Alternatives to Intensive Treatment in Patients With AML

Gracie Himmelstein, MD,[1] John Mascarenhas, MD,[2] and Bridget K. Marcellino, MD[2]

[1]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

[2]Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York

Corresponding author:
Bridget K. Marcellino, MD
Assistant Professor of Medicine
Icahn School of Medicine at Mount Sinai
One Gustave L. Levy Place, Box 1079
New York, NY 10029
Tel: (212) 241-3476
Fax: (212) 876-5276
Email: bridget.marcellino@mssm.edu

Abstract: A significant proportion of patients with acute myeloid leukemia (AML) are unable to tolerate standard induction chemotherapy regimens. This is particularly true for patients who are of advanced age, have a poor performance status, and/or have significant medical comorbidities. Recent advances in understanding the genetic and molecular properties of AML have led to a spate of new treatment options for patients considered ineligible for standard chemotherapy. Here, we discuss these new treatment options, provide an overview of the completed and ongoing trials of the new agents, and highlight promising future directions in the treatment of AML in patients ineligible for intensive induction chemotherapy.

Keywords
Acute myeloid leukemia, novel therapies

Background

Acute myeloid leukemia (AML) is a common leukemia that affects primarily older adults, with more than half of new diagnoses made among those older than 65 years of age.[1] Standard induction treatment for AML frequently involves intensive cytarabine-based chemotherapy regimens. Treatment-related morbidity and mortality are likely to occur in many patients with these regimens, however, so they may be deemed ineligible for intensive chemotherapy (IC). For decades following the introduction of cytarabine- and anthracycline-based induction chemotherapy in the 1970s, no new treatments were approved for patients with AML. However, recent therapeutic advances show promise for improving survival among patients ineligible for IC. Herein, we present an overview of the treatments for patients with AML ineligible for IC, including both those with US Food and Drug Administration (FDA) approval in AML (Table 1) and those currently under investigation in AML (Table 2). We also review each drug's mechanism (Figure) and discuss the potential benefits and limitations of the treatments.

Determining Ineligibility for Intensive Chemotherapy

Older patients with AML, especially those aged 75 years and older, are more likely to experience treatment-related morbidity and mortality, have lower rates of complete remission (CR), and have relapsed

Table 1. Therapies With FDA-Approved Indications in the Treatment of AML

Novel Therapies for AML	FDA-Approved Indication in AML
Hypomethylating agents	
Azacitidine	Treatment of AML in combination with venetoclax for adults 75+ or with comorbidities that preclude IC
Decitabine	Treatment of AML in combination with venetoclax for adults 75+ or with comorbidities that preclude IC
CC-486	Maintenance therapy in patients who have AML with CR/CRi after induction chemotherapy and who cannot complete intensive curative therapy
BCL-2 inhibitors	
Venetoclax	In combination with AZA, DEC, or LDAC for adults 75+ or with comorbidities that preclude IC
IDH1/2 inhibitors	
Ivosidenib (IDH1)	Treatment of adults age 75+ who have AML with a susceptible *IDH1* mutation or with comorbidities that preclude IC, and treatment of R/R AML
Enasidenib (IDH2)	Treatment of adults who have R/R AML with a susceptible *IDH2* mutation
FLT3 inhibitors	
Midostaurin	In combination with IC, for treatment of adults who have AML with a *FLT3* mutation
Gilteritinib	Treatment of adults who have R/R AML with a *FLT3* mutation
Hedgehog pathway inhibitors	
Glasdegib	Treatment of AML in combination with LDAC for adults 75+ or with comorbidities that preclude IC
Antibody-drug conjugates	
Gemtuzumab ozogamicin	Treatment of newly diagnosed and refractory CD33+ AML

AML, acute myeloid leukemia; AZA, azacitidine; BCL-2, B-cell lymphoma 2; DEC, decitabine; CR, complete response; CRi, complete response with incomplete hematologic recovery; FDA, US Food and Drug Administration; FLT3, FMS-like tyrosine kinase 3; IC, intensive chemotherapy; IDH, isocitrate dehydrogenase; LDAC, low-dose cytarabine; R/R, relapsed or refractory.

or refractory (R/R) disease.[2] In particular, the combination of advanced age and poor performance status (ie, an Eastern Cooperative Oncology Group performance status of at least 3) is associated with a high likelihood of death within 30 days of the start of IC.[2] Additionally, the presence of a comorbidity such as ischemic heart disease, chronic kidney disease, or cerebral vascular disease is a significant pretreatment risk factor.[3] To determine their eligibility for IC, prognostic models incorporating cytogenetic information, age, and clinical indicators attempt to risk-stratify patients according to their likelihood of experiencing treatment-related morbidity and mortality, but no prognostic scoring system has become standard.[4,5] Thus, studies of therapies for patients ineligible for IC often differ in eligibility criteria.

Cytarabine-Based Therapies

Until recently, few AML treatment options were available for patients ineligible for IC. These patients were generally offered best supportive care (BSC), therapy based on low-dose cytarabine (LDAC), or hospice care. Although LDAC improves survival relative to BSC or hospice care, 1-year survival rates with LDAC remain at approximately 20% to 30%.[6] Because of recent advances in the treatment of patients ineligible for IC, LDAC has largely been replaced as the standard of care, but interest continues in the possibility of alternative cytarabine formulations and combination therapies of LDAC with other agents.

In 2017, the FDA approved a liposomal cytarabine/daunorubicin formulation (CPX-351) for the treatment of therapy-related AML and AML with myelodysplasia-related changes. Approval was based on a phase 3 trial that randomly assigned 309 patients ages 60 to 75 years with newly diagnosed high-risk AML to receive either intensive induction chemotherapy or up to 2 cycles of CPX-351. Overall survival (OS) was significantly longer in the patients who were treated with CPX-351 (OS, 9.56 vs 5.95 months; P=.003), and its safety profile was similar

Table 2. Therapies Under Investigation Without FDA Approval for Use in AML

Therapies Under Investigation in AML	Mechanisms
Cladribine	Antimetabolite
Hypomethylating agents	
Guadecitabine	Second-generation hypomethylating agent
CC-486	Oral azacitidine
Specific inhibitors	
Quizartinib	FLT3 inhibitor
Iadademstat	LSD-1 inhibitor
Bemcentinib	AXL inhibitor
CB-5339	VCP/p97 inhibitor
Sorafenib	Multikinase inhibitor
Immunotherapies	
Nivolumab	Anti–PD-1 monoclonal antibody
Pembrolizumab	Anti–PD-1 monoclonal antibody
Atezolizumab	Anti–PD-L1 monoclonal antibody
Durvalumab	Anti–PD-L1 monoclonal antibody
Sabatolimab	Anti-TIM3 monoclonal antibody
Magrolimab	Anti-CD47 monoclonal antibody
Vibecotamab	Anti-CD123 and anti-CD3 bispecific antibody
IMGN2	Anti-CD123 antibody-drug conjugate
Flotetuzumab	CD3×CD123 dual-affinity retargeting antibody

AML, acute myeloid leukemia; FDA, US Food and Drug Administration; PD-1, programmed death 1; PD-L1, programmed death ligand 1.

to that of conventional induction chemotherapy.[7] A phase 2 trial of CPX-351 in patients unfit for IC randomly assigned them to receive CPX-351 at 50 U/m^2, 75 U/m^2, or 100 U/m^2 and found the median OS to be 4.3 months among those receiving 50 U/m^2, vs 8.6 months among those receiving 75 U/m^2 and 6.2 months among those receiving 100 U/m^2 (P=.04). The most common nonhematologic grade 3/4 adverse events were febrile neutropenia (34%) and pneumonia (23%).[8]

Hypomethylating Agents

Many cancers exhibit abnormal DNA methylation patterns affecting gene expression, which can promote the growth and survival of leukemic cells. DNA hypomethylating agents (HMAs) such as decitabine (DEC) and azacitidine (AZA) decrease DNA methylation and may sensitize cells to chemotherapy and immunotherapy.[9] Clinical trials have found a survival advantage with HMA treatment relative to both LDAC and BSC. A phase 3 study (NCT01074047) compared the efficacy and safety of AZA administered subcutaneously (SC) at 75 mg/m^2/d for 7 days per 28-day cycle for at least 6 cycles with the efficacy and safety of conventional care regimens in 488 patients aged 65 years and older with newly diagnosed AML; results indicated that the median OS was increased with AZA relative to OS with conventional care regimens (10.4 vs 6.5 months; P=.1009).[10] In another phase 3 trial (NCT00260832), which compared DEC at 20 mg/m^2 per day for 5 consecutive days every 4 weeks vs BSC or cytarabine-based treatments in 485 patients with newly diagnosed AML aged 65 years and older, no significant differences in median OS were found, but improvements in CR plus CR with incomplete hematologic recovery (CRi) were observed with DEC (17.8 % vs 7.8% with other treatment options; P=.001).[11]

Azacitidine vs Decitabine

AZA and DEC have been shown to have somewhat different effects in vivo.[12] Whereas DEC metabolites are incorporated only into DNA, AZA metabolites are incorporated into DNA and RNA. This may account for some of the differences in the effects of these 2 agents. Population-based studies have found no substantial differences

in survival or transfusion independence between patients with AML treated with AZA and those treated with DEC.[13] However, a meta-analysis of 14 studies of HMA therapy in patients with myelodysplastic syndromes (MDS) and AML found a significantly greater risk for high-grade neutropenia in patients treated with DEC, but no difference in risk for febrile neutropenia or anemia.[14] DEC and AZA were directly compared in patients with AML ineligible for IC in the phase 3 ASTRAL-1 trial (NCT02348489), in which patients were randomly assigned to receive AZA (n=171) or DEC (n=167) at standard doses and schedules. This trial found no significant difference in CR rates (17.5% in the AZA group vs 19.2% in the DEC group) or in the 1- and 2-year OS rates (39% and 15% in the AZA group vs 32% and 14% in the DEC group, respectively).[15] Although, as noted above, a meta-analysis showed a greater risk for high-grade neutropenia in patients treated with DEC than in those treated with AZA, the ASTRAL-1 trial conversely found that serious adverse events (AEs) leading to death occurred more frequently in the AZA arm (38% with AZA vs 26% with DEC; *P*=.02), leaving it unclear if a safety advantage is associated with either DEC or AZA.[15]

Oral Hypomethylating Agents

The QUAZAR AML-001 maintenance trial is a phase 3 trial (NCT01757535) comparing CC-486, an oral formulation of AZA, with placebo in patients with AML who achieved CR/CRi following induction therapy (and in some cases, limited consolidation therapy) but were not candidates for hematopoietic stem cell transplant. At a median follow-up of 41.2 months, OS in patients given CC-486 at 300 mg/d on days 1 to 14 of a 28-day treatment cycle was significantly improved relative to OS in the placebo group (24.7 vs 14.8 months; *P*=.0009).[16] The FDA therefore approved CC-486 in September 2020 for maintenance therapy in patients with AML and in CR/CRi after IC who cannot complete curative therapy.[17] The FDA also approved an oral combination of DEC and cedazuridine (Inqovi, Astex/Taiho/Otsuka), a cytidine deaminase inhibitor that overcomes metabolism in the liver and other organs, for the treatment of certain patients with MDS or chronic myelomonocytic leukemia (CMML). Approval was based on the results of 2 crossover trials (NCT0210347 and NCT03306264) that showed similar safety, efficacy, and pharmacokinetic profiles for the combination oral regimen and intravenous (IV) DEC.[18] Although trial results are not available for oral AZA or DEC in treatment-naive patients with AML who are ineligible for IC, the promising trial results in other patient groups offer the possibility that these patients may eventually have access to an all-oral regimen.

Venetoclax

Members of the BCL-2 family of proteins promote the survival of cancers cells by sequestering pro-apoptotic proteins such as BIM.[19] BCL-2 overexpression has been observed in AML,[20] making it a therapeutic target. Venetoclax (VEN; Venclexta, AbbVie) is a selective small-molecule inhibitor of BCL-2. On the basis of trial findings reviewed below, VEN in combination with LDAC or HMA therapy received accelerated FDA approval in November 2018 and full FDA approval in October 2020 for the treatment of newly diagnosed AML in patients ineligible for IC.

Hypomethylating Agents/Venetoclax

A phase 1b trial (NCT02203773) evaluated either AZA at 75 mg/m^2 on days 1 to 7 or DEC at 20 mg/m^2 on days 1 to 5 in combination with VEN (400, 800, or 1200 mg daily) for a median of 5 cycles in treatment-naive patients ineligible for IC. The trial overall found rates of CR and CRi of 67% and 73%, respectively, in the AZA/VEN 400-mg cohort.[21] The most common grade 3/4 AEs were febrile neutropenia (43%), leukopenia (31%), anemia (25%), and thrombocytopenia (24%).[21]

A phase 2 trial (NCT03403193) of 168 patients with AML ineligible for IC evaluated DEC at 20 mg/m^2 IV for 10 days with VEN at 400 mg/d for induction, followed by DEC for 5 days with VEN at 400 mg/d.[22] The trial found an overall response rate (ORR) of 74% (89% in newly diagnosed AML), with a median OS of 18.1 months in newly diagnosed AML, 7.8 and 6.0 months in untreated and treated secondary AML, respectively, and 7.8 months in R/R AML.[22] However, the DEC/VEN regimen was less effective in patients with *TP53* mutations. CR rates were lower in patients with mutated *TP53* than in those with wild-type *TP53* (35% vs 57%; *P*=.026), and median OS was shorter (5.2 vs 19.4 months; *P* <.001).[23]

The phase 3 VIALE-A trial (NCT02993523) enrolled 431 patients with a median age of 76 years and previously untreated AML who were ineligible for IC. The trial compared treatment with AZA at 75 mg/m^2 given SC or IV on days 1 to 7 per 28-day cycle with or without VEN at 400 mg/d. At a median follow-up of 20.5 months, the median OS was significantly longer in the AZA/VEN group, at 14.7 vs 9.6 months, and the CR rate was 36.7% in the AZA/VEN group vs 17.9% in the AZA-alone group (*P*<.001); however, these benefits were accompanied by higher rates of thrombocytopenia and febrile neutropenia.[24] Subgroup analyses of patients with mutated *FLT3* and mutated *IDH1/2* showed significantly higher CR/CRi rates and longer median OS in patients treated with AZA/VEN than in those treated with AZA alone. Among the patients with mutated *FLT3*,

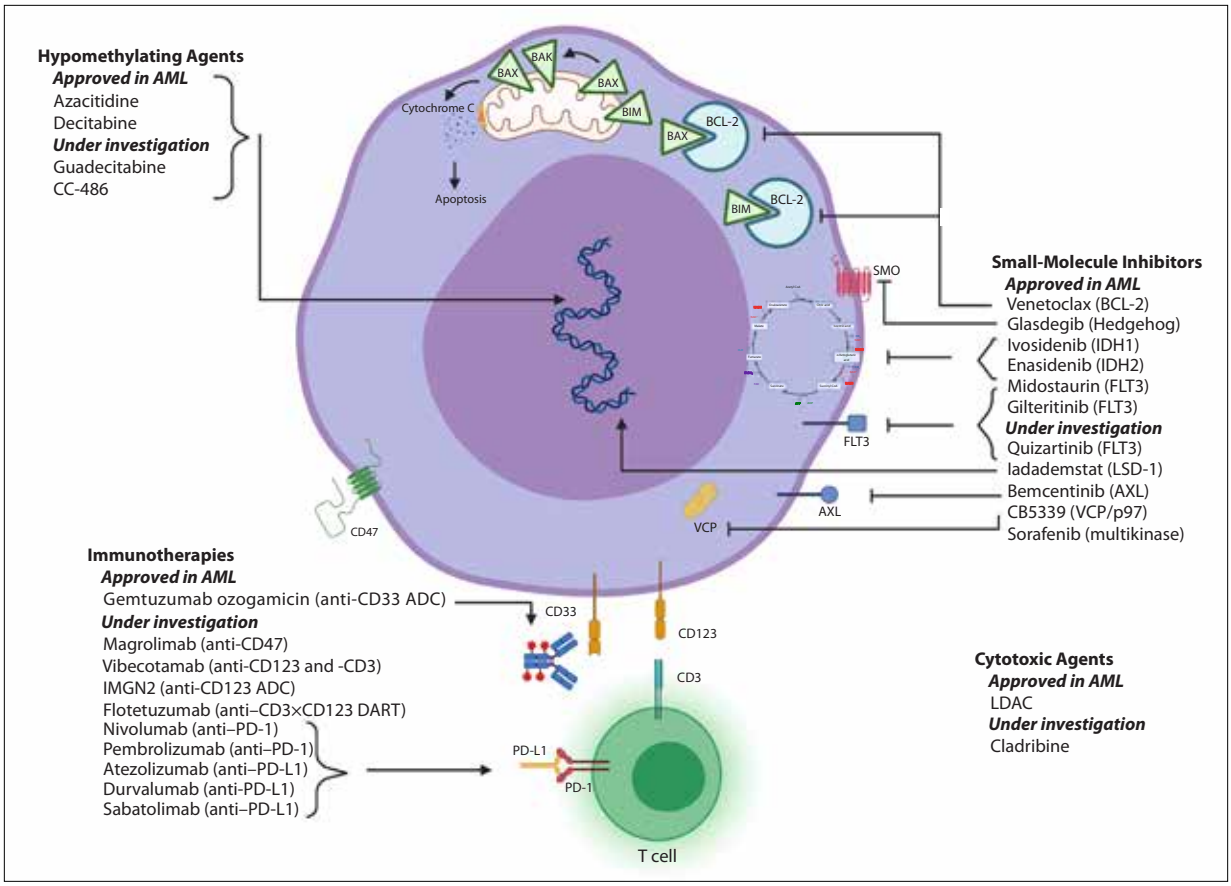

Figure. Schematic illustrating the main therapeutic targets approved or under investigation for patients with AML who are ineligible for intensive chemotherapy.

ADC, antibody-drug conjugate; DART, dual-affinity retargeting antibody; PD-1, programmed death 1; PD-L1, programmed death ligand 1; BCL-2, B-cell lymphoma 2; IDH, isocitrate dehydrogenase; FLT3, FMS-like tyrosine kinase 3; LDAC, low-dose cytarabine; LSD-1, lysine-specific histone demethylase 1A; VCP, valosin-containing protein.

the CR/CRi rate was 65% and median OS was 13.3 months with AZA/VEN, whereas the CR/CRi rate was 18% and median OS was 8.6 months with AZA alone. These improvements were driven primarily by patients with *FLT3* tyrosine kinase domain mutations.[25] Among patients with *IDH1/2* mutations, the CR/CRi rate was 72% and median OS was 24.5 months with AZA/VEN vs a CR/CRi rate of 7% and median OS of 6.2 months with AZA alone.[25,26]

Low-Dose Cytarabine/Venetoclax

Recent research has investigated combining LDAC with other treatments, notably with VEN. In the phase 3 VIALE-C trial (NCT03069352), 221 patients with AML who were ineligible for IC were randomly assigned to receive LDAC SC at 20 mg/m^2/d for days 1 to 10 per 28-day cycle with or without VEN started at 100 mg on day 1, increased over 4 days to a target dose of 600 mg/d, and continued from day 4 to day 28. Patients who received LDAC/VEN demonstrated improvements in rates of CR (27% vs 7%; *P*<.001) and CR/CRi (48% vs 13%; *P*<.001), with significant improvements in median OS (8.4 vs 4.1 months; *P*=.04), relative to patients who received LDAC alone.[27] LDAC/VEN was well tolerated; the most frequent AEs were febrile neutropenia (32% with LDAC/VEN vs 29% with LDAC alone), neutropenia (46% with LDAC/VEN vs 16% with LDAC alone), thrombocytopenia (45% with LDAC/VEN vs 37% with LDAC alone), and anemia (25% with LDAC/VEN vs 22% with LDAC alone).[27] Trials of LDAC/VEN and trials of HMAs/VEN reported prolonged myelosuppression requiring cycle interruptions for count recovery.[24,27]

Analysis of patient-reported outcomes from the VIALE-A trial of AZA with VEN and the VIALE-C trial of LDAC with VEN showed delays in time to deterioration with the addition of VEN to either regimen.[28]

However, the majority of patients treated with AZA/VEN in the VIALE-A trial required VEN dosing modifications or delays in cycles to manage cytopenias.[29] Examination of the exposure-efficacy and the exposure-safety relationships supports the use of VEN at 400 mg/d in combination with an HMA, and at 600 mg/d in combination with LDAC.[30,31] Although no head-to-head trials have compared LDAC/VEN vs HMAs/VEN, it appears that the HMAs/VEN combination likely offers better efficacy. However, recent trials have shown promising results in regard to the possibility of adding cladribine (Mavenclad, EMD Serono), a purine nucleoside approved for the treatment of hairy cell leukemia, to LDAC and alternating this combination with a traditional HMA (DEC or AZA).[32]

IDH1 and IDH2 Inhibitors

Mutations in the isocitrate dehydrogenase genes (*IDH1* and *IDH2*) occur in approximately 20% of patients with AML, with *IDH2* mutations seen more commonly.[33,34] These mutations contribute to impaired hematopoietic differentiation,[35] making them potential therapeutic targets in AML. Enasidenib (Idhifa, Celgene), a small-molecule inhibitor of mutant *IDH2,* was approved by the FDA in 2017 for adults with R/R *IDH2*-mutated AML on the basis of phase 1/2 trials demonstrating its safety and efficacy at 100 mg/d in this group, with a CR rate of 19% for a median duration of 8.2 months and a CRi rate of 4% for a median duration of 9.6 months.[36] In the phase 3 IDHENTIFY study (NCT02577406), enasidenib led to no improvement in OS compared with conventional care regimens in patients with R/R AML.[37] A phase 1/2 trial of enasidenib in patients with newly diagnosed *IDH2*-mutated AML ineligible for IC showed good safety and tolerability at 100 mg/d; the most common grade 3/4 AEs were cytopenias and IDH-mediated differentiation syndrome.[38] In a phase 2 trial (NCT02677922) comparing enasidenib at 100 mg/d plus AZA at 75 mg/m^2 on days 1 to 7 of every 28-day cycle vs AZA alone in patients with newly diagnosed *IDH2*-mutated AML ineligible for IC, enasidenib/AZA produced higher response rates than AZA alone (ORR, 68% vs 42%; *P*=.0155; CR rate, 50% vs 12%; *P*=.0002),[39] suggesting a role for enasidenib in the treatment of *IDH2*-mutated AML.

A phase 1 trial (NCT02074839) investigating the safety and activity of ivosidenib (Tibsovo, Agios), a small-molecule inhibitor of mutated IDH1, found that at a dose of 500 mg/d, the frequency of grade 3 or higher treatment-related AEs (most commonly differentiation syndrome and febrile neutropenia) was minimized.[40] Among patients with newly diagnosed *IDH1*-mutated AML ineligible for IC, an ORR of 54.5% and a median OS of 12.6 months (with a median follow-up of 23.5 months) was observed.[40] Ivosidenib was approved for patients with *IDH1*-mutated R/R AML in 2018, and in 2019 the FDA extended the approval to include patients with newly diagnosed *IDH1*-mutated AML ineligible for IC.[41] Also promising were results from a phase 1b/2 trial (NCT02677922) of combination ivosidenib at 500 mg/d and AZA at 75 mg/m^2 in patients with *IDH1*-mutated AML ineligible for IC, with an ORR of 78% and a CR rate of 61%.[42] The ongoing phase 3 AGILE trial (NCT03173248) is comparing the combination of ivosidenib at 500 mg taken continuously and AZA at 75 mg/m^2 for 7 days in 28-day cycles vs AZA alone in patients with *IDH1*-mutated AML ineligible for IC.[43] A phase 2 trial of the combination of ivosidenib/VEN/AZA is also underway.[44]

Because no trials have directly compared HMAs plus an IDH inhibitor vs HMAs/VEN, it remains unclear which agents should be used in the initial treatment of patients with *IDH*-mutated AML who are ineligible for IC. Clinical trials will be needed to determine the correct sequencing of these therapies. However, given the significant risk for myelosuppression associated with VEN, IDH inhibitors may be a better choice for patients with *IDH*-mutated AML who present with significant cytopenias.

FLT3 Inhibitors

Mutations in the FMS-like tyrosine kinase 3 (*FLT3*) gene are seen in approximately 30% of patients with AML.[45] Among patients with *FLT3* mutations, internal tandem duplication (ITD) is more common, but point mutations in the tyrosine kinase domain are also seen.[46] ITD *FLT3*-mutated AML in particular has been associated with a poor prognosis,[47] and interest has grown in FLT3 as a potential therapeutic target in AML.

A phase 2 trial (NCT01093573) of the combination of the multikinase inhibitor midostaurin (Rydapt, Novartis) and AZA in patients with AML ineligible for IC found that multiple cycles of AZA at 75 mg/m^2 per day for days 1 to 7 of a 28-day cycle plus midostaurin at 75 mg orally twice daily on days 8 to 21 were poorly tolerated, causing hematologic, gastrointestinal, and infectious toxicities, but that intermittent dosing of midostaurin may be beneficial.[48]

Another multikinase inhibitor, sorafenib (Nexavar, Bayer), which is FDA-approved for use in some solid tumors, has also been investigated in AML. An analysis of 27 patients aged 61 to 86 years with newly diagnosed *FLT3*-mutated AML treated with sorafenib/AZA under 2 different trial protocols (NCT02196857 and NCT01254890) found a CR rate of 26%, a CRi rate of 44%, and a median OS of 8.3 months, with no early deaths reported.[48]

In a phase 2 trial of the FLT3 inhibitor quizartinib in combination with AZA or LDAC, patients who had AML with an ITD *FLT3* mutation received quizartinib at either of 2 planned dose levels (60 or 90 mg) orally twice a day along with either AZA at 75 mg/m^2 for 7 days per cycle or cytarabine at 20 mg twice daily for 10 days per cycle. The median OS was 13.4 months in the quizartinib/AZA arm vs 6.7 months in the quizartinib/LDAC arm (P=.407).[49]

The phase 3 ADMIRAL trial (NCT02421939) comparing the second-generation FLT3 inhibitor gilteritinib (Xospata, Astellas) at 120 mg/d with salvage chemotherapy in patients with R/R *FLT3*-mutated AML found improved median OS with gilteritinib (9.3 vs 5.6 months; P<.001),[50] resulting in the approval of gilteritinib as a single agent for patients with *FLT3*-mutated R/R AML.[51] Follow-up analyses of these patients continued to show benefits, with median 18-month survival rates of 27% in the gilteritinib arm vs 15% in the salvage chemotherapy arm.[52] An ongoing phase 3 trial (NCT02752035) is comparing gilteritinib at 120 mg/d plus AZA at 75 mg/m^2 per day for days 1 to 7 of a 28-day cycle vs AZA alone in patients with newly diagnosed *FLT3*-mutated AML who are ineligible for IC. An initial safety cohort showed no new safety signals with the combination of gilteritinib and AZA,[53] and randomization of approximately 250 patients is ongoing.[54] Despite these promising results with multikinase and FLT3 inhibitors in patients with *FLT3* mutations, it remains unclear whether patients with newly diagnosed *FLT3*-mutated AML who are ineligible for IC would be better served by starting treatment with an HMA/FLT3 inhibitor or with an HMA/VEN, as no direct comparisons of these regimens have been made.

Hedgehog Pathway Inhibitors

AML blasts overexpress components of the Hedgehog signaling pathway, which induces expression of pro-survival genes and is associated with chemoresistance and worse patient survival.[55] Glasdegib (Daurismo, Pfizer) is an oral antagonist of Smoothened (SMO), a Hedgehog pathway activator. The phase 2 BRIGHT-AML trial (NCT01546038) compared glasdegib/LDAC vs LDAC alone. A total of 115 patients aged 75 years and older with newly diagnosed AML or with comorbidities precluding treatment with IC were randomly assigned to receive LDAC with or without glasdegib at 100 mg/d.[56] At a median follow-up of 20 months, the median OS was 8.3 months in the glasdegib/LDAC combination arm and 4.3 months in the LDAC-alone arm (P=.004). CR rates were also significantly higher in the glasdegib arm (17% vs 2.3%, respectively; P<.05; with a median duration of 9.9 vs 6.5 months, respectively. Glasdegib had an acceptable safety profile, with pneumonia (16.7%) and fatigue (14.3%) among the most common grade 3/4 AEs.[56] These results were confirmed in a follow-up study with an additional 20 months of observation,[57] after which the FDA approved glasdegib for the treatment of newly diagnosed AML in patients aged 75 years and older or with comorbidities that preclude treatment with IC.[58]

A phase 1b trial (NCT02367456) evaluated the safety of a combination of glasdegib and AZA in patients with MDS, AML, or CMML ineligible for IC. Among 30 patients with AML who received glasdegib at 100 mg/d and AZA at 75 mg/m^2 per day on days 1 to 7 of a 28-day cycle, the most common serious AEs were febrile neutropenia (20%) and pyrexia (13%); 20% of the patients achieved a CR, and the probability of 6-month survival was 70%, although the median OS was not evaluable.[59] The combination of glasdegib and an HMA is being further evaluated in the ongoing phase 2 GLAD-AML study (NCT03798678), designed to investigate the efficacy of glasdegib at 100 mg/d in combination with either 5 or 10 days of treatment with DEC.[60]

Additional Small-Molecule Inhibitors Under Investigation

The search for other specific targets in patients with AML ineligible for IC is ongoing. Other therapies currently in phase 1 and 2 trials include iadademstat, an inhibitor of LSD1 (a regulator of stem cell differentiation)[61]; bemcentinib, an inhibitor of AXL (a surface membrane protein kinase receptor that contributes to the growth of AML cells)[62]; CB5339, an inhibitor of VCP/p97 (an enzyme vital for cancer cell growth)[63]; and CFI-400945, an inhibitor of PLK4 (a regulator of centriole duplication).[64]

Antibody-Drug Complexes and Immunotherapy

Gemtuzumab

Gemtuzumab ozogamicin (GO; Mylotarg, Pfizer) is a conjugate comprising an anti-CD33 monoclonal antibody and a chemotherapeutic agent. CD33 is expressed on leukemic blasts in more than 80% of patients with AML but is not present on normal hematopoietic pluripotent stem cells, offering the possibility of antitumor effects with reduced systemic toxicity.[65] GO was initially approved by the FDA in 2000 for patients with R/R AML and patients with AML ineligible for IC; however, it was withdrawn from the market in 2010 after a phase 3 trial demonstrated higher rates of fatal toxicity (most notably, from veno-occlusive liver disease) with GO than with

standard therapy.[66] In 2017, GO was restudied in a phase 3 trial (NCT00091234) that used a different administration schedule. This trial compared GO monotherapy with BSC as first-line therapy in 237 adults with AML ineligible for IC.[67] Median OS was significantly longer in the patients who received GO at 6 mg/m^2 on day 1 and at 3 mg/m^2 on day 3 than in those who received BSC (4.9 months with GO vs 3.6 months with BSC; *P*=.005).[67] On the basis of these results, GO was reapproved by the FDA in 2017 as monotherapy for patients with CD33-positive AML ineligible for IC.[66]

PD-1 and PD-L1 Inhibitors

A promising area of immunotherapy is investigating the activation of an antitumor immune response through the inhibition of immune control checkpoints. Two potential targets that serve as negative control checkpoints in AML are programmed death 1 (PD-1) and its cognate ligand, programmed death ligand 1 (PD-L1). PD-1 overexpression has been observed in AML and is thought to cause T-cell dysfunction and impaired antitumor immune responses.[68] Two PD-1 inhibitors, nivolumab (Opdivo, Bristol Myers Squibb) and pembrolizumab (Keytruda, Merck), and two anti–PD-L1 monoclonal antibodies (atezolizumab [Tecentriq, Genentech] and durvalumab [Imfinzi, AstraZeneca]), have shown promise in AML. Nivolumab is FDA-approved for the treatment of a variety of cancers, including melanoma and small cell lung cancers. A phase 2 trial (NCT02397720) of nivolumab at 3 mg/kg on days 1 and 14 every 4 to 6 weeks in combination with AZA at 75 mg/m^2 on days 1 to 7 in 70 patients with R/R AML found an ORR of 33%, with 22% achieving CR/CRi[69]; nivolumab has not yet been studied in patients with newly diagnosed AML who are ineligible for standard chemotherapy. A phase 2 trial (NCT04284787) is currently underway to evaluate the utility of adding pembrolizumab to a combination of VEN and AZA in patients with newly diagnosed AML ineligible for IC.[70]

A phase 2 trial (NCT02775903) randomly assigned 129 patients with AML ineligible for IC to receive either AZA alone at 75 mg/m^2 on days 1 to 7 or AZA in combination with durvalumab at 1500 mg on day 1 of each 28-day cycle. The trial found no significant difference in the ORRs and no new safety signals with the combination of AZA and durvalumab.[71] A phase 1b trial of atezolizumab in combination with AZA in treatment-naive patients with higher-risk MDS was terminated early owing to high rates of treatment-related early death.[72]

Other Immunotherapies

T-cell immunoglobulin and mucin domain 3 (TIM3) is another negative regulatory immune checkpoint, and anti-TIM3 antibodies such as sabatolimab (MGB453) have been shown to improve eradication of AML leukemic stem cells in preclinical models.[73] A phase 1b trial (NCT03066648) of sabatolimab in combination with an HMA in 48 patients with newly diagnosed AML ineligible for IC found the combination to be well tolerated. Patients received sabatolimab IV at a dose of 240 or 400 mg every 2 weeks or at 800 mg every 4 weeks in combination with DEC (20 mg/m^2 IV on days 1-5) or AZA (75 mg/m^2 IV/SC on days 1-7) per 28-day cycle; the maximum tolerated dose was not reached.[74] The most common AEs were cytopenias. Trial participants had an ORR of 41.2% and an estimated 12-month progression-free survival (PFS) rate of 44%.[74] The phase 2 STIMULUS-AML1 trial (NCT04150029), planned to further evaluate the safety and efficacy of sabatolimab in combination with AZA and VEN in patients with AML ineligible for IC, is underway.[75]

Another antibody being assessed in AML is magrolimab, which blocks CD47, a macrophage immune checkpoint. In a phase 1b trial, treatment-naive patients with AML unfit for IC were treated with a dose-escalation regimen of magrolimab IV weekly at 1 to 30 mg/kg, followed by 30 mg/kg IV every 2 weeks for cycles 3 and beyond, in combination with AZA at 75 mg/m^2 on days 1 to 7 of a 28-day cycle. The most common AEs were anemia (31%) and neutropenia (19%), and no grade 4 or 5 AEs were observed. Overall, 44% of patients achieved CR (an additional 12% achieved CRi), and the median OS was 18.9 months. Results were also encouraging in patients with *TP53* mutations, in whom the CR rate, CRi rate, and median OS were 48%, 19%, and 12.9 months, respectively.[76] Trials of magrolimab in combination with AZA and VEN are currently underway.[77]

Several additional immunotherapies are currently under study for R/R AML. Although these trials are in relatively early stages, it is possible that similar immunotherapies may have utility in treating patients with newly diagnosed AML who are ineligible for IC. CD123 is overexpressed in AML, making it a potential therapeutic target. Vibecotamab is a bispecific antibody that targets CD123 and CD3 to stimulate the T-cell–mediated destruction of CD123+ cells; it is being studied in a phase 1 trial (NCT02730312) in patients with R/R AML, among other cancers.[78] IMGN263, a CD123-targeted antibody-drug conjugate that has been shown to have a synergistic antileukemic effect with AZA and VEN in preclinical models,[79] is currently in phase 1/2 trials (NCT03386513) in patients with R/R AML.[80] Another bispecific antibody, the CD3×CD123 dual-affinity retargeting antibody flotetuzumab, is also in phase 1/2 trials (NCT02152956) in patients with R/R AML, with a maximum tolerated dose of 500 ng/kg per day, and early

results have demonstrated an ORR of 30% and median OS of 10.2 months.[81] AMG 330, a bispecific T-cell engager molecule that binds CD3+ T cells and CD33+ AML blasts, is in phase 1 trials (NCT02520427) in patients with R/R AML.[82]

Conclusions

Significant progress has been made in the development of therapeutic regimens for patients with AML who are unfit for IC; however, challenges remain. Although the performance status of a small subset of patients improves as a result of these nonintensive regimens, so that they can proceed to more intensive treatment, including hematopoietic cell transplant,[83] the therapies reviewed here should be viewed primarily as life-prolonging, not curative.

One challenge encountered in comparing treatments for medically unfit adults with AML across trials is the lack of standardization regarding who is deemed ineligible for standard IC. For example, some trials include patients of all ages who are ineligible for IC because of poor performance status or comorbidities, whereas other trials include only patients 65 years of age and older. Furthermore, trials may differ in the endpoints they examine, with recent evidence suggesting that measurable residual disease is an independent prognostic indicator in patients treated with HMAs and may thus be a useful endpoint.[84]

HMA therapy quickly became a mainstay of treatment in adults with AML who are ineligible for IC. The promising results reported from trials of HMA/VEN combinations suggest that this ambulatory regimen should be considered the first-line treatment in this setting. In patients with specific actionable mutations (eg, *IDH1*, *IDH2*, *FLT3*), targeted inhibitors may also be an attractive option. Several of the therapies presented here have been shown in preclinical models and early-stage clinical trials to have synergistic antileukemic effects while maintaining good patient tolerability, and investigations of combinations of drugs, in particular HMAs, VEN, and other therapies, are ongoing. Given the broad activity of HMA/VEN combinations across distinct mutational profiles, an emerging challenge is selection of the optimal first-line therapy in patients with actionable mutations. This challenge highlights the need to develop molecularly informed, personalized treatment plans for patients from diagnosis to relapse.

References

1. Cancer Stat Facts: Leukemia — acute myeloid leukemia (AML). Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/amyl.html. Accessed November 28, 2020.
2. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood*. 2006;107(9):3481-3485.
3. Djunic I, Virijevic M, Novkovic A, et al. Comorbidity as a risk factor for overall survival and decision criteria for intensity of chemotherapy in elderly patients with acute myeloid leukemia. *Med Oncol*. 2012;29(2):1077-1081.
4. Pettit K, Odenike O. Defining and treating older adults with acute myeloid leukemia who are ineligible for intensive therapies. *Front Oncol*. 2015;5:280.
5. Kantarjian H, O'brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer*. 2006;106(5):1090-1098.
6. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer*. 2007;109(6):1114-1124.
7. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;36(26):2684-2692.
8. Issa GC, Kantarjian HM, Xiao L, et al. Phase II trial of CPX-351 in patients with acute myeloid leukemia at high risk for induction mortality. *Leukemia*. 2020;34(11):2914-2924.
9. Sato T, Issa JJ, Kropf P. DNA Hypomethylating drugs in cancer therapy. *Cold Spring Harb Perspect Med*. 2017;7(5):a026948.
10. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126(3):291-299.
11. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2012;30(21):2670-2677.
12. Hollenbach PW, Nguyen AN, Brady H, et al. A comparison of azacitidine and decitabine activities in acute myeloid leukemia cell lines. *PLoS One*. 2010;5(2):e9001.
13. Zeidan AM, Wang R, Wang X, et al. Clinical outcomes of older patients with AML receiving hypomethylating agents: a large population-based study in the United States. *Blood Adv*. 2020;4(10):2192-2201.
14. Gao C, Wang J, Li Y, et al. Incidence and risk of hematologic toxicities with hypomethylating agents in the treatment of myelodysplastic syndromes and acute myeloid leukopenia: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2018;97(34):e11860.
15. Zeidan AM, Fenaux P, Gobbi M, et al. Comparative results of azacitidine and decitabine from a large prospective phase 3 study in treatment naive patients with acute myeloid leukemia not eligible for intensive chemotherapy [ASH abstract 1037]. *Blood*. 2020;136(1)(suppl).
16. Wei AH, Döhner H, Pocock C, et al. The QUAZAR AML-001 maintenance trial: results of a phase III international, randomized, double-blind, placebo-controlled study of CC-486 (oral formulation of azacitidine) in patients with acute myeloid leukemia (AML) in first remission [ASH abstract LBA3]. *Blood*. 2019;134(2)(suppl).
17. FDA approves oral azacitidine as maintenance therapy for adults with AML in first remission. *The ASCO Post*. https://ascopost.com/issues/september-25-2020/fda-approves-oral-azacitidine-as-maintenance-therapy-for-adults-with-aml-in-first-remission/. Posted September 25, 2020. Accessed November 29, 2020.
18. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. *Blood*. 2020;136(6):674-683.
19. Konopleva M, Letai A. BCL-2 inhibition in AML: an unexpected bonus? *Blood*. 2018;132(10):1007-1012.
20. Zhou JD, Zhang TJ, Xu ZJ, et al. BCL2 overexpression: clinical implication and biological insights in acute myeloid leukemia. *Diagn Pathol*. 2019;14(1):68.
21. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood*. 2019;133(1):7-17.
22. DiNardo CD, Maiti A, Rausch CR, et al. 10-day decitabine with venetoclax for newly diagnosed intensive chemotherapy ineligible, and relapsed or refractory acute myeloid leukaemia: a single-centre, phase 2 trial. *Lancet Haematol*. 2020;7(10):e724-e736.
23. Kim K, Maiti A, Kadia TM, et al. Outcomes of TP53-mutant acute myeloid leukemia with venetoclax and decitabine [ASH abstract 693]. *Blood*. 2020;136(1)(suppl).
24. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.

25. Konopleva M, Thirman M, Pratz KW, et al. Results of venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with FLT3 mutations [ASH abstract 1904]. *Blood*. 2020;136(1)(suppl).
26. Pollyea DA, Dinardo CD, Arellano ML, et al. Results of venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with IDH 1/2 mutations [ASH abstract 461]. *Blood*. 2020;136(1)(suppl).
27. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135(24):2137-2145.
28. Pratz KW, Panayiotidis P, Recher C, et al. Delays in time to deterioration of health-related quality of life were observed in patients with acute myeloid leukemia receiving venetoclax in combination with azacitidine or in combination with low-dose cytarabine [ASH abstract 589]. *Blood*. 2020;136(1)(suppl).
29. Pratz K, DiNardo CD, Selleslag D, et al. Cytopenia management in patients with newly diagnosed acute myeloid leukemia treated with venetoclax plus azacitidine in the VIALE-A study [ASH abstract 1944]. *Blood*. 2020;136(1)(suppl).
30. Eckert D, Brackman D, Menon R, et al. Venetoclax exposure-efficacy and exposure-safety relationships in subjects with treatment-naïve acute myeloid leukemia who are ineligible for intensive chemotherapy [ASH abstract 52]. *Blood*. 2020;136(1)(suppl).
31. Agarwal S, Gopalakrishnan S, Mensing S, et al. Optimizing venetoclax dose in combination with low intensive therapies in elderly patients with newly diagnosed acute myeloid leukemia: an exposure-response analysis. *Hematol Oncol*. 2019;37(4):464-473.
32. Kadia TM, Cortes J, Ravandi F, et al. Cladribine and low-dose cytarabine alternating with decitabine as frontline therapy for older patients with acute myeloid leukemia: a phase 2 single-arm trial. *Lancet Haematol*. 2018;5(9):e411-e421.
33. DiNardo CD, Ravandi F, Agresta S, et al. Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. *Am J Hematol*. 2015;90(8):732-736.
34. Patel KP, Ravandi F, Ma D, et al. Acute myeloid leukemia with IDH1 or IDH2 mutation: frequency and clinicopathologic features. *Am J Clin Pathol*. 2011;135(1):35-45.
35. Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. *Cancer Cell*. 2010;18(6):553-567.
36. FDA approves new targeted treatment for relapsed or refractory acute myeloid leukemia. US Food & Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-new-targeted-treatment-relapsed-or-refractory-acute-myeloid-leukemia. Published August 1, 2017. Accessed December 5, 2020.
37. Bristol Myers Squibb provides update on phase 3 iDHENTIFY trial in patients with relapsed or refractory acute myeloid leukemia. Bristol Myers Squibb. https://news.bms.com/news/details/2020/Bristol-Myers-Squibb-Provides-Update-on-Phase-3-IDHENTIFY-Trial-in-Patients-with-Relapsed-or-Refractory-Acute-Myeloid-Leukemia/default.aspx. Published August 25, 2021. Accessed June 23, 2021.
38. Pollyea DA, Tallman MS, de Botton S, et al. Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia. *Leukemia*. 2019;33(11):2575-2584.
39. DiNardo CD, Schuh AC, Stein EM, et al. Enasidenib plus azacitidine significantly improves complete remission and overall response compared with azacitidine alone in patients with newly diagnosed acute myeloid leukemia (AML) with isocitrate dehydrogenase 2 (IDH2) mutations: interim phase II results from an ongoing, randomized study [ASH abstract 643]. *Blood*. 2019;134(1)(suppl).
40. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*. 2020;135(7):463-471.
41. FDA approves ivosidenib as first-line treatment for AML with IDH1 mutation. US Food & Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-first-line-treatment-aml-idh1-mutation. Updated May 3, 2019. Accessed December 5, 2020.
42. Daigle SR, Choe S, Quek L, et al. High rate of IDH1 mutation clearance and measurable residual disease negativity in patients with IDH1-mutant newly diagnosed acute myeloid leukemia treated with ivosidenib (AG-120) and azacytidine [ASH abstract 2706]. *Blood*. 2019;134(1)(suppl).
43. ClinicalTrials.gov. A phase 3, multicenter, double-blind, randomized, placebo-controlled study of AG-120 in combination with azacitidine in subjects ≥ 18 years of age with previously untreated acute myeloid leukemia with an IDH1 mutation. https://clinicaltrials.gov/ct2/show/NCT03173248. Updated June 14, 2021. Accessed June 23, 2021.
44. Lachowiez CA, Borthakur G, Loghavi S, et al. Phase Ib/II study of the IDH1-mutant inhibitor ivosidenib with the BCL2 inhibitor venetoclax +/- azacitidine in IDH1-mutated hematologic malignancies [ASCO abstract 7500]. *J Clin Oncol*. 2020;38(15)(suppl).
45. Daver N, Schlenk RF, Russell NH, Levis MJ. Targeting FLT3 mutations in AML: review of current knowledge and evidence. *Leukemia*. 2019;33(2):299-312.
46. Short NJ, Kantarjian H, Ravandi F, Daver N. Emerging treatment paradigms with FLT3 inhibitors in acute myeloid leukemia. *Ther Adv Hematol*. 2019;10:2040620719827310.
47. Kayser S, Schlenk RF, Londono MC, et al. Insertion of FLT3 internal tandem duplication in the tyrosine kinase domain-1 is associated with resistance to chemotherapy and inferior outcome. *Blood*. 2009;114(12):2386-2392.
48. Tomlinson BK, Gallogly MM, Kane DM, et al. A phase II study of midostaurin and 5-azacitidine for untreated elderly and unfit patients with FLT3 wild-type acute myelogenous leukemia. *Clin Lymphoma Myeloma Leuk*. 2020;20(4):226-233.e1.
49. Swaminathan M, Kantarjian HM, Levis M, et al. A phase I/II study of the combination of quizartinib with azacitidine or low-dose cytarabine for the treatment of patients with acute myeloid leukemia and myelodysplastic syndrome [published online April 15, 2021]. *Haematologica*. doi:10.3324/haematol.2020.263392.
50. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated aml. *N Engl J Med*. 2019;381(18):1728-1740.
51. FDA approves gilteritinib for relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation. US Food & Drug Administration. https://www.fda.gov/drugs/fda-approves-gilteritinib-relapsed-or-refractory-acute-myeloid-leukemia-aml-flt3-mutatation. Updated December 14, 2018. Accessed December 5, 2020.
52. ASCO20: 1-year ADMIRAL trial update on gilteritinib in resistant AML. JNCCN 360. https://jnccn360.org/aml/news/1-year-admiral-trial-update-on-gilteritinib-in-resistant-aml/. Updated June 26, 2020. Accessed February 18, 2021.
53. Esteve J, Schots R, Bernal Del Castillo T, et al. Multicenter, open-label, 3-arm study of gilteritinib, gilteritinib plus azacitidine, or azacitidine alone in newly diagnosed FLT3 mutated (FLT3mut+) acute myeloid leukemia (AML) patients ineligible for intensive induction chemotherapy: findings from the safety cohort [ASH abstract 2736]. *Blood*. 2018;132(1)(suppl).
54. Wang E. Phase 3, multicenter, open-label study of gilteritinib, gilteritinib plus azacitidine, or azacitidine alone in newly diagnosed FLT3 Mutated ($FLT3^{mut+}$) acute myeloid leukemia (AML) patients ineligible for intensive induction chemotherapy [ASH abstract 27]. *Blood*. 2020;136(1)(suppl).
55. Terao T, Minami Y. Targeting hedgehog (Hh) pathway for the acute myeloid leukemia treatment. *Cells*. 2019;8(4):312.
56. Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*. 2019;33(2):379-389.
57. Smith BD, Papayannidis C, Heuser M, et al. Low-dose cytarabine with or without glasdegib in newly diagnosed patients with acute myeloid leukemia: long-term analysis of a phase 2 randomized trial [ASCO abstract 7010]. *J Clin Oncol*. 2019;37(15)(suppl).
58. FDA approves glasdegib for AML in adults age 75 or older or who have comorbidities. US Food & Drug Administration. https://www.fda.gov/drugs/fda-approves-glasdegib-aml-adults-age-75-or-older-or-who-have-comorbidities. Updated December 14, 2018. Accessed December 2, 2020.
59. Sekeres MA, Schuster MW, Joris M, et al. A phase 1b study of glasdegib in combination with azacitidine in patients with untreated higher-risk myelodysplastic syndromes, acute myeloid leukemia, and chronic myelomonocytic leukemia [ASH abstract 177]. *Blood*. 2019;134(1)(suppl).
60. Shallis RM, Podoltsev NA, Prebet T, Zeidan AM. Trial in progress: Glad-AML - a randomized, phase 2 trial of glasdegib with two standard decitabine regimens for older patients with newly-diagnosed, poor-risk acute myeloid leukemia [ASH abstract 29]. *Blood*. 2020;136(1)(suppl).
61. Salamero O, Somervaille TC, Molero A, et al. Robust efficacy signals in elderly AML patients treated with iadademstat in combination with azacitidine (ALICE phase IIa trial) [ASH abstract 1916]. *Blood*. 2020;136(1)(suppl).
62. ClinicalTrials.gov. Evaluating the efficacy and safety of bemcentinib in patients with myelodysplastic syndromes. https://clinicaltrials.gov/ct2/show/NCT03824080. Updated January 8, 2021. Accessed June 23, 2021.
63. Benajiba L, Carraway HE, Hamad N, et al. Trials in progress: a phase I study to evaluate the safety and pharmacokinetic profiles of CB-5339 in participants with relapsed/refractory acute myeloid leukemia or relapsed/refractory intermediate or high-risk myelodysplastic syndrome [ASH abstract 2870]. *Blood*. 2020;136(1)(suppl).
64. Johas BA, Bixby DL, Brandwein JM, et al. A phase 2 open-label, multicenter, dose optimization clinical study of the safety, tolerability, and pharmacokinetic (PK) and pharmacodynamic (PD) profiles of CFI-400945 as a single agent or in combination with azacitidine or decitabine in patients with acute myeloid leukemia [ASH abstract 1974]. *Blood*. 2020;136(1)(suppl).

(Continues on page 510)

help ensure that the best new models and data computation algorithms become available in the coming years.

H&O What is next for these technologies?

AP Deployment of these technologies is starting. In the European Union, a machine learning–assisted digital pathology tool received the "CE" designation for breast cancer and prostate cancer, indicating that it met certain health, safety, and environmental protection requirements. (These tools are known as the Paige Prostate Clinical [CE-IVD] and Paige Breast Clinical [CE-IVD] devices). As models continue to improve, it may be possible to reliably extract "hidden" molecular information from samples in a rapid, efficient way. The goal is to decrease the time and cost that is required to obtain accurate, personalized information to guide the treatment of patients. Machine learning–based digital models have the potential to be transformative in the development of these new domains.

Disclosure

Dr Pearson is a member of the advisory board of Prelude Therapeutics.

Suggested Readings

Echle A, Grabsch HI, Quirke P, et al. Clinical-grade detection of microsatellite instability in colorectal tumors by deep learning. *Gastroenterology*. 2020;159(4):1406-1416.e11.

Echle A, Rindtorff NT, Brinker TJ, Luedde T, Pearson AT, Kather JN. Deep learning in cancer pathology: a new generation of clinical biomarkers. *Br J Cancer*. 2021;124(4):686-696.

Howard FM, Pearson AT. Prognosis and treatment of non-small cell lung cancer in the age of deep learning. *JAMA Netw Open*. 2020;3(6):e206368. doi:10.1001/jamanetworkopen.2020.6368.

Kather JN, Heij LR, Grabsch HI, et al. Pan-cancer image-based detection of clinically actionable genetic alterations. *Nat Can*. 2020;1(8):789-799.

Kather JN, Pearson AT, Halama N, et al. Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer. *Nat Med*. 2019;25(7):1054-1056.

Krause J, Grabsch HI, Kloor M, et al. Deep learning detects genetic alterations in cancer histology generated by adversarial networks. *J Pathol*. 2021;254(1):70-79.

(Continued from page 535)

65. Linenberger ML. CD33-directed therapy with gemtuzumab ozogamicin in acute myeloid leukemia: progress in understanding cytotoxicity and potential mechanisms of drug resistance. *Leukemia*. 2005;19(2):176-182.

66. FDA approves gemtuzumab ozogamicin for CD33-positive AML. US Food & Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-gemtuzumab-ozogamicin-cd33-positive-aml. Updated September 1, 2017. Accessed December 6, 2020.

67. Amadori S, Suciu S, Selleslag D, et al. Gemtuzumab ozogamicin versus best supportive care in older patients with newly diagnosed acute myeloid leukemia unsuitable for intensive chemotherapy: results of the randomized phase III EORTC-GIMEMA AML-19 trial. *J Clin Oncol*. 2016;34(9):972-979.

68. Giannopoulos K. Targeting immune signaling checkpoints in acute myeloid leukemia. *J Clin Med*. 2019;8(2):236.

69. Daver N, Garcia-Manero G, Basu S, et al. Efficacy, Safety, and biomarkers of response to azacitidine and nivolumab in relapsed/refractory acute myeloid leukemia: a nonrandomized, open-label, phase II study. *Cancer Discov*. 2019;9(3):370-383.

70. Zeidan AM, Boddu P, Wood BL, et al. Blast MRD AML-2: blockade of PD-1 added to standard therapy to target measurable residual disease (MDR) in acute myeloid leukemia (AML) 2- a randomized phase 2 study of the venetoclax, azacitidine, and pembrolizumab versus venetoclax and azacitidine as first line therapy in older patients with AML who are ineligible or who refuse intensive chemotherapy [ASH abstract 2809]. *Blood*. 2020;136(1)(suppl).

71. Zeidan AM, Cavenagh J, Voso MT, et al. Efficacy and safety of azacitidine (AZA) in combination with the anti-PD-l1 durvalumab (durva) for the front-line treatment of older patients (pts) with acute myeloid leukemia (AML) who are unfit for intensive chemotherapy (IC) and pts with higher-risk myelodysplastic syndromes (HR-MDS): results from a large, international, randomized phase 2 study [ASH abstract 829]. *Blood*. 2019;134(1)(suppl).

72. Gerds AT, Scott BL, Greenberg PL, et al. PD-L1 blockade with atezolizumab in higher-risk myelodysplastic syndrome: an initial safety and efficacy analysis [ASH abstract 466]. *Blood*. 2018;132(1)(suppl).

73. Kikushige Y, Miyamoto T. TIM-3 as a novel therapeutic target for eradicating acute myelogenous leukemia stem cells. *Int J Hematol*. 2013;98(6):627-633.

74. Brunner AM, Esteve J, Porkka K, et al. Efficacy and safety of sabatolimab (MBG453) in combination with hypomethylating agents (HMAs) in patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (HR-MDS): updated results from a phase 1b study. *Blood*. 2020;136(1)(suppl):1-2.

75. Zeidan AM, Esteve J, Giagounidis A, et al. The STIMULUS program: clinical trials evaluating sabatolimab (MBG453) combination therapy in patients (pts) with higher-risk myelodysplastic syndromes (HR-MDS) or acute myeloid leukemia (AML) [ASH abstract 1294]. *Blood*. 2020;136(1)(suppl).

76. Sallman DA, Asch AS, Kambhampati S, et al. The first-in-class anti-CD47 antibody magrolimab combined with azacitidine is well-tolerated and effective in AML patients: phase 1b results [ASH abstract 330]. *Blood*. 2020;136(1)(suppl).

77. ClinicalTrials.gov. An open-label phase Ib/II study of magrolimab in combination with azacitidine and venetoclax for the treatment of patients with acute myeloid leukemia (AML). https://clinicaltrials.gov/ct2/show/NCT04435691. Updated May 17, 2021. Accessed June 23, 2021.

78. Ravandi F. Complete responses in relapsed/refractory acute myeloid leukemia (aml) patients on a weekly dosing schedule of vibecotamab (XmAb14045), a CD123 x CD3 T cell-engaging bispecific antibody; initial results of a phase 1 study [ASH abstract 460]. *Blood*. 2020;136(1)(suppl).

79. Kuruvilla VM, McCarthy R, Zhang Q, et al. IMGN632, a CD123-alkylating ADC bearing a DNA-alkylating IGN payload, combines effectively with azacitidine and venetoclax in vivo, prolonging survival in preclinical models of human acute myeloid leukemia (AML) [ASH abstract 1375]. *Blood*. 2019;134(1)(suppl).

80. Daver NG, Montesinos P, DeAngelo DJ, et al. A phase I/II study of IMGN632, a novel CD123-targeting antibody-drug conjugate, in patients with relapsed/refractory acute myeloid leukemia, blastic plasmacytoid dendritic cell neoplasm, and other CD123-positive hematologic malignancies [ASCO abstract TPS7563]. *J Clin Oncol*. 2020;38(15)(suppl).

81. Uy GL, Aldoss I, Foster MC, et al. Flotetuzumab as salvage immunotherapy for refractory acute myeloid leukemia. *Blood*. 2021;137(6):751-762.

82. Ravandi F, Walter RB, Subklewe M, et al. Updated results from phase I dose-escalation study of AMG 330, a bispecific T-cell engager molecule, in patients with relapsed/refractory acute myeloid leukemia (R/R AML) [ASCO abstract 7508]. *J Clin Oncol*. 2020;38(15)(suppl).

83. Kennedy VE, Hui G, Gaut D, et al. Hypomethylating agents in combination with venetoclax as a bridge to allogeneic transplant in acute myeloid leukemia [ASH abstract 1526]. *Blood*. 2020;136(1)(suppl).

84. Paiva B, Martínez-Cuadron D, Bergua Burgues JMM, et al. Role of measurable residual disease (MRD) in redefining complete response (CR) in elderly patients with acute myeloid leukemia (AML): results from the PETHEMA-FLUGAZA phase III clinical trial [ASH abstract 433]. *Blood*. 2018;132(1)(suppl).