New Drug Approvals in Acute Myeloid Leukemia: An Unprecedented Paradigm Shift

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Abstract: We are witnessing an unprecedented paradigm shift in the treatment of acute myeloid leukemia (AML). For nearly 4 decades—since the introduction of cytarabine- and anthracycline-based induction chemotherapy in the 1970s—treatment options for patients with AML have remained limited, and outcomes remain poor for the majority of patients, particularly the elderly. Over the past 10 to 15 years, we have better elucidated the genetic and molecular basis of AML, which has led to our current understanding of disease heterogeneity. We now appreciate that numerous distinct disease subtypes exist, each with their own disease characteristics and risk profile. In keeping with this improved understanding, we have seen the introduction of numerous new agents that are mechanistically targeted against a specific mutation, a deranged cellular pathway, and/or a specific AML disease subset. Within the last 3 years alone, the US Food and Drug Administration has approved 8 new targeted agents for the treatment of AML. With their introduction comes a new sense of optimism, along with questions about how to best use these agents. In this article, we discuss the recently approved agents in AML, the rationale behind their development and the trials that served as the basis for their approval, and the implications of their introduction into the treatment armamentarium.

Introduction

Historically, the standard of care for patients with acute myeloid leukemia (AML) has been treatment with a combination of cytarabine (also known as cytosine arabinoside or ara-C) and an anthracycline (most frequently daunorubicin). This combination, commonly known as "7+3," dates back to the early 1970s, when its use in AML was first reported.[1] In the ensuing 4 decades, 7+3 has remained the backbone of treatment for all patients who can tolerate such intensive chemotherapy. Chemotherapy is followed by hematopoietic stem cell transplant (HSCT) in patients who have a greater than 30% to 40% risk of relapse, along with a relatively

low risk of post-HSCT nonrelapse mortality and a low risk of severe complications such as graft-versus-host disease. Those deemed unfit for intensive induction therapy owing to advanced age, particularly if accompanied by a poor Eastern Cooperative Oncology Group performance status or medical comorbidities, are often treated with a hypomethylating agent (HMA)—azacitidine or decitabine—in lieu of intensive chemotherapy.

More than 21,000 new cases of AML will be diagnosed in the United States in 2019, and survival remains poor for most patients.[2] Even in younger adults (<60 years), the 5-year overall survival (OS) rate is 35% to 40%. The median age at diagnosis is close to 70 years, however, and the 5-year median OS in patients older than 60 years is 5% to 15%. For elderly patients who do not receive chemotherapy, median survival is on the order of months.[3-5] However, over the past 10 to 15 years we have seen the identification of numerous AML-specific genetic mutations (eg, in *NPM1, FLT3, CEBPA, TP53, RUNX1, ASXL1, IDH1,* and *IDH2*) and/or rearrangements (eg, *PML-RARA*). Such identification has led to improved risk stratification. More importantly, various relatively nontoxic drugs have been developed to target some of these genetic aberrations, reducing their ability to promote the development of AML. The best example is acute promyelocytic leukemia. Acute promyelocytic leukemia is caused by the PML-RARA fusion protein, a result of chromosomal translocation t(15;17) that juxtaposes the *PML* and *RARA* genes. All-trans retinoic acid and arsenic trioxide degrade PML-RARA, and in combination routinely cure acute promyelocytic leukemia without the need for conventional chemotherapy.[6]

This review article focuses on drugs that are more recent, although much less successful to date. These include the fms-related tyrosine kinase 3 (FLT3) inhibitors midostaurin (Rydapt, Novartis) and gilteritinib (Xospata, Astellas), as well as the isocitrate dehydrogenase 1 (IDH1) inhibitor ivosidenib (Tibsovo, Agios) and the IDH2 inhibitor enasidenib (Idhifa, Celgene). In addition to mutations, dysregulated pathways such as those involving B-cell leukemia/lymphoma 2 (BCL2) and Hedgehog have been implicated in the development of AML, with these now targeted by venetoclax (Venclexta, AbbVie/Genentech) and glasdegib (Daurismo, Pfizer), respectively. Because the surface antigen CD33 is highly expressed on AML blasts but only moderately expressed on normal hematopoietic cells, with very little expression on nonhematopoietic cells, gemtuzumab ozogamicin, or GO (Mylotarg, Pfizer)—a combination of an anti-CD33 antibody and the calicheamicin toxin—has also been used to treat AML. Although not a targeted therapy per se, a liposomal formulation of cytarabine and daunorubicin known as CPX-351 (Vyxeos, Jazz) has also received atten-

tion. The US Food and Drug Administration (FDA) has approved each of these 8 drugs in the past 3 years. In this review, we discuss the data that prompted their approvals, their indications, and the important but perhaps underappreciated limitations that form a basis for future investigations.

Midostaurin and Gilteritinib

FLT3 is a tyrosine kinase found on hematopoietic cells that is involved in cell growth and proliferation. Approximately 25% to 30% of patients with AML have a FLT3 internal tandem duplication (*FLT3-ITD*) mutation, and approximately 5% to 10% have a FLT3 tyrosine kinase domain (*FLT3-TKD*) mutation.[7,8] Patients with *FLT3-ITD* mutations often present with a high white blood cell count. In contrast to the ratio of alleles with wild-type *FLT3* (the *FLT3* allelic ratio), the ratio with the *FLT3-ITD* mutation is prognostic, with an allelic ratio of greater than 0.5 considered by the European LeukemiaNet to be associated with a poorer prognosis largely owing to a higher relapse rate, even following HSCT. The prognostic implication of mutated *FLT3-TKD* remains unclear.[4,7,9] It cannot be overemphasized that the effect of a given genetic aberration, such as *FLT3-ITD*, is heavily influenced by the presence or absence of other mutations. For example, patients with a *FLT3-ITD* mutation and an *NPM1* mutation have a better prognosis than those without an *NPM1* mutation.[4,7] Even after considering the mutation status of *NPM1* and *FLT3*, other mutations—such as in *DNMT3A*—influence prognosis. Hence it is preferable to speak of a given mutation in the context of other mutations. Age also factors in, with reports that the "favorable" configuration of an *NPM1* mutation without a *FLT3-ITD* mutation is much less favorable in older patients. The effect of mutations also may depend on the therapy given. Although HSCT decreases relapse rates in fit patients with a *FLT3-ITD* mutation, the relatively unfavorable impact of a *FLT3-ITD* mutation is still observed post-HSCT, as is the case with adverse cytogenetics and the presence of measurable (or "minimal") residual disease.

In this context, use of the FLT3 inhibitors midostaurin and gilteritinib may lead to fewer relapses in patients with *FLT3-ITD* mutations. Midostaurin is a tyrosine kinase inhibitor that, in addition to being active against the FLT3 tyrosine kinase, is also active against numerous other protein kinases (eg, VEGF, PDGF, KIT). Midostaurin was approved by the FDA in 2017 in combination with standard 7+3 induction for the treatment of *FLT3*-mutated AML (*ITD* or *TKD*, as determined by an approved laboratory assay),[10] and is now considered along with postremission therapy, including HSCT, in eligible patients as the standard of care. The basis for the FDA

approval of midostaurin was the RATIFY trial (Randomized AML Trial in FLT3-Mutated Adults Younger Than 60 Years Old), which randomly assigned patients younger than 60 years with an *ITD* or *TKD* mutation to 7+3 plus midostaurin or placebo for induction and standard high-dose cytarabine plus midostaurin or placebo after remission followed by 1 year of maintenance treatment with midostaurin vs placebo.[11] Patients randomly assigned to midostaurin received it throughout, and likewise for those assigned to placebo. More than 700 patients were enrolled in this study (after investigators screened more than 3000 patients with AML for *FLT3* mutations), with the primary endpoint being OS. The results demonstrated a clear survival benefit in the midostaurin arm vs placebo, with a 23% reduction in the risk of death at 4 years. Improvements in event-free survival (EFS) and relapse-free survival paralleled those in OS.[11] Including patients with incomplete observations ("censored" patients) at the time of HSCT did not alter the results.[11] The utility of postremission maintenance with midostaurin has not been demonstrated, although given that the drug has limited toxicity, benefit/risk considerations support using it as maintenance, at least in people with high *FLT3* allelic ratios.

The FDA approved midostaurin for adults regardless of age, even though none of the patients in the RATIFY study were 60 years or older.[10,11] This may be particularly notable because German randomized studies have found that the EFS benefit of sorafenib (Nexavar, Bayer), which like midostaurin is an inhibitor of multiple tyrosine kinases including FLT3-ITD, was limited to patients younger than 60 years. The possible effect of selection bias in all studies should also be borne in mind. For example, 20% of the patients found to have a *FLT3-ITD* or *FLT-TKD* mutation were not randomized into RATIFY. The ability to generalize results to all patients younger than 60 years would be greater if information were available comparing outcomes in the 80% of patients who received 7+3 as part of RATIFY and the 20% of patients who may have received 7+3 outside the trial.

Although the addition of midostaurin to 7+3 almost certainly results in improved OS, EFS, and relapse-free survival in patients younger than 60 years with *FLT3* aberrations, the results are far from ideal. Because of this, other agents targeting *FLT3*-mutated AML are of interest, including gilteritinib, quizartinib, and crenolanib. Each of these is a more-specific inhibitor of FLT3-ITD and FLT3-TKD than midostaurin is.[12] Of course, it remains possible that some of the effectiveness of midostaurin reflects its ability to inhibit kinases other than FLT3, and so comparisons of these newer agents with midostaurin are important. Other than midostaurin, gilteritinib is the only agent approved for the treatment of *FLT3*-mutated

AML. Gilteritinib first attracted attention following a phase 1/2 dose-escalation/dose-expansion study in the treatment of *FLT3*-mutated relapsed or refractory (R/R) AML, in which it demonstrated potent FLT3 inhibition and a favorable safety profile.[13] Ultimately, the FDA approval for gilteritinib was based on results from the phase 3 ADMIRAL trial (A Trial of the FMS-Like Tyrosine Kinase 3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients With FLT3/Internal Tandem Duplication Acute Myeloid Leukemia), in which *FLT3*-mutated (either *ITD* or *TKD*) patients with R/R AML were randomly assigned in a 2:1 ratio to single-agent gilteritinib vs the investigator's choice of an HMA, low-dose cytarabine (LDAC), mitoxantrone/etoposide/cytarabine (MEC), or fludarabine/cytarabine/granulocyte colony–stimulating factor/idarubicin (FLAG-Ida). Median OS was 9.3 in the gilteritinib arm vs 5.6 months in the comparison arm; 1-year survival was 37.1% vs 16.7%, respectively, with a 36% reduction in the risk of death at 1 year. The rate of composite complete remission (cCR, a combination of CR and CR with incomplete hematologic recovery) was 34.0% vs 15.3%.[14] However, this trial raises several issues. First, the number of patients in each of the conventional therapy arms was probably insufficient to establish whether gilteritinib was superior to each of these arms. Second, midostaurin will likely become a standard addition for newly diagnosed patients with mutated *FLT3-ITD* or *FLT3-TKD*. It is unknown, however, whether response to gilteritinib will differ in patients who have not received midostaurin vs those who relapsed after treatment. Third, the effectiveness of midostaurin is greatly enhanced when combined with conventional chemotherapy, but it is unclear whether the same will be true for gilteritinib. Gilteritinib was approved by the FDA as a single agent in the treatment of *FLT3*-mutated R/R AML (*ITD* or *TKD*).[15] Recently the FDA decided not to approve quizartinib based on the results of a randomized trial similar to that undertaken with gilteritinib (although not including patients with mutated *FLT3-TKD*).[14,16] Ongoing trials are evaluating all 3 newer-generation agents: crenolanib (NCT02298166, NCT02400255), gilteritinib (NCT03836209, NCT02927262), and quizartinib (NCT02668653, NCT03735875). Of particular interest are trials combining these drugs with conventional chemotherapy in newly diagnosed patients.

Gemtuzumab Ozogamicin

GO is an antibody-drug conjugate that is directed against the protein CD33, which is expressed frequently on the cell surface of myeloid blasts in AML. This treatment provides an example of the potential benefit that follows

combination of "targeted" agents with chemotherapy. (Of course, in a strict sense, chemotherapy is itself targeted because remissions would not occur without a greater effect on leukemic blasts than normal blasts.) GO is a humanized anti-CD33 antibody conjugated to a derivative of the cytotoxic molecule calicheamicin: upon binding to CD33 on myeloid blasts, the antibody-drug conjugate is internalized, triggering release of the cytotoxic molecule and resulting in cell death.[5,17,18] GO is relatively old compared with many of the other agents discussed in this review; its development dates back to 1991. Based on data from 3 pooled single-arm trials, GO initially achieved accelerated approval in 2000 for the treatment of patients older than 60 years who were in their first relapse and deemed unfit for standard chemotherapy. The main toxicities were myelosuppression and hepatic sinusoidal obstruction syndrome (previously referred to as veno-occlusive disease), the latter earning a boxed warning shortly after GO's initial FDA approval. The accelerated approval was contingent upon larger controlled trials taking place. In 2004, investigators initiated the phase 3 randomized controlled SWOG S0106 trial (Cytarabine and Daunorubicin w/ or w/o Gemtuzumab Followed by HD Cytarabine and Either Gemtuzumab or Nothing in de Novo AML) examined standard intensive chemotherapy with or without GO. This larger trial not only failed to show a survival benefit in the GO arm, but also demonstrated higher induction mortality in GO (5%) compared with the control arm (1%),[19] leading to the premature closure of the study and the ultimate voluntary removal of GO from the market in June 2010.

Since the SWOG S0106 trial, several studies have been conducted that have favored the use of GO in AML. These culminated in a meta-analysis of 5 large randomized controlled trials (involving more than 3000 patients) that suggested that although GO added to chemotherapy failed to improve CR rates, it did lead to decreased relapse rates and improved overall survival (the benefit was limited to those with favorable and intermediate cytogenetic profiles, and the benefit among patients with core binding factor AML was notable).[20] The trial that formed the basis for the reapproval of GO was ALFA-0701 (A Randomized Study of Gemtuzumab Ozogamicin With Daunorubicine and Cytarabine in Untreated Acute Myeloid Leukemia), a phase 3 trial examining the addition of GO to standard induction chemotherapy in adults aged 50 to 70 years with newly diagnosed AML. The addition of GO resulted in a significant improvement in the primary endpoint of 2-year EFS compared with the control arm (40.8% vs 17.1%), but no significant difference in the secondary endpoint of OS.[21] Two other trials examined single-agent GO. First, a phase 3 study called AML-19 (Gemtuzumab Ozogamicin in Treating Older Patients With Previously Untreated Acute Myeloid Leukemia) investigating single-agent GO in the treatment of elderly, unfit patients with AML compared with best supportive care found that treatment with GO led to an OS of 4.9 months compared with 3.6 months in the best supportive care arm, and a 1-year OS of 24.3% in GO recipients vs 9.7% in those who received best supportive care only; cCR in GO recipients was 27%.[22] Second, a phase 2 open-label study called MyloFrance-1 (High Efficacy and Safety Profile of Fractionated Doses of Mylotarg as Induction Therapy in Patients With Relapsed Acute Myeloblastic Leukemia) treated patients with AML in their first relapse with single-agent GO, with 15 patients (26%) achieving CR and 4 patients (7%) achieving CR with incomplete hematologic recovery. Both sets of patients had a relapse-free survival of approximately 11 months.[23] Although GO was originally given and approved as 2 doses of 9 mg/m^2 each on days 1 and 8, subsequent studies have used lower doses. Today, a widely accepted dose is 3 mg/m^2 on days 1, 3, and 5.[19,21-24] This reduced, "fractionated" schedule appears to increase tolerance and decrease the incidence of sinusoidal obstruction syndrome, which is of particular importance in patients subsequently receiving HSCT. GO was approved in July 2017 by the FDA for the treatment of newly diagnosed CD33-positive patients with AML in combination with standard chemotherapy (cytarabine and daunorubicin) or as a single agent; it was also approved for the treatment of R/R CD33-positive AML.[24]

Venetoclax

BCL2 is an antiapoptotic protein that has been implicated as an important oncogene in numerous different lymphoid and myeloid malignancies, including AML.[25] Venetoclax is a potent and selective small-molecule inhibitor of BCL2.[26] Venetoclax was first studied in AML as a single agent, in a phase 2 study in which patients with high-risk R/R AML received 800 mg daily by mouth (PO). This study yielded modest results, with a cCR rate of 19% (CR, 6%) and a median progression-free survival of 2.5 months.[27] However, 2 recent trials served as the basis for the accelerated FDA approval of venetoclax in November 2018, in combination with either an HMA (azacitidine or decitabine) or LDAC in the treatment of elderly (>75 years) or "unfit" patients with AML. Venetoclax was combined with azacitidine or decitabine in a phase 1 dose-escalation study in elderly (>65 years), unfit patients with AML. Venetoclax was dosed at 400, 800, or 1200 mg PO daily. The results were promising, with a cCR of 67% irrespective of the venetoclax dose (with a cCR of 73% in the 400 mg PO group), a median OS of 17.5 months, and a response

duration of 11.3 months.[28] The other notable study was a phase 1/2 study investigating the combination of venetoclax (dosed at 600 mg PO daily) with LDAC in patients aged 75 years or older or those deemed unfit based on a performance status of 2 or other medical comorbidities. Perhaps because many of those enrolled had already received an HMA, the outcomes (cCR of 54%, median OS of 10.1 months, and median response duration of 8.1 months)[29] were inferior to those seen with venetoclax/HMA. Based on the results from these 2 trials, venetoclax is approved in combination with HMA at 400 mg PO daily, and in combination with LDAC at 600 mg PO daily, as frontline therapy in the treatment of elderly (>75 years) or unfit patients with AML. It should be noted that both of the combinations were well tolerated in these trials. The most frequent adverse events—nausea, vomiting, mucositis, and neutropenic fever—mirrored those commonly reported with other similar regimens.[28,29] Clinically significant tumor lysis syndrome—a well-known entity related to treatment with venetoclax—was not seen in either study.[28,29] A phase 3, randomized, double-blind, placebo-controlled trial comparing azacitidine/placebo vs azacitidine/venetoclax in newly diagnosed unfit patients with AML—with OS and cCR as the primary endpoints—is fully accrued, and we are awaiting results (NCT02993523).

These phase 1/2 trials have been criticized for several reasons. First, European LeukemiaNet guidelines from 2017 clearly note that an age of 75 years or older is not per se an indication for reduced-intensity therapy.[4] Second, 84% of 145 patients enrolled in the venetoclax/ HMA trial had a performance status of 0 to 1, raising doubts as to how unfit they were.[28] Third, comorbidities were not explicitly detailed in the relevant papers. In any event, it is intuitive and can be demonstrated statistically that prediction of treatment-related mortality is more accurate when covariates are examined simultaneously rather than 1 or 2 at a time. For example, it can be shown that a 70-year-old patient with a creatinine level of 1.7 mg/dL can have a probability of treatment-related mortality of only 7% after intense induction therapy, depending on covariates such as performance status, albumin, platelet count, and blood blast count.[30] This 7% would have to be weighed against the relative efficacies of venetoclax and more-intense therapies. Fourth, observational studies, such as all of those involving venetoclax to date, are much more likely to suggest survival benefits than subsequent randomized studies. Furthermore, later confirmatory studies typically are unable to show that most drugs that receive an accelerated approval from the FDA are associated with survival benefits. Although a randomized study might be ethically dubious if a single-arm trial demonstrated benefits similar to those seen with arsenic trioxide/all-trans retinoic acid in acute promyelocytic leukemia or with imatinib in CML, the benefits seen with the venetoclax combinations were not of this order of magnitude. Finally, given an enthusiastic marketing campaign, it is plausible that widespread use of venetoclax in community practice will reduce enrollment in clinical trials.

Ivosidenib and Enasidenib

IDH isoforms 1 and 2 (of 3 known human isoforms) are important enzymes in cellular metabolism, catalyzing the oxidative decarboxylation of isocitrate to alfa-ketoglutarate.[31] IDH has emerged in recent years as an important target in the pathogenesis of AML. *IDH1* mutations are found in 6% to 10% of patients with AML, and *IDH2* mutations are found in 9% to 13% of patients with AML.[32] In contrast to mutations in *FLT3-ITD*, mutations in *IDH* are thought to be prognostically neutral in AML, not affecting risk positively or adversely. Mechanistically, mutations in both isoforms behave in similar fashions: mutations in *IDH* lead to an accumulation of the metabolite 2-hydroxyglutarate, which in turn leads to epigenetic derangements and a block in cellular differentiation.[32] Both isoforms have small-molecule inhibitors that have recently been approved as single agents in the treatment of *IDH1*- or *IDH2*-mutated R/R AML, with ivosidenib targeting IDH1 and enasidenib targeting IDH2. The approval for ivosidenib is based on the recent, relatively large phase 1 dose-escalation/dose-expansion trial in which patients with *IDH1*-mutated R/R AML were treated with single-agent ivosidenib, resulting in an OS of 8.8 months, an objective response rate of 41.6%, and a cCR rate of 30.4%.[32] Ivosidenib was approved as a single agent for adults with *IDH1*-mutated R/R AML in July 2018. Likewise, enasidenib was approved by the FDA in August 2017 based on a phase 1/2 study, the results of which closely mirror the aforementioned response to ivosidenib: patients with *IDH2*-mutated R/R AML who were treated with single-agent enasidenib demonstrated an objective response rate of 40.3%, a CR rate of 19.3%, and median OS of 9.3 months (median OS was 19.7 months in those achieving CR).[33] Both of these single agents were well tolerated.[32,33] Experience with enasidenib, however, suggests that although the drug maintains suppression of 2-hydroxyglutarate, new genetic abnormalities arise that lead to relapse.[34]

CPX-351

Since the 1970s, the combination of cytarabine and daunorubicin (or another anthracycline) has remained the standard of care for most subsets of patients who can

tolerate intensive chemotherapy. CPX-351, a liposomal formulation of cytarabine and daunorubicin in a 5:1 molar ratio, demonstrated superior in vivo activity against AML in preclinical studies compared with nonliposomal cytarabine and daunorubicin delivered in the same 5:1 molar ratio. Furthermore, phase 2 data suggested a survival benefit for elderly patients and those with secondary AML.[35] The ultimate FDA approval of CPX-351 was based on the findings from a phase 3 study in which 300 patients aged 60 to 75 years with either therapy-related AML or AML with myelodysplasia-related changes were randomly assigned to receive CPX-351 or conventional cytarabine and daunorubicin (7+3) induction therapy. This study demonstrated a significant survival benefit for those treated with CPX-351, with a median OS of 9.56 vs 5.95 months and a cCR rate of 47.7% vs 33.3% in the CPX-351 arm vs the conventional chemotherapy arm. Toxicities were similar between the arms, with the safety profile of CPX-351 similar to that of conventional 7+3 therapy.[35] CPX-351 was approved in August 2017 for the treatment of newly diagnosed therapy-related AML and AML with myelodysplasia-related changes.[36] Of note, and by analogy to the RATIFY trial, the FDA approved CPX-351 for use in all adults regardless of age, although the trial leading to approval was conducted only in adults ages 60 to 75 years.[10,11,35,36]

Glasdegib

Hedgehog signaling pathway derangements promote oncogenesis in AML, and inhibition of this pathway is the mechanism of glasdegib, a small-molecule oral inhibitor of the protein smoothened (encoded by *SMO*), a component of the Hedgehog signaling pathway. This agent was approved in November 2018 in combination with LDAC for the treatment of elderly patients (>75 years) or those unfit for intensive chemotherapy.[37] The basis for the approval of glasdegib/LDAC came from a phase 2 trial in which 115 patients with newly diagnosed AML or myelodysplastic syndrome with excess blasts 2 (MDS-EB-2) who were older than 75 years, or older than 55 years with significant comorbidities, were treated with either glasdegib/LDAC or LDAC alone. The median OS was 8.3 months in the glasdegib/LDAC arm compared with 4.9 months in the LDAC arm, for a 49% reduction in the risk of death with the combination vs LDAC alone. The CR rate was 17.0% with glasdegib/LDAC vs 2.3% with LDAC alone.[38] Although this was a randomized trial, a potential shortcoming is the fact that the control arm, LDAC, was shown in a randomized trial to be associated with shorter survival than either azacitidine or decitabine. One of these latter drugs might have served as a better control arm than LDAC.

Discussion

A surge in interest has occurred in less-intense, "targeted" therapies for newly diagnosed AML, many of which we discussed above. The number of these therapies is likely to increase. Although they undoubtedly hold appeal, several points should be kept in mind. None that have been used as single agents have come close to approximating the success seen following use of all-trans retinoic acid or arsenic trioxide in acute promyelocytic leukemia, or of imatinib and congeners in CML.[6,39-41] In addition to the issue of selection bias common to all trials, the trials employing venetoclax and glasdegib are difficult to interpret because some of the patients enrolled may not have been truly unfit and/or may have been eligible for more-intense therapy. The need to develop objective, reproducible criteria, including geriatric assessment for "fitness," cannot be overstated.[41] Of course, intense therapy is not limited to 7+3 or FLAG-Ida and indeed may combine less- and more-intense agents, such as 7+3 plus venetoclax. Certainly, the results with venetoclax or glasdegib do not appear good enough to warrant the decreased accrual to clinical trials that might occur if physicians decide to administer these undoubtedly appealing, orally administered agents rather than referring patients to trials.

One direction that future trials could take would be to combine targeted agents with each other or with chemotherapy. The experience with enasidenib referred to above suggests that success with targeted agents used singly will be limited by the development of new mutations.[34] Furthermore, although midostaurin and GO produce responses when used alone, their single-agent activity pales compared to that seen when they are combined with chemotherapy. Hence, the distinction between less- and more-intense therapy may become outmoded as these agents are used together, bearing in mind that even in fit patients in their 70s, the main problem in AML remains ineffective treatment rather than treatment-related mortality.

Disclosures
Drs Kopmar and Estey have no conflicts to declare.

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