all of this information into the final report as quickly as possible to allow the clinician to make timely treatment decisions. Because an accurate diagnosis of AML-MRC requires critical clinical information, as well as integration of morphology, cytogenetics, and, at times, molecular genetic studies, such a diagnosis creates reporting challenges. Timing of the analyses to accurately diagnose patients with AML-MRC also represents a significant challenge to the optimal treatment of patients. Such challenges in the reporting of AML specimens have been summarized in more detail elsewhere,[20-22] but all reports need to record information related to prior MDS or MDS/MPN and morphologic descriptions with quantification of dysplasia in nonblast cells, when present. Subsequent cytogenetic and molecular genetic findings must be integrated into a final report to ensure an accurate diagnosis. Ultimately, changes in the diagnostic and therapeutic pathways may be needed to provide optimal treatment of patients with AML-MRC.

Assessments Necessary for AML-MRC Diagnosis

The 2017 guidelines from the College of American Pathologists and the American Society of Hematology specify that the following assessments and testing

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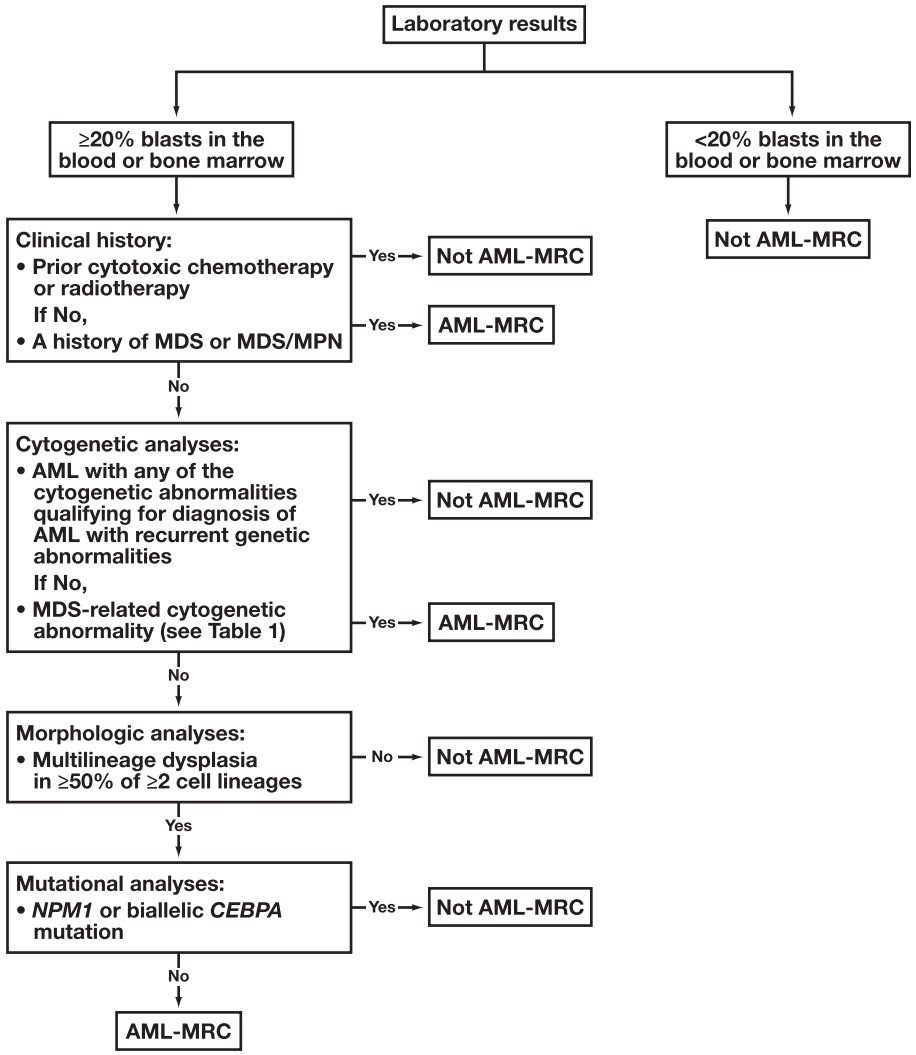
methods should be employed to accurately identify different subtypes of AML, including AML-MRC.[20] These assessments can help to differentiate AML-MRC from other subtypes of AML ▮Figure 1▮.

A thorough patient history and relevant clinical data, including a physical examination, imaging findings, and blood laboratory values, should be obtained.[20] Patient medical history is important for identifying and excluding individuals with therapy-related AML.[3] According to the current WHO classification, patients with a history of prior cytotoxic therapy should be diagnosed as having therapy-related AML even if they also have features of AML-MRC (eg, antecedent therapy-related MDS that develops into AML).[1]

Metaphase cytogenetic analysis, fluorescent in situ hybridization (FISH) testing, and/or reverse transcriptase–polymerase chain reaction (RT-PCR) should be performed to identify cytogenetic abnormalities and differentiate AML-MRC from the WHO classification category of AML with recurrent cytogenetic abnormalities. FISH analysis (as opposed to metaphase karyotype) of de novo AML may be able to more rapidly identify patients with AML-MRC based on MDS-related cytogenetic abnormalities. AML FISH panels typically include probes for −5, del(5q), −7, and del(7q), which may aid in identifying patients with AML-MRC. Furthermore, probes for other translocations could identify deletions on other chromosomes; if three or more abnormalities are detected, a diagnosis of AML-MRC could be considered. Finally, FISH panels will exclude t(8;21), inv(16), and t(15;17), which are excluded from AML-MRC regardless of the complexity of the karyotype.[1] However, it should be noted that the WHO classification is based on karyotype and not FISH findings, and the significance



▮Figure 1▮ Simplified diagnostic algorithm for AML-MRC.[1,3] AML, acute myeloid leukemia; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

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of an abnormal FISH result in the setting of a normal karyotype with 20 metaphases remains to be determined. A study from the University of Pennsylvania compared results of rapid FISH testing (MDS panel; turnaround time of <6 hours) with those of metaphase chromosome analysis in 31 adults thought to potentially have therapy-related AML or AML-MRC. Fifteen (48%) patients were identified as having MDS-related cytogenetics by metaphase chromosome analysis; of these, 12 (80%) patients were also identified by rapid FISH analysis and one additional patient was known to have a history of MDS, demonstrating the feasibility of rapid FISH analysis in combination with clinical history for identifying patients with AML-MRC.[23] While one could argue that rapid FISH testing is not necessary when an adequate karyotype is available, such testing may allow patients to receive specialized therapy for AML-MRC earlier, which might justify the added expense. Furthermore, the karyotypic analysis may fail due to lack of metaphases; the FISH analysis could provide valuable clinical information in this setting as well.

A fresh bone marrow aspirate smear in conjunction with a bone marrow trephine core biopsy specimen, bone marrow trephine touch preparations, and/or marrow clots should undergo morphologic evaluation by a hematopathologist. There are a few specific situations in which bone marrow may have some of the features of AML-MRC but cannot be classified as such. For example, AML not otherwise specified (AML-NOS) categories, including acute megakaryoblastic leukemia, may have dyspoiesis in one cell line but cannot be considered AML-MRC based on the presence of unilineage dysplasia alone. Cases of pure erythroid leukemia and cases previously diagnosed as acute erythroleukemia (erythroid/myeloid type) may have myelodysplasia-related cytogenetic abnormalities and dyspoiesis in multiple cell lines, but these cases do not have 20% or more myeloblasts.[1,3,20] Cases meeting prior criteria of the erythroid/myeloid type of erythroleukemia are now classified as MDS.[1,24]

Finally, mutational analysis should minimally be performed for *FLT3*, *NPM1*, *CEBPA*, *RUNX1*, *IDH1*, and *IDH2* based on various guidance[1,20,25,26]; although these mutational analyses are currently insufficient for a diagnosis of AML-MRC by themselves, additional mutational analyses can be useful for estimating prognosis and informing treatment decisions. While *TP53* mutations are commonly associated with a complex karyotype in AML and therefore a diagnosis of either AML-MRC or therapy-related AML,[13] such testing is not included in most guidelines since other features are present in these cases to determine the diagnosis. Immunohistochemical analysis of p53 shows an increase in some patients with AML-MRC,[27] but this is generally related to a complex karyotype and other features of AML-MRC and is not usually needed for diagnosis.

Clinical and Prognostic Features of AML-MRC

AML-MRC represents up to 48% of all adult AML cases.[3,4] It occurs primarily in elderly patients (median age, 68 years) and is uncommon in children.[3,4,14,15] AML-MRC occurs more often as de novo AML with MDS-related cytogenetic changes or multilineage dysplasia than as AML arising secondarily from prior documented MDS or MDS/MPN.[4,12] By definition, patients with AML-MRC have a high frequency of adverse cytogenetics, including complex karyotype, and they often present with severe pancytopenia.[3,4,7,14,15] AML-MRC is also characterized by a relatively high frequency of *ASXL1* mutations (35% of patients) and low frequencies of *FLT3* and *DNMT3A* mutations.[14] A recent study that evaluated mutation frequencies also found that patients with de novo AML-MRC tended to have a higher frequency of *TP53* mutations, and those with antecedent MDS or MDS/MPN had a higher frequency of *SETBP1*, *RUNX1*, and *SRSF2* mutations compared with the other evaluated groups; meanwhile, patients with AML-MRC tended to have lower frequency of *SF3B1* mutations than patients with MDS and *NPM1*, *FLT3*-ITD, and *NRAS* mutations than patients with AML other than AML-MRC.[28] Characteristics of 262 patients with AML-MRC underscored the challenging nature of this group: 57% were 75 years or older, 53% had poor-risk cytogenetics, and approximately one-third were reported to have had antecedent MDS.[29]

In general, patients with AML-MRC have a worse prognosis, with lower remission rates and shorter OS, compared with patients who have most other AML subtypes. In a cohort of 100 patients with AML, those with AML-MRC had significantly shorter median OS and progression-free survival, as well as a lower complete remission (CR) rate, than those with AML-NOS. AML-MRC was identified as a predictor of poor OS independent of age or cytogenetic risk.[17] Similarly, in a cohort of 85 patients with AML, those with AML-MRC had a significantly lower CR rate (48% vs 78%) than those with other AML subtypes, although the 2-year OS rates were similar for the two groups.[14] Results from a larger-scale retrospective analysis of a cohort of 449 patients with AML indicated that those with AML-MRC had significantly shorter median OS (10 vs 16 months) and disease-free survival (5 vs 12 months), as well as a lower CR rate (61% vs 78%), compared with patients with AML-NOS.[7]

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Different multivariate analyses have reported conflicting results regarding factors associated with a poorer prognosis among patients with AML-MRC. Results from one study identified older age (≥60 years), adverse cytogenetics, and antecedent MDS or MDS/MPN as independent factors associated with shorter OS and disease-free survival in patients with AML-MRC.[7] A separate study also identified antecedent MDS or MDS/MPN and de novo AML with MDS-related cytogenetics as conferring a worse prognosis compared with patients with AML-MRC who had a diagnosis based on multilineage dysplasia (median OS of 5.3 and 6.3 vs 20.4 months).[8] In contrast, results from a second analysis indicated that MDS-related cytogenetics, antecedent MDS, and multilineage dysplasia did not influence OS in patients with AML-MRC. Of note, this analysis did identify *ASXL1* and *TP53* mutations as independent factors associated with shorter OS.[15] Another study found that patients with AML-MRC who had *RUNX1* mutations had shorter OS compared with those who had any AML with *RUNX1* mutations or AML-NOS with wild-type *RUNX1* (11 vs 19 months and not reached, respectively), suggesting AML-MRC with a *RUNX1* mutation represents a poor prognosis group.[30]

Current Treatment Options for Patients With AML-MRC

The selection of treatment for patients with AML can be influenced by multiple factors, including age, cytogenetic risk, performance status, and others,[29] but there has been very limited evaluation of variables that might influence selection of therapy for patients with AML-MRC. Physicians must carefully consider the goals of therapy (curative vs palliative) prior to finalizing a treatment plan. Traditional combination chemotherapy and CPX-351 (Vyxeos; Jazz Pharmaceuticals; daunorubicin and cytarabine liposome for injection) are the most common intensive induction therapies for patients with AML-MRC, although patients who also have certain mutations and clinical features may benefit from targeted therapy, and patients who are frail may be appropriate for less-intensive treatment approaches.

Conventional Chemotherapy

Combination chemotherapy regimens are the historical standard of care for intensive induction in AML, including AML-MRC, and commonly consist of continuous cytarabine infusion for 7 days plus 3 days of an anthracycline ("7 + 3" regimen).[25] However, this approach has not provided satisfactory OS in patients with AML-MRC.[2,5-7] A retrospective analysis of results for 449 adults with AML-MRC (n = 115) or AML-NOS who were treated with conventional chemotherapy indicated a lower median OS of 10 months and CR rate of 52% among patients with AML-MRC, compared with 16 months and 77% for those with AML-NOS.[7]

CPX-351

CPX-351 is a dual-drug liposomal encapsulation of daunorubicin and cytarabine at a synergistic 1:5 molar drug ratio. The liposomal-based carrier system maintains the synergistic drug ratio for over 24 hours after administration, resulting in longer drug exposure; in vitro studies also demonstrated preferential uptake of CPX-351 by leukemic blasts compared with normal cells in the bone marrow. Together, these properties contribute to increased antileukemic activity.[31,32] CPX-351 is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of adults with newly diagnosed AML-MRC and therapy-related AML.[33,34] In addition, the National Cooperative Cancer Network guidelines for AML recommend CPX-351 for adults younger than 60 years (category 2B) and adults 60 years or older who are candidates for intensive therapy (category 1) who have antecedent MDS/CMML, cytogenetic changes consistent with MDS, or therapy-related AML (other than core binding factor/acute promyelocytic leukemia).[25]

The approval of CPX-351 for patients with AML-MRC was based on results from a multicenter, randomized, open-label, phase 3 clinical study of CPX-351 vs conventional 7 + 3 chemotherapy in 309 patients aged 60 to 75 years with newly diagnosed, high-risk, or secondary AML.[35,36] Of the 246 patients with AML-MRC enrolled in this study (n = 123 in each treatment arm), 59.0% had antecedent MDS, 9.3% had antecedent CMML, and 31.7% had de novo AML with MDS karyotype. Results of an exploratory subgroup analysis in patients with AML-MRC indicated prolonged median OS with CPX-351 vs 7 + 3 chemotherapy (9.07 vs 5.95 months; hazard ratio [HR], 0.70; 95% CI, 0.53-0.93)[36]; prolonged median OS was observed with CPX-351 among patients with antecedent MDS/CMML (7.38 vs 5.95 months; HR, 0.70; 95% CI, 0.50-0.99) and de novo AML with MDS karyotype (10.09 vs 7.36 months; HR, 0.71; 95% CI, 0.42-1.20).[35] CPX-351 also demonstrated higher rates vs 7 + 3 of patients with AML-MRC who achieved CR (37.4% vs 24.4%; odds ratio [OR], 1.80; 95% CI, 1.02-3.17) and CR or CR with incomplete neutrophil or platelet recovery (CRi; 48.0% vs 32.5%; OR, 1.83; 95% CI, 1.09-3.09).[36]

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Hematopoietic cell transplantation (HCT) could be received at the discretion of the treating physician and was reported for 33.3% of patients in the CPX-351 arm vs 24.4% of patients in the 7 + 3 arm (OR, 1.53; 95% CI, 0.86-2.74). Median OS landmarked from the date of HCT was not reached for CPX-351 vs 10.68 months for 7 + 3 (HR, 0.48; 95% CI, 0.24-0.96). The safety profile of CPX-351 in patients with AML-MRC was generally consistent with that for conventional 7 + 3, except that the time to neutrophil and platelet count recovery was longer for patients achieving CR + CRi following CPX-351 compared with 7 + 3. However, the early mortality rates for CPX-351 and 7 + 3, respectively, were 5% and 9% within 30 days and 14% and 20% within 60 days. Grade 5 treatment-emergent adverse events occurring in more than one patient in a treatment arm included sepsis (2.4% and 0.8%), disease progression (1.6% and 3.4%), multiorgan failure (0.8% and 1.7%), and respiratory failure (0.8% and 1.7%).[36]

Targeted Agents

No targeted therapies are specifically approved or recommended for patients with AML-MRC, but some patients with AML-MRC may also have mutations or clinical features that make them candidates for treatment with these agents.

Gemtuzumab Ozogamicin

Studies showing a higher expression of CD33 on granulocytic cells from individuals with AML-MRC vs AML-NOS[37] and a high proportion (69%) of CD33-positive AML-MRC cases[38] suggest CD33 might be a therapeutic target for some patients with AML-MRC. Gemtuzumab ozogamicin (Mylotarg; Pfizer) is approved by the FDA for the treatment of adults with newly diagnosed CD33-positive AML and adults or pediatric patients 2 years or older with relapsed/refractory CD33-positive AML. Approval of gemtuzumab ozogamicin was based on the ALFA-0701 study, which was a multicenter, open-label, phase 3 study of 280 patients aged 50 to 70 years with newly diagnosed, de novo AML who were randomized to receive 7 + 3 with or without the addition of gemtuzumab ozogamicin.[39,40] However, at present there is no information regarding the efficacy or safety of gemtuzumab ozogamicin in patients with AML-MRC. The ALFA-0701 study excluded patients with prior MDS or MDS/MPN, and there has not been an analysis of the effect of multilineage dysplasia on outcomes in the ALFA-0701 study. However, patients with poor-risk karyotype (such as those seen in de novo AML-MRC) did not benefit from the addition of gemtuzumab ozogamicin.[40]

Midostaurin and Gilteritinib

FLT3–internal tandem duplication (ITD) mutations are relatively common in AML, reported in approximately 25% to 30% of AML cases overall[41,42] and in 13.5% of patients with AML-MRC.[7] Midostaurin (Rydapt; Novartis Pharmaceuticals) and gilteritinib (Xospata; Astellas Pharma) are small-molecule *FLT3* inhibitors that are approved for the treatment of adults with newly diagnosed *FLT3*-mutated AML in combination with conventional cytarabine/daunorubicin or adults with relapsed/refractory *FLT3*-mutated AML, respectively. Although these agents are not approved specifically in patients with AML-MRC, they could be appropriate for some patients who have an *FLT3* mutation. The approval of midostaurin was based on the results from the phase 3 RATIFY trial (CALGB 10603; n = 717), a randomized, placebo-controlled study carried out to determine whether the addition of midostaurin to standard 7 + 3 chemotherapy would improve the OS of patients (aged 18-59 years) with *FLT3*-mutated AML.[43] The approval of gilteritinib was based on an interim analysis of results from the ADMIRAL trial, which included 138 adults with relapsed/refractory AML who had an *FLT3*-ITD, *FLT3*-D835, or *FLT3*-I836 mutation.[44] Studies of both agents showed promising outcomes in their overall study populations[43,45]; however, no subanalyses of patients with AML-MRC have been reported.

Ivosidenib and Enasidenib

IDH1 and *IDH2* mutations have been reported at frequencies of approximately 4% and 21%, respectively, among patients with AML-MRC.[14] Ivosidenib (Tibsovo; Agios Pharmaceuticals) and enasidenib (Idhifa; Celgene) are approved for the treatment of adults with relapsed/refractory AML with susceptible *IDH1* and *IDH2* mutations, respectively. Ivosidenib monotherapy (500 mg/d for ≥6 months) was assessed in a phase 1 study of patients with relapsed/refractory, *IDH1*-mutated AML (n = 125 evaluable).[46] The efficacy of enasidenib was assessed in an open-label, single-arm study that included 199 adult patients with relapsed/refractory *IDH2*-mutated AML.[47] Although promising efficacy was observed with both agents, neither of the studies evaluated outcomes in the subgroup of patients with AML-MRC.

Lower-Intensity Therapies

AML-MRC is primarily diagnosed in older adults,[4] and some may not be considered healthy enough to receive intensive induction chemotherapy because of the presence of significant comorbidities. These patients may

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be appropriate candidates for lower-intensity therapies, including hypomethylating agents (HMAs; azacitidine or decitabine) with or without venetoclax, or low-dose cytarabine (LDAC) with or without either venetoclax or glasdegib.

A subanalysis of results from a phase 3 study that compared clinical outcomes for 262 patients with AML-MRC who were treated with azacitidine or conventional regimens (primarily LDAC) indicated that the median OS was significantly prolonged with azacitidine vs conventional care (8.9 vs 4.9 months; HR, 0.74; 95% CI, 0.57-0.97).[29]

Venetoclax has been approved in combination with either HMAs or LDAC for the treatment of newly diagnosed AML in patients who are 75 years or older or have comorbidities that preclude the use of intensive induction chemotherapy. A phase 1b study evaluated outcomes for venetoclax in combination with HMAs in 145 patients 65 years or older with untreated AML who were considered ineligible for intensive chemotherapy; the study included 36 (25%) patients with secondary AML (none with prior HMA therapy). The CR + CRi rate was 67% for patients with either de novo or secondary AML. Median OS was 12.5 months (95% CI, 10.3-24.4) for patients with de novo AML and was not reached (95% CI, 14.6 to not reached) for those with secondary AML.[48] A phase 1/2 study of venetoclax plus LDAC in 82 adults aged 60 years or older with untreated AML who were ineligible for intensive chemotherapy included 40 (49%) patients with secondary AML (24 with prior HMA exposure). CR and CR + CRi rates were lower for patients with secondary AML (CR, 5%; CR + CRi, 35%) vs de novo AML (CR, 45%; CR + CRi, 71%). Median OS was also shorter for patients with secondary AML (4.1 months; 95% CI, 2.9-10.1) vs de novo AML (13.5 months; 95% CI, 7.0-18.4). Outcomes for the 24 patients with prior HMA exposure were similar to those for the overall secondary AML subgroup, with a CR + CRi rate of 33%, including 4% who achieved CR, and a median OS of 4.1 months (95% CI, 2.9-10.1).[49] A subsequent randomized, phase 3 study in a similar population failed to meet its primary end point of improved median OS for venetoclax plus LDAC vs placebo plus LDAC (7.2 vs 4.1 months; HR, 0.75; 95% CI, 0.52-1.07) in the overall study population, which included 38% with secondary AML (primarily prior hematologic disorder) and 20% with prior HMA exposure.[50] Higher remission rates and longer median OS with the addition of venetoclax to LDAC were noted across patient subgroups, but specific data were not included with the online manuscript publication. However, a multivariable Cox regression analysis identified de novo vs secondary AML as significantly correlated with OS (HR, 0.59; 95% CI, 0.41-0.85).[50]

Glasdegib is also approved in combination with LDAC for the treatment of patients with newly diagnosed AML who are 75 years or older or have comorbidities that precluded the use of intensive induction chemotherapy. This approval was based on results from the BRIGHT AML 1003, a randomized trial of LDAC with or without glasdegib in 115 patients. The addition of glasdegib improved median OS in the overall study population,[51] but no analysis of patients with AML-MRC has been performed.

Discussion

AML-MRC accounts for a substantial proportion of AML cases and includes patients with antecedent hematologic malignancies (eg, MDS) as well as those with de novo AML who have multilineage dysplasia and/or MDS-related cytogenetic abnormalities. AML-MRC primarily occurs in elderly patients and is associated with an increased probability of adverse cytogenetics and worse clinical outcomes. Therefore, there is a need for rapid karyotype analysis or, if not possible, the use of FISH panels to quickly identify the majority of patients with AML-MRC who do not have a history of MDS or multilineage dysplasia. The extra expense of such testing should be balanced with the treatment benefit afforded to the patient by making a diagnosis quickly. *NPM1* and *CEBPA*, along with *FLT3*, should be evaluated by RT-PCR, as these results typically are obtained more quickly than next-generation sequencing panels, and the results are important for the diagnosis of AML-MRC and for informing treatment decisions.

If therapy is pursued with curative intent in patients with AML-MRC, then allogeneic HCT should be considered in the first-line treatment plan. The use of regimens capable of inducing remission in this population is critical, since patients are typically not considered eligible for allogeneic HCT unless in complete remission. Furthermore, these remissions ideally should be durable and deep, as well as not lead to excessive toxicity so as not to preclude subsequent allogeneic HCT. Recently approved chemotherapeutic regimens have been shown to induce such remissions in this patient population. Therefore, the identification of patients with AML-MRC at the time of initial diagnosis is critical to the optimal treatment of these patients.

CPX-351 was the first agent to demonstrate improved outcomes, including a higher HCT rate compared with conventional chemotherapy (7 + 3 regimen) in patients with AML-MRC, and it is currently the only agent specifically approved for this high-risk population.

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It is not yet understood how this regimen may compare with less-intensive strategies, such as venetoclax in combination with HMAs, or more intensive regimens such as FLAG-IDA (fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin). The combination of CPX-351 chemotherapy with targeted agents has also not yet been evaluated. Given the suboptimal outcomes for patients with AML-MRC, clinicians may choose to combine targeted agents with active chemotherapy regimens, such as CPX-351, instead of waiting for safety and efficacy data from combination studies. Therefore, clinical studies of these combinations are needed urgently; until such data are available, clinicians should exercise great caution when combining agents, as they may have overlapping toxicities, particularly myelosuppression. The goal of therapy (ie, curative approach vs palliative treatment) may help to inform regimen selection until randomized trial data are available in specific subpopulations of patients, including AML-MRC.

Genomics, epigenetics, and proteomics may ultimately identify more precise definitional markers in AML and eliminate the need for the current category of AML-MRC. As understanding of the biologic drivers of AML improves, it is expected that therapy selection may transition to targeting relevant biologic drivers of different AML subgroups.

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References

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127:2391-2405.
2. Hulegårdh E, Nilsson C, Lazarevic V, et al. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish Acute Leukemia Registry. *Am J Hematol.* 2015;90:208-214.
3. Weinberg OK, Arber DA. Acute myeloid leukemia with myelodysplasia-related changes: a new definition. *Surg Pathol Clin.* 2010;3:1153-1164.
4. Nagy A, Neubauer A. Acute myeloid leukemia with myelodysplasia related changes. *Atlas Genet Cytogenet Oncol Haematol.* 2017;21:404-408.
5. Granfeldt Østgård LS, Medeiros BC, Sengeløv H, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. *J Clin Oncol.* 2015;33:3641-3649.
6. Szotkowski T, Muzik J, Voglova J, et al. Prognostic factors and treatment outcome in 1,516 adult patients with de novo and secondary acute myeloid leukemia in 1999-2009 in 5 hematology intensive care centers in the Czech Republic. *Neoplasma.* 2010;57:578-589.
7. Xu XQ, Wang JM, Gao L, et al. Characteristics of acute myeloid leukemia with myelodysplasia-related changes: a retrospective analysis in a cohort of Chinese patients. *Am J Hematol.* 2014;89:874-881.
8. Fang H, He R, Chiu A, et al. Genetic factors in acute myeloid leukemia with myelodysplasia-related changes. *Am J Clin Pathol.* 2020;153:656-663.
9. Gahn B, Haase D, Unterhalt M, et al. De novo AML with dysplastic hematopoiesis: cytogenetic and prognostic significance. *Leukemia.* 1996;10:946-951.
10. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood.* 2002;100:2292-2302.
11. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood.* 2009;114:937-951.
12. Vardiman J, Reichard K. Acute myeloid leukemia with myelodysplasia-related changes. *Am J Clin Pathol.* 2015;144:29-43.
13. Ohgami RS, Ma L, Merker JD, et al. Next-generation sequencing of acute myeloid leukemia identifies the significance of *TP53*, *U2AF1*, *ASXL1*, and *TET2* mutations. *Mod Pathol.* 2015;28:706-714.
14. Devillier R, Gelsi-Boyer V, Brecqueville M, et al. Acute myeloid leukemia with myelodysplasia-related changes are characterized by a specific molecular pattern with high frequency of *ASXL1* mutations. *Am J Hematol.* 2012;87:659-662.
15. Devillier R, Mansat-De Mas V, Gelsi-Boyer V, et al. Role of *ASXL1* and *TP53* mutations in the molecular classification and prognosis of acute myeloid leukemias with myelodysplasia-related changes. *Oncotarget.* 2015;6:8388-8396.
16. Bacher U, Schnittger S, Macijewski K, et al. Multilineage dysplasia does not influence prognosis in *CEBPA*-mutated AML, supporting the WHO proposal to classify these patients as a unique entity. *Blood.* 2012;119:4719-4722.
17. Weinberg OK, Seetharam M, Ren L, et al. Clinical characterization of acute myeloid leukemia with myelodysplasia-related changes as defined by the 2008 WHO classification system. *Blood.* 2009;113:1906-1908.
18. Park SH, Chi HS, Park SJ, et al. Clinical importance of morphological multilineage dysplasia in acute myeloid leukemia with myelodysplasia related changes. *Korean J Lab Med.* 2010;30:231-238.

DOI: 10.1093/ajcp/aqaa107

19. Díaz-Beyá M, Rozman M, Pratcorona M, et al. The prognostic value of multilineage dysplasia in de novo acute myeloid leukemia patients with intermediate-risk cytogenetics is dependent on *NPM1* mutational status. *Blood.* 2010;116:6147-6148.
20. Arber DA, Borowitz MJ, Cessna M, et al. Initial diagnostic workup of acute leukemia: guideline from the College of American Pathologists and the American Society of Hematology. *Arch Pathol Lab Med.* 2017;141:1342-1393.
21. Ohgami RS, Arber DA. Challenges in consolidated reporting of hematopoietic neoplasms. *Surg Pathol Clin.* 2013;6:795-806.
22. Sever C, Abbott CL, de Baca ME, et al. Bone marrow synoptic reporting for hematologic neoplasms: guideline from the College of American Pathologists Pathology and Laboratory Quality Center. *Arch Pathol Lab Med.* 2016;140:932-949.
23. McMahon CM, Nelson N, Ganetsky A, et al. Limited FISH testing for MDS-defining cytogenetic abnormalities rapidly identifies patients with newly diagnosed AML eligible for CPX-351. *Blood.* 2018;132(suppl 1):Abstract 4785.
24. Arber DA. Revisiting erythroleukemia. *Curr Opin Hematol.* 2017;24:146-151.
25. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Acute Myeloid Leukemia, Version 3. 2020. https://NCCN.org.
26. 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;129:424-447.
27. Fernandez-Pol S, Ma L, Ohgami RS, et al. Immunohistochemistry for p53 is a useful tool to identify cases of acute myeloid leukemia with myelodysplasia-related changes that are *TP53* mutated, have complex karyotype, and have poor prognosis. *Mod Pathol.* 2017;30:382-392.
28. Badar T, Szabo A, Sallman D, et al. Interrogation of molecular profiles can help in differentiating between MDS and AML with MDS-related changes. *Leuk Lymphoma.* 2020;61:1418-1427.
29. Seymour JF, Döhner H, Butrym A, et al. Azacitidine improves clinical outcomes in older patients with acute myeloid leukaemia with myelodysplasia-related changes compared with conventional care regimens. *BMC Cancer.* 2017;17:852.
30. Nguyen L, Zhang X, Roberts E, et al. Comparison of mutational profiles and clinical outcomes in patients with acute myeloid leukemia with mutated *RUNX1* versus acute myeloid leukemia with myelodysplasia-related changes with mutated *RUNX1*. *Leuk Lymphoma.* 2020;61:1395-1405.
31. Talati C, Lancet JE. CPX-351: changing the landscape of treatment for patients with secondary acute myeloid leukemia. *Future Oncol.* 2018;14:1147-1154.
32. Lim WS, Tardi PG, Dos Santos N, et al. Leukemia-selective uptake and cytotoxicity of CPX-351, a synergistic fixed-ratio cytarabine:daunorubicin formulation, in bone marrow xenografts. *Leuk Res.* 2010;34:1214-1223.
33. Umukoro C. Vyxeos (CPX-351) granted approval in the EU for the treatment of therapy-related acute myeloid leukemia or AML-MRC. 2018. https://amlglobalportal.com/medical-information/vyxeos-cpx-351-granted-approval-in-the-eu-for-the-treatment-of-therapy-related-acute-myeloid-leukemia-or-aml-with-myelodysplasia-related-changes. Accessed January 15, 2020.
34. US Food and Drug Administration. FDA approves first treatment for certain types of poor-prognosis acute myeloid leukemia. 2017. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-certain-types-poor-prognosis-acute-myeloid-leukemia. Accessed January 15, 2020.
35. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol.* 2018;36:2684-2692.
36. Ryan DH, Uy GL, Cortes JE, et al. Efficacy and safety of CPX-351 versus 7 + 3 in a subgroup of older patients with newly diagnosed acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) enrolled in a phase 3 study. *Blood.* 2018;132(suppl 1):Abstract 1425.
37. Weinberg OK, Hasserjian RP, Li B, et al. Assessment of myeloid and monocytic dysplasia by flow cytometry in de novo AML helps define an AML with myelodysplasia-related changes category. *J Clin Pathol.* 2017;70:109-115.
38. Ehninger A, Kramer M, Röllig C, et al. Distribution and levels of cell surface expression of CD33 and CD123 in acute myeloid leukemia. *Blood Cancer J.* 2014;4:e218.
39. US Food and Drug Administration. FDA approves gemtuzumab ozogamicin for CD33-positive AML. 2017. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm574518.htm. Accessed January 15, 2020.
40. Castaigne S, Pautas C, Terré C, et al; Acute Leukemia French Association. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet.* 2012;379:1508-1516.
41. Levis M. Midostaurin approved for FLT3-mutated AML. *Blood.* 2017;129:3403-3406.
42. Thiede C, Steudel C, Mohr B, et al. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. *Blood.* 2002;99:4326-4335.
43. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a *FLT3* mutation. *N Engl J Med.* 2017;377:454-464.
44. US Food and Drug Administration. FDA approves gilteritinib for relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation. 2018. https://www.fda.gov/drugs/fda-approves-gilteritinib-relapsed-or-refractory-acute-myeloid-leukemia-aml-flt3-mutatation. Accessed March 12, 2020.
45. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory *FLT3*-mutated AML. *N Engl J Med.* 2019;381:1728-1740.
46. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in *IDH1*-mutated relapsed or refractory AML. *N Engl J Med.* 2018;378:2386-2398.
47. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. *Blood.* 2017;130:722-731.
48. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood.* 2019;133:7-17.

DOI: 10.1093/ajcp/aqaa107

49. Wei AH, Strickland SA Jr, Hou JZ, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. *J Clin Oncol.* 2019;37:1277-1284.
50. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood.* 2020;135:2137-2145.
51. US Food and Drug Administration. FDA approves glasdegib for AML in adults age 75 or older or who have comorbidities. 2018. https://www.fda.gov/drugs/fda-approves-glasdegib-aml-adults-age-75-or-older-or-who-have-comorbidities. Accessed January 15, 2020.

DOI: 10.1093/ajcp/aqaa107