Current and Emerging Therapies for Patients With Acute Myeloid Leukemia: A Focus on MCL-1 and the CDK9 Pathway

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ABSTRACT

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy that largely impacts the elderly population. Not all AML patients are candidates for the mainstay induction and consolidation treatment options. In addition, despite available therapies, most patients will eventually relapse on, or be refractory to, standard induction therapy, with limited subsequent choices and poor prognosis. Recently, several new and emerging therapies, with a variety of mechanisms of action, have broadened the treatment landscape in newly diagnosed and relapsed/refractory (R/R) AML, providing patients and healthcare providers with more options and several targeted treatment approaches. Preclinical data indicate that the anti-apoptotic protein myeloid cell leukemia-1 (MCL-1) is important to AML cell survival. Cyclin-dependent kinase 9 (CDK9), a transcriptional activator necessary for the expression of MCL-1, represents a promising target for future AML therapies. A number of CDK9 inhibitors, as well as several direct MCL-1 inhibitors, are currently in clinical or preclinical development. The CDK9 inhibitors alvocidib, atuveciclib, and TG02 have completed phase 1/2 clinical trials, with results available for the alvocidib trial showing improved complete remission rates (70% vs 46%; $P = .003$) for alvocidib in combination with cytarabine and mitoxantrone, versus cytarabine/daunorubicin, in patients with newly diagnosed AML. In addition, several phase 1 clinical trials with CDK9 inhibitors are currently recruiting for treatment of advanced AML. A phase 1b study is also ongoing to investigate alvocidib in combination with B-cell lymphoma-2 inhibitor venetoclax for R/R AML. Although further research is needed, CDK9 inhibitors represent a promising new approach for the treatment of AML.

***Am J Manag Care*. 2018;24:S356-S365**

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Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy that can affect individuals of any age but is most frequently diagnosed in those aged 65 to 74 years, with a median age at diagnosis of 68 years.[1,2] AML is the most common acute leukemia in adults but represents approximately 1.1% of all new cancer cases in the United States.[1,2] AML can arise de novo or from other factors, including previous cytotoxic or radiation therapy or from antecedent hematologic disorders.[2] Prognosis is generally poor and worsens with advanced age.[1,3] Poor prognosis is associated with certain chromosomal and genetic aberrations (ie, complex karyotype, *MLL* rearrangements, *FLT3* mutations).[4] Novel, targeted treatment options are urgently needed for AML to prolong survival and improve patient outcomes.[2]

Standard-of-Care Therapy for AML

Current first-line treatment options for AML include induction chemotherapy. The goals of induction therapy in AML are to reduce leukemic burden by inducing complete remission (CR) and to restore normal hematopoiesis.[2] The primary option for induction therapy in the first-line AML setting has been for many years the "7 + 3" regimen, composed of 7 days of cytarabine, an analog of cytosine that incorporates into DNA during replication and inhibits DNA synthesis, and 3 days of an anthracycline, one in a cytotoxic class of drugs with multiple mechanisms of action, including DNA intercalation, inhibition of topoisomerase II, and generation of free radicals.[5-8]

Recently, several new drugs with varied mechanisms of action have been approved by the FDA for the treatment of AML in the first-line setting, adding to the treatment options for patients and healthcare providers. These include midostaurin, a small-molecule multiple tyrosine kinase inhibitor with FMS-like tyrosine kinase 3 (*FLT3*) inhibitory activity; CPX-351, a fixed-combination of daunorubicin and cytarabine; and gemtuzumab ozogamicin, a CD33-directed antibody-drug conjugate (**Table 1**).[9-16] Emerging therapeutic options include venetoclax, a small-molecule inhibitor of anti-apoptotic B-cell lymphoma-2 (BCL-2) protein.[17-19]

Venetoclax in combination with low-dose cytarabine has received a breakthrough therapy designation from the FDA for

TABLE 1. Approved First-Line Therapies for AML in 2017[9-16]

Agent	Indications	Clinical Evidence		
		Trial and Population	Treatment	Efficacy and Safety
CPX-351 (danorubicin and cytarabine liposomal injection)[9,10]	• Newly diagnosed therapy-related AML • AML with myelodysplasia-related changes	**Phase 3 (NCT01696084)** Patients aged 60-75 years with untreated AML with a history of prior cytotoxic treatment, antecedent MDS or CMML (+/– prior hypomethylator treatment), or AML with WHO-defined MDS-related cytogenetic abnormalities (N = 309)	1:1 CPX-351 (cytarabine 100 mg/m2 and daunorubicin 44 mg/m2 on days 1, 3, 5) vs 7 + 3 (cytarabine 100 mg/m2/day x 7 days, daunorubicin 60 mg/m2 days 1, 2, 3) induction therapy	Superior OS (HR, 0.69; *P* = .005) Median OS 9.56 vs 5.95 months Superior EFS (HR, 0.74; *P* = .021) Superior CR + CRi: 47.7% vs 33.3%; *P* = .016 Favorable 60-day mortality: 13.7% vs 21.2% Grade 3-5 AEs similar between groups: 92% vs 91%
Enasidenib[11,12]	• R/R AML with *IDH2* mutation	**Phase 1/2 (NCT01915498)** Adult patients with R/R AML who had an *IDH2* mutation (N = 176)	Enasidenib 100 mg (n = 109)	CR: 20.2% ORR: 38.5% Most common TRAEs were indirect hyperbilirubinemia (38%) and nausea (23%); need to be aware and rapidly manage IDH-inhibitor-associated differentiation syndrome and leukocytosis, which occurred as serious TRAEs in 8% and 4%, respectively
Gemtuzumab ozogamicin[13,14]	• Newly diagnosed, CD33-positive AML (combination regimen) • R/R, CD33-positive AML (single-agent regimen) • Pediatric patients ≥2 years old	**Phase 3 EudraCT** Patients aged 50-70 years with previously untreated de novo AML (N = 280)	1:1 to control and IV gemtuzumab ozogamicin 3 mg/m^2 on days 1, 4, 7 and day 1 of each of the consolidating chemotherapy courses	EFS at 2 years: 40.8% (95% CI, 32.8-50.8) with gemtuzumab ozogamicin vs 17.1% (95% CI, 10.8-27.1) with control (HR, 0.58, *P* = .0003) Hematologic toxicity, particularly persistent thrombocytopenia, was more common in the gemtuzumab ozogamicin group than in the control group (16% vs 3%; *P* <.0001)
Midostaurin (PKC 412)[15,16]	• Newly diagnosed AML with *FLT3* mutation in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation	**Phase 3 (NCT00651261)** Patients aged 18-59 years with newly diagnosed AML with *FLT3* mutations (N = 717)	Standard chemotherapy (induction therapy with daunorubicin and cytarabine and consolidation therapy with high-dose cytarabine) plus either midostaurin or placebo	Superior OS: HR for death, 0.78; *P* = .009 No significant difference in CR: 58.9% with midostaurin vs 53.5% with placebo, *P* = 0.15 Rates of severe AEs were similar in both groups

AE indicates adverse event; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CD, cluster of differentiation; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; EFS, event-free survival; FLT3, fms-like tyrosine kinase 3; IV, intravenous; MDS, myelodysplastic syndromes; ORR, objective response rate; OS, overall survival; R/R, relapsed/refractory; TRAE, treatment-related adverse event; WHO, World Health Organization.

use in frontline therapy in elderly patients with AML who are not eligible for intensive chemotherapy.[20] Venetoclax has also been granted FDA breakthrough therapy designation for use with hypomethylating agents as frontline therapy in elderly patients with AML who are not eligible for intensive induction therapy.[21] Venetoclax is also being studied in combination with dose-modified intensive chemotherapy.[22] Furthermore, the histone deacetylase inhibitor pracinostat, plus azacitidine, received a breakthrough therapy designation from the FDA in August 2016 for use in elderly patients with AML who are not eligible for induction therapy.[23]

Consolidation therapy in AML generally consists of chemotherapy to maintain control of the disease or hematopoietic stem cell transplantation as a potentially curative option in certain patients.[5,24] However, many patients with AML are not considered to be candidates for current treatment strategies because of significant comorbidities, poor performance status, and older age, among

other factors.[3,25] In addition, available therapies are not effective for all patients, and resistance to and/or relapse on chemotherapy is common. Depending on a variety of factors, including age and type of induction therapy, only approximately two-thirds of patients achieve CR after induction therapy, and the majority will relapse or die from their disease.[24,26,27]

Several new and emerging therapies are now available or under investigation in the relapsed/refractory (R/R) setting, which may help to improve the prognosis of certain patients with R/R disease. These therapies include enasidenib, a small-molecule inhibitor approved by the FDA in 2017 for patients with R/R AML with an isocitrate dehydrogenase-2 (*IDH2*) mutation; ivosidenib, an investigational small-molecule inhibitor for the treatment of patients with R/R AML with an isocitrate dehydrogenase-1 (*IDH1*) mutation; and quizartinib, gilteritinib, and crenolanib, investigational small-molecule inhibitors for the treatment of patients with R/R AML with an *FLT3* mutation (**Table 2**).[17-23, 28-41]

Targeting Apoptosis as a Therapeutic Approach in AML

Historically, the primary mechanism of action of treatments for AML, in particular the 7 + 3 regimen, has involved the disruption of cell proliferation.[6,7] With progress being made in elucidating the underlying biology behind AML, new potential treatment strategies are being identified. Targeting anti-apoptotic proteins, such as myeloid cell leukemia-1 (MCL-1), could positively impact the balance of pro- versus anti-apoptotic proteins and result in increased death of cancer cells and improved disease control.[42,43]

MCL-1 in AML

MCL-1 is a member of the BCL-2 family of apoptosis-regulating proteins. MCL-1 blocks pro-apoptotic proteins, such as BAK and BAX, thereby preventing programmed cell death through apoptosis.[44] Preclinical studies have suggested a role for MCL-1 in the disease etiology of AML. Clinical samples (leukemic blasts and primary human hematopoietic subsets) from 111 patients with AML demonstrated high levels of MCL-1 protein expression.[43] MCL-1 levels have been observed to increase by approximately 2-fold at the time of disease recurrence compared with pretreatment (n = 19).[45] Patients with increased MCL-1 levels have showed poor prognosis and/or response to chemotherapy, suggesting that at least some AML malignancies are MCL-1 dependent.[45] Downregulation of MCL-1 has been shown to result in the death of murine and human AML cells.[42] MCL-1 has also been found to be important for the survival of leukemia stem cells, further underscoring the importance of MCL-1 in the survival of AML cancer cells.[46]

Preclinical data also suggest possible activity of some agents in targeting multiple pathways. The kinase inhibitor PIK-75 has been found to inhibit both cyclin-dependent kinases (CDK) and BCL-2

TABLE 2. Investigational Agents in AML With Varied Mechanisms of Action[18-23, 28-40]

Investigational Agent	FDA Status
Quizartinib[28-30]	Breakthrough therapy designation; fast track designation, August 2018 • R/R AML with *FLT3*-IDT mutation
Gilteritinib (ASP2215)[31-36]	Priority review, May 2018 • R/R AML with *FLT3* mutation
Crenolanib (CP-868596)[37,38]	Fast track designation, December 2017 • R/R AML with *FLT3* mutation

Key Clinical Trials		
Design	**Treatment**	**Results**
Phase 3 (NCT02039726) Patients with *FLT3*-ITD positive R/R AML after first-line treatment with or without HSCT (N = 367)	Quizartinib 20 or 30 mg quizartinib tablets vs salvage chemotherapy (LoDAC, MEC, or FLAG-IDA)	Study ongoing Preliminary results: Median OS was 27.0 and 20.4 weeks with quizartinib and salvage chemotherapy, respectively; rates of TRAEs were similar between treatment arms
Phase 3 (NCT02668653) Patients aged 18 to 75 years with newly diagnosed *FLT3*-ITD positive AML (N = 536)	Standard chemotherapy (cytarabine and daunorubicin/ idarubicin) plus quizartinib vs standard chemotherapy plus placebo	Study ongoing
Phase 1/2 (NCT02014558) Patients with R/R AML (N = 258)	Open-label dose escalation with gilteritinib and concomitant dose expansion in cohorts with *FLT3*$^{mut+}$ AML	Heavily pretreated patients with *FLT3*$^{mut+}$ AML achieved higher ORR (49%) vs *FLT3* wildtype (12%) Most common TRAEs of any grade were diarrhea (16%) fatigue (15%), elevated aspartate aminotransferase (13%), and increased alanine amonitransferase (10%)
Phase 3 (NCT02421939) Patients with R/R AML with *FLT3* mutation (n = 371)	Gilteritinib once daily vs salvage chemotherapy (LoDAC, azacitidine, MEC, FLAG-IDA)	Study ongoing
Phase 3 (NCT02997202) Patients with *FLT3*-ITD AML (n = 346)	Gilteritinib once daily vs placebo	Study ongoing
Phase 3 (NCT02927262) Patients with *FLT3*-ITD AML in first CR (n = 354)	Gilteritinib once daily vs placebo for up to 2 years	Study ongoing
Phase 2/3 (NCT02752035) Patients with newly diagnosed AML with *FLT3* mutation in patients not eligible for intensive induction chemotherapy (n = 540)	Gilteritinib daily (days 1-28) and azacitidine daily for 7 days (days 1-7) in each 28-day cycle	Study ongoing
Phase 2 (NCT01522469) Patients with R/R AML with *FLT3* activating mutations (n = 20)	Crenolanib administered at 200 mg/m^2/day 3 times a day continuously in 28-day cycles	CR: 12% ORR: 47% PD: 21% Median EFS: 8 weeks OS: 19 weeks Most common grade 3 AEs were abdominal pain and nausea

(continued)

family members, inducing apoptosis in a BAK-dependent mechanism.[47] Another kinase inhibitor, TG02, has been found to inhibit multiple CDK members as well as other, frequently mutated genes in hematologic malignancies, including janus kinase 2 (*JAK2*) and *FLT3*.[48]

Given the findings of these preclinical studies, targeting MCL-1 seems a reasonable approach for future AML therapies. The short half-life of MCL-1 should be considered as a possible attribute because inhibition of MCL-1 synthesis should rapidly reduce levels of the protein.[44] In addition, MCL-1 expression is tightly regulated, suggesting that regulators of expression would be potential targets for new therapies.[49] The promising preclinical data and the feasibility of MCL-1 as a possible target of treatment suggest a possible future role for MCL-1 as a biomarker in personalized cancer therapy.[45,50]

Potential Targets for Reducing Levels of MCL-1

Strategies to reduce MCL-1 expression include direct targeting of MCL-1 and indirect targeting by disruption of transcription/translation. Small-molecule inhibitors are currently in development to directly target MCL-1 and other BCL-2 family members with similar topologies (**Table 3**).[51-55] The second possible avenue—and the overall focus of this report—is targeting the synthesis of MCL-1, which could involve multiple components, including the promoter sequence, transcription/translation machinery, and transcription/translation regulators.

MCL-1 transcription is controlled by the positive transcription elongation factor b (P-TEFb) complex. P-TEFb, which is made up of CDK9 and cyclin T proteins, activates transcription elongation of multiple genes, including *MCL-1*.[56] CDK9, a transcriptional activator, contains a catalytic domain and phosphorylates the C-terminal domain of RNA polymerase II to activate transcription and elongation, while the cyclin T protein stabilizes CDK9 and plays a regulatory role.[57,58] BRD4, a bromodomain protein, anchors the P-TEFb complex to the DNA strand and acts as a positive regulator of transcription.[59] CDK9, which is part of a large family of CDKs, represents a possible therapeutic target for reducing MCL-1 synthesis (**Figure 1**).[60-67] Inhibition of CDK9 is known to prevent phosphorylation of the RNA polymerase II C-terminal domain, suggesting that inhibiting CDK9 may prevent the production of anti-apoptotic protein MCL-1, thereby increasing apoptosis.[47] Several CDK9 inhibitors are in exploratory and clinical development (**Table 4**).[48,61,63-77]

Preclinical and Clinical Evidence of CDK9 Inhibition in AML

As shown in Table 4, a number of CDK9 inhibitors are in development, most in early-stage clinical or preclinical studies.[48,61,63-77] TG02, a multi-kinase inhibitor of CDKs, including CDK9, has preliminary results from a dose-escalation phase 1 trial in advanced hematologic malignancies or newly diagnosed AML, which identified a maximally tolerated dose of 50 mg daily.[68] Treatment-related adverse events (AEs) included nausea (42%), vomiting (23%), fatigue (18%), decreased appetite (15%), constipation, and diarrhea (13% each).[68]

TABLE 2. *(Continued)* Investigational Agents in AML With Varied Mechanisms of Action[18-23, 28-40]

Investigational Agent	FDA Status
Ivosidenib (AG-120)[39,40]	Priority review, February 2018 • R/R AML with *IDH1* mutation
Venetoclax (ABT-199)[17-21]	Breakthrough therapy designation, July 2017 • In combination with low-dose cytarabine for elderly patients with treatment-naïve AML who are ineligible for intensive chemotherapy
	Breakthrough therapy designation, January 2016 • In combination with hypomethylating agents for patients with treatment-naïve AML who are ineligible for standard induction therapy
Pracinostat[23,40]	Breakthrough therapy designation, August 2016 • In combination with azacitidine for patients with newly diagnosed AML who are aged ≥75 years or unfit for intensive chemotherapy

Alvocidib

Alvocidib, also known as flavopiridol, was evaluated in a randomized, phase 2 trial in combination with cytarabine and mitoxantrone (ACM), compared with cytarabine plus daunorubicin (7 + 3), in 165 patients with core binding factor-negative newly diagnosed AML.[61] For the primary end point, the ACM regimen resulted in higher CR

Key Clinical Trials		
Design	**Treatment**	**Results**
Phase 1 (NCT02074839) Patients with *IDH1* mutation positive AML (N = 258)	Dose escalation with starting dose of ivosidenib of 500 mg daily	**In the R/R AML population (n = 179):** CR: 21.8% ORR: 39.1% **In the primary efficacy population (n = 125):** CR: 21.6% ORR: 41.6% Most common grade 3 or higher TRAEs in overall population were prolongation of the QT interval on ECG (7.0%), IDH differentiation syndrome (4.7%), and anemia (2.3%)
Phase 1b/2 (NCT02287233) Patients 65 years and older with previously untreated AML who were ineligible for intensive chemotherapy and had adequate hepatic and renal function (n = 71)	Venetoclax dose escalation to 600 or 800 mg/day on days 6-28, plus low-dose cytarabine 20 mg/m^2/day on days 1-10 of each cycle	CR/CRi: 62% CR/CRi from updated analysis: 54% Median OS: 11.4 months Most common grade 3/4 TRAEs were thrombocytopenia (59%), neutropenia (46%), febrile neutropenia (36%), anemia (28%), and decreased WBC count (26%)
Phase 1b (NCT02203773) Patients 65 years and older with previously untreated AML who are ineligible for standard induction therapy (n = 57)	Dose escalation of venetoclax up to 400, 800, or 1200 mg/day (orally) Addition of decitabine 20 mg/m^2/day IV on days 1-5 of each cycle (group A) or azacitadine 75 mg/m^2/day IV or SQ on days 1-7 of each cycle (group B)	**Group A, venetoclax + decitabine (n = 23):** CR/CRi: 61% Median OS: 15.2 months **Group B, venetoclax + azacitadine (n = 22):** CR/CRi: 59% Median OS: 14.2 months Most common grade 3-4 TRAEs were thrombocytopenia, febrile neutropenia, and neutropenia
Phase 3 (NCT03151408) Patients with newly diagnosed AML (n = 500 estimated)	Pracinostat 60 mg once a day, 3 times a week for 3 weeks, followed by 1 week of rest of each 28-day cycle plus azacytidine 75 mg/m^2 daily for 7 days of each 28-day cycle	Study ongoing

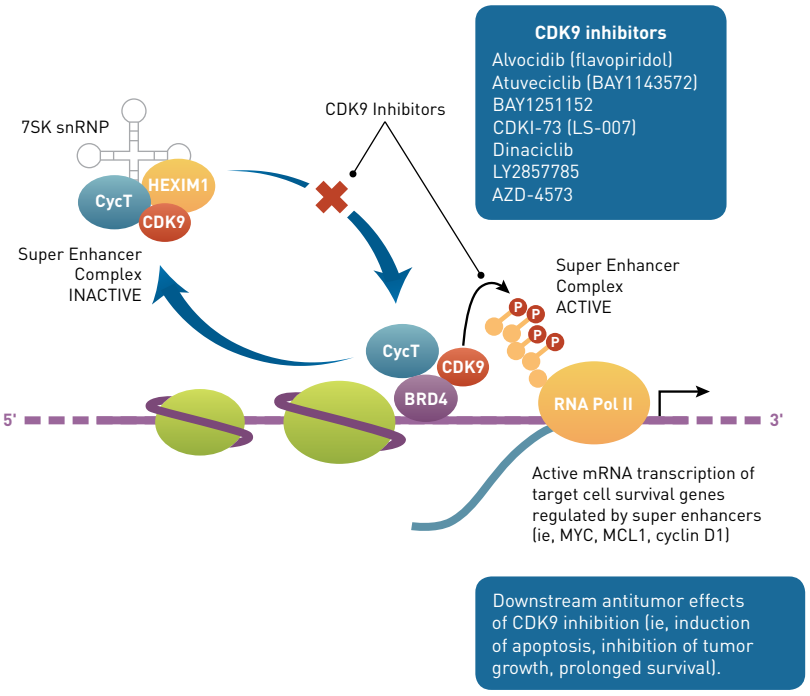
AE indicates adverse event; AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; ECG, electrocardiogram; EFS, event-free survival; FLAG-Ida, fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin; FLT3, fms-like tyrosine kinase 3; HSCT, hematopoietic stem cell transplantation; IV, intravenous; LoDAC, low-dose cytarabine; MEC, mitoxantrone, etoposide, and intermediate-dose cytarabine; ORR, overall response rate; OS, overall survival; PD, progressive disease; R/R, relapsed/refractory; SC, subcutaneous; TRAE, treatment-related adverse event; WBC, white blood count.

TABLE 3. Selected Direct MCL-1 Inhibitors in Development in AML[51-55]

Agent	Development	Clinicaltrials.gov Identifier	Intervention/Treatment and Patient Population	Status
AMG176	Phase 1	NCT02675452	Single agent; R/R AML	Recruiting[51]
	Preclinical	N/A	N/A	Preclinical results available[52]
S63845	Preclinical	N/A	N/A	Preclinical results available[53]
S64315	Phase 1	NCT02979366	Single agent; AML or MDS[54]	Recruiting[54]
AZD5991	Phase 1	NCT03218683	Single agent; R/R hematologic malignancies	Recruiting[55]

AML indicates acute myeloid leukemia; MCL-1, myeloid cell leukemia-1; MDS, myelodysplastic syndromes; R/R, relapsed/refractory.

FIGURE 1. MCL-1 Transcription Controlled by the P-TEFb Complex[60-67]



BRD4 indicates bromodomain protein 4; CDK9, cyclin-dependent kinase 9; CycT, cyclin T1; HEXM1, hexamethylene bisacetamide-inducible protein 1; MCL-1, myeloid cell leukemia-1; RNA Pol II, RNA polymerase II; snRNP, small nuclear ribonucleo proteins.

rates versus 7 + 3 (70% vs 46%, $P = .003$). In an exploratory subgroup analysis of treatment efficacy by aged cohorts, patients younger than 50 years experienced greater benefit from ACM treatment than from 7 + 3.[61] No significant survival advantage was documented (median overall survival, 17.5 months with ACM versus 22.2 months with 7 + 3; $P = .39$), whereas event-free survival, although not significantly different, demonstrated possible clinical improvement with ACM (median event-free survival, 9.7 months with ACM versus 3.4 months with 7 + 3, $P = .15$).[78] Overall, toxicities of grade 3 or higher were comparable in both treatment arms. In the ACM treatment arm, there were 2 early deaths due to tumor lysis syndrome (TLS) and 3 grade 4 TLS toxicities.[61]

In addition, preclinical data suggest that using a BH3 profiling assay to assess response to NOXA, a selective modulator of MCL-1, may be a viable way to predict response to AML therapy, which supports MCL-1 as a potential biomarker.[79] In a recent phase 2, open-label trial that used BH3 profiling, 17 patients with R/R AML (first relapse with CR duration of less than 2 years or primary refractory to 1 to 2 cycles of induction therapy) and a median MCL-1 dependency of 61% (range, 41%-98%, as determined by BH3 profiling) were administered alvocidib as timed sequential therapy prior to cytarabine and mitoxantrone.[80] The overall CR/complete remission with incomplete hematologic recovery (CRi) rate was 59% in 10 patients, and CR rate was 53%.[80] Six of 8 (75%) patients with refractory AML (no response to induction therapy or CRi duration less than 90 days) achieved CR, and 5 of these patients were able to proceed to allogeneic stem cell transplant.[80] Grade 3 or higher treatment-related nonhematologic AEs seen in more than 1 patient included hypophosphatemia (41%), TLS (35%; 5 grade 3 and 1 grade 4), hypokalemia (29%), elevated aspartate aminotransferase and diarrhea (23% each); hyponatremia, sepsis, and elevated alanine aminotransferase (18% each); and acute kidney injury, hypoalbuminemia, and fainting (12% each).[80]

Dinaciclib

Initial results were reported from a phase 2 study of the CDK inhibitor dinaciclib in patients with R/R AML (n = 14) or acute lymphoid leukemia (ALL; n = 6).[63] The study was terminated early due to a change in the sponsor.[63] In the 20 patients who received dinaciclib before study termination, no objective responses were observed.[63] Fifteen patients (75%) experienced grade 3 or higher treatment-related AEs, with the most common being hematologic toxicities and fatigue.[63] The most common nonhematologic AEs were gastrointestinal effects, fatigue, and disturbances in laboratory values.[63] Three patients had grade 3 or higher TLS.[63]

Atuveciclib (BAY 1143572)

Atuveciclib is a specific, highly selective inhibitor of PTEFb/CDK9. Results from preclinical studies suggest a promising efficacy and tolerability profile of atuveciclib in xenograph models in mice and rats.[62] Atuveciclib is currently being investigated in phase 1 clinical studies for its safety and efficacy in patients with AML.[71]

Combination Therapy With CDK9 Inhibitors and BCL-2 Inhibitors

Several preclinical and clinical studies are also examining CDK9 inhibitors in combination with the BCL-2-selective inhibitor venetoclax, including an ongoing phase 1b study with alvocidib plus venetoclax in patients with R/R AML; however, only preclinical results have been reported to date (**Table 4**).[48,61,63-77]

Conclusions

AML remains a serious condition with poor outcomes, particularly in elderly patients. A large proportion of patients relapse on or after standard induction therapy or hypomethylator therapy (the

TABLE 4. Selected CDK9 Inhibitors in Clinical or Preclinical Development for AML[48,61,63-77]

Agent	Phase of Development	Clinical Trial Identifier	Intervention/Treatment and Patient Population	Status
Alvocidib (flavopiridol)	Phase 2	NCT01349972	Alvocidib, cytarabine, and mitoxantrone vs cytarabine and daunorubicin; newly diagnosed AML	Completed and has results[61]
		NCT02520011	Alvocidib, cytarabine, mitoxantrone; R/R AML with exploratory arm in newly diagnosed high-risk AML	Recruiting[69]
	Phase 1	NCT03298984	Alvocidib and cytarabine/daunorubicin; newly diagnosed AML	Recruiting[70]
Atuveciclib (BAY1143572)	Preclinical	N/A	N/A	Preclinical results available[62]
	Phase 1	NCT02345382	Single agent; advanced acute leukemias	Completed, no results posted[71]
BAY1251152	Phase 1	NCT02745743	Single agent; advanced hematologic malignancies[72]	Recruiting[72]
CDKI-73 (LS-007)	Preclinical	N/A	N/A	Preclinical results available[66,67]
Dinaciclib (MK7965; formerly SCH 727965)	Phase 2	NCT00798213	Single agent; R/R AML	Study terminated, initial results available[63]
LY2857785	Preclinical	N/A	N/A	Preclinical results available[64]
TG02 (multi-kinase inhibitor of CDKs, *JAK2*, and *FLT3*)	Phase 1/1b	NCT01204164	Single agent; acute leukemias	Study completed, initial results presented[68]
	Preclinical	N/A	N/A	Preclinical results available[48]
AZD-4573	Phase	NCT03263637	Single agent; R/R hematologic malignancies including AML	Recruiting[65,73]
CDK9 and BCL-2 Inhibitor Venetoclax (ABT-199) in Combination				
Alvocidib plus venetoclax	Phase 1b	NCT03441555	Venetoclax and alvocidib; R/R AML[74]	Ongoing[74]
	Preclinical	N/A	N/A	Preclinical results available[75,76]
Dinaciclib plus venetoclax	Phase 1	NCT03484520	Venetoclax and dinaciclib; R/R AML	Not yet recruiting[77]
4520 CDKI-73 plus venetoclax	Preclinical	N/A	N/A	Preclinical results available[67]

AML indicates acute myeloid leukemia; BCL-2, B-cell lymphoma 2; CDK9, cyclin dependent kinase 9; FLT3, fms-like tyrosine kinase 3; JAK2, janus kinase 2; N/A, not applicable; R/R, relapsed/refractory.

current backbones of AML therapy), with limited future treatment options. New treatment approaches that use novel mechanisms of action are needed and are rapidly being developed to broaden the AML treatment landscape and improve patient outcomes, with a special focus on elderly AML and R/R AML, the areas of greatest unmet need. Preclinical data indicate that AML cells have a high dependency on MCL-1, a protein responsible for suppressing apoptosis. As a transcriptional activator necessary for the expression of MCL-1, CDK9 is a promising target for future AML therapies. Several CDK9 inhibitors are currently in phase 1/2 clinical development as single agents and in combination with chemotherapy, hypomethylating agents, and novel agents, such as venetoclax, in both frontline and R/R AML. Although still in the early stages of clinical research, CDK9 inhibitors represent a promising new avenue for AML therapies. More research is needed to identify optimal dosing strategies, including best combinations, and to increase awareness and improve management of specific AEs to achieve better patient outcomes. ■

Acknowledgement: Medical writing support was provided by Rebecca Miles, PhD.

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Funding source: Publication support provided by Boston Biomedical, Inc.

Author disclosures: Dr Daver reports serving as a consultant or on a paid advisory board for AbbVie Inc., Bristol-Myers Squibb, Daiichi-Sankyo, Jazz Pharmaceuticals, Novartis International AG, Otsuka Pharmaceutical, Pfizer Inc. He also reports receipt of honorarium for Bristol-Myers Squibb, Incyte Corporation, Jazz Pharmaceuticals, Novartis International AG; and research funding from Abbvie Inc., Bristol-Myers Squibb, Daiichi-Sankyo, Genentech, GlycoMimetics Inc., Incyte Corporation, Karyopharm Therapeutics, Laboratoires Servier, Pfizer Inc., Sunesis Pharmaceuticals. Dr Lyle reports serving as a consultant or on a paid advisory board for Agios Pharmaceuticals, Celgene, Incyte Corporation, Novartis International AG, and Takeda Oncology.

Authorship information: Acquisition of data (ND); administrative, technical, or logistic support (ND); concept and design (LL); critical revision of the manuscript for important intellectual content (ND, LL); drafting of the manuscript (ND, LL).

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