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REVIEW ARTICLE

New drugs creating new challenges in acute myeloid leukemia

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The therapeutic landscape is rapidly changing, with eight new drugs approved by the Food and Drug Administration within the last 2 years, including midostaurin and gilteritinib for *FLT3* mutant newly diagnosed and relapsed/refractory (R/R) acute myeloid leukemia (AML), respectively; CPX-351 (liposomal cytarabine and daunorubicin) for therapy-related AML and AML with myelodysplasia-related changes; gemtuzumab ozogamicin (anti-CD33 monoclonal antibody conjugated with calicheamicin) for newly diagnosed and R/R CD33-positive AML; enasidenib and ivosidenib for *IDH2* and *IDH1* mutant R/R AML, respectively. Novel therapies have also emerged for newly diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy. These include venetoclax (BCL-2 inhibitor) in combination with hypomethylating agents (azacitidine or decitabine) or low-dose cytarabine (LDAC), and glasdegib (sonic hedgehog pathway inhibitor) in combination with LDAC. This flurry of new drug approvals has markedly altered the treatment landscape in AML and provided new opportunities, as well as new challenges for treating clinicians. This review will focus on how these drugs might shape clinical practice and the hurdles likely to be faced by new therapies seeking entry into this dynamic and rapidly changing therapeutic landscape.

KEYWORDS

acute myeloid leukemia review, elderly AML, new challenges, recent drug approvals

1 | INTRODUCTION

After being in the therapeutic wilderness for several decades, acute myeloid leukemia (AML) has recently been thrust into the limelight with a series of drug approvals including midostaurin (RYDAPT; Novartis) and gilteritinib (XOSPATA; Astellas Pharma) for *FLT3* mutant (both internal tandem duplication [ITD] and tyrosine kinase domain [TKD] mutations) newly diagnosed and relapsed/refractory (R/R) AML, respectively; CPX-351 (VYXEOS; Jazz Pharmaceuticals) for secondary AML (including AML with myelodysplasia-related changes [AML-MRC] and therapy-related AML [t-AML]); gemtuzumab ozogamicin (MYLOTARG; Pfizer Inc.) for newly diagnosed and R/R CD33-positive AML; enasidenib (IDHIFA; Celgene Corp.) and ivosidenib (TIBSOVO; Agios Pharmaceuticals Inc.) for *IDH2* and *IDH1* mutant R/R AML, respectively; venetoclax (VENCLEXTA; AbbVie Inc.) in combination with hypomethylating agents (HMAs; azacitidine or decitabine) or low-dose cytarabine (LDAC), and glasdegib (DAURISMO; Pfizer Inc.) in combination with LDAC for newly diagnosed AML in adults age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy (Table 1). This review will focus on how these drugs might now shape clinical practice and the challenges for future drug developers seeking to bring new therapies into this dynamic and rapidly changing therapeutic landscape.

2 | NEW FRONTIERS IN FRONTLINE AML THERAPY IN PATIENTS FIT FOR INTENSIVE CHEMOTHERAPY

2.1 | The changing face of FLT3 mutant AML

Activating *FLT3*-ITD and TKD mutations were first reported in 1996[1] and 2001,[2] respectively. Recognition that *FLT3*-ITD was associated with inferior prognosis in cytogenetically normal AML, led to the common practice of allogeneic hematopoietic stem cell transplant (HSCT) for patients in first remission.[3] The failure to demonstrate a benefit for HSCT among patients with *FLT3*-ITD mutant: wild-type allelic ratios <0.5 (*FLT3*-ITD^{low}) led the European LeukemiaNet (ELN) Committee to designate patients with *NPM1*^{MUT} and *FLT3*-ITD^{low} as representing a more favorable risk subgroup.[4]

On April 28, 2017, the United States Food and Drug Administration (FDA) approved the use of the FLT3 inhibitor midostaurin in combination with intensive induction and consolidation therapy for patients with *FLT3*

TABLE 1 Overview of recent novel therapies in acute myeloid leukemia

Population	Current therapy	Mechanism of action	Regulatory status
Newly diagnosed AML			
Fit adults	("7 + 3" chemotherapy)	Cytarabine: pyrimidine analog (antimetabolite) Anthracycline: topoisomerase II inhibitor	Combination in use since 1973
- *FLT3* mutant	+ Midostaurin	Multitargeted kinase (including type 1 FLT3) inhibitor	FDA: April 28, 2017 EMA: September 20, 2017
- *FLT3* wild-type, (nonadverse CG)	+ Gemtuzumab ozogamicin	Anti-CD33 monoclonal antibody conjugated to calicheamicin	FDA: September 1, 2017 EMA: May 4, 2018
- t-AML or AML-MRC	CPX-351	Liposomal formulation of cytarabine and daunorubicin at fixed 5:1 M ratio	FDA: August 3, 2017
Unfit (elderly) adults			
	Venetoclax + HMA/LDAC	BCL-2 inhibitor, promoting apoptotic cell death	FDA: November 21, 2018
	Glasdegib + LDAC	Inhibitor of Sonic hedgehog pathway	FDA: November 21, 2018
Relapsed/refractory AML			
IDH1 mutant	Ivosidenib	IDH1 inhibitor	FDA: July 20, 2018
IDH2 mutant	Enasidenib	IDH2 inhibitor	FDA: August 1, 2017
FLT3 mutant	Gilteritinib Quizartinib	Type 1 FLT3 and AXL inhibitor Type 2 FLT3 inhibitor (inactive against TKD mutation mutations)	FDA: November 28, 2018 FDA priority review November 21, 2018
CD33 positive (regardless of *IDH1/2* and *FLT3* status)	Gemtuzumab ozogamicin	Anti-CD33 monoclonal antibody conjugated to calicheamicin	FDA: September 1, 2017 EMA: May 4, 2018

mutant AML. Midostaurin was initially characterized as a protein kinase C inhibitor and later as a VEGF/angiogenesis inhibitor (see review by Stone et al).[5] A drug screen identified midostaurin to have FLT3 inhibitory activity, which led to its redevelopment as a drug for *FLT3* mutant AML.[6] After a decade-long clinical development journey, midostaurin was evaluated in the pivotal "RATIFY" randomized trial, which combined midostaurin or placebo with standard induction and consolidation chemotherapy, followed by 12 months of midostaurin or placebo maintenance in patients with *FLT3*-ITD low (0.05-0.7) and high allelic ratio (>0.7), as well as in patients with *FLT3*-TKD. RATIFY was a mammoth effort involving 13 cooperative groups and 225 sites from 17 countries, and screened 3277 patients to randomize 717 patients between the ages of 18 and 59 with *FLT3*-ITD or *FLT3*-TKD AML.[7] The trial demonstrated an improved overall survival (OS) for patients randomized to midostaurin vs placebo (median OS increased from 26 to 75 months and 4-year OS increased from 44% to 51%).[7]

One of the most challenging questions now for clinical practice is deciding which patients with *FLT3*-ITD should undergo HSCT in the midostaurin era. Post hoc analyses have indicated that midostaurin was particularly beneficial in patients with *NPM1*^{MUT}*FLT3*-ITD^{low} with 5-year OS exceeding 70%.[8] Although *NPM1*^{MUT}*FLT3*-ITD^{low} is listed as a favorable entity in the ELN2017 classification,[4] this view has been challenged by some groups.[9–11] *NPM1*^{MUT} MRD monitoring in this subgroup of patients may have utility in identifying patients at higher risk of relapse.[12] Therefore, patients with *NPM1*^{MUT}*FLT3*-ITD^{low} receiving midostaurin and found to be low/negative for *NPM1*^{MUT} MRD after induction therapy may represent a very favorable risk that could be reasonably followed by MRD surveillance without proceeding to allogeneic HSCT in first remission.

Although the RATIFY trial did not include patients ≥60 years, the FDA did not impose an upper age limit to the use of midostaurin. The German AML Study Group has demonstrated the feasibility of combining midostaurin with intensive chemotherapy for patients up to 70 years in single-arm AMLSG 16-10 study. The complete remission (CR) rate including CR with incomplete hematologic recovery (CRi) was 78% in patients aged 61 to 70 years, with 2-year event-free survival (EFS) 35% and OS 46%.[13] However, caution should be exercised when adding midostaurin to standard induction chemotherapy, as the cardiac adverse events appeared higher in older patients.[13] In another randomized study by Study Alliance Leukemia, sorafenib was combined with standard chemotherapy in the older patients regardless of *FLT3* mutation status. This study also observed higher toxicity when sorafenib was combined with intensive chemotherapy in older AML populations.[14]

2.2 | Challenges for developing FLT3 inhibitors in the frontline AML space

The approval of midostaurin has transformed the treatment landscape for *FLT3* mutant AML and made the development of new drugs in this space potentially more difficult and complicated. In countries where midostaurin is now available, the comparator arm will now need to include midostaurin in the chemotherapy backbone, rather than chemotherapy alone. Therefore, any new FLT3 inhibitor must demonstrate superiority over and above midostaurin. Midostaurin improved OS with a HR of 0.78. Any new FLT3 inhibitor attempting to enter the market will need to show superiority over chemotherapy *in combination with* midostaurin, as it would now be difficult to conduct a study in patients with FLT3 mutation without a FLT3 inhibitor incorporated into the control arm.

2.3 | Newer FLT3 inhibitors

Several FLT3 inhibitors are in first-line registration trials aiming to emulate the success of the RATIFY trial (see several reviews).[9,15–17]

Sorafenib has been shown to improve EFS, but not OS in younger adults with AML.[18] The study was not limited to patients with *FLT3* mutant AML and there were only 46/267 (17%) patients with *FLT3*-ITD, which was, therefore, insufficient to enable definitive conclusions to be drawn. The Australasian Leukemia and Lymphoma Group has recently completed a randomized frontline trial in younger adults with *FLT3*-ITD AML up to the age of 65 combining sorafenib vs placebo with intensive induction and consolidation therapy, followed by 12 months of maintenance treatment (ALLG AMLM16; ACTRN12611001112954).

Quizartinib is a more selective type 2 FLT3 inhibitor being examined in younger adults with newly diagnosed *FLT3*-ITD mutated AML (NCT02668653). The study commenced prior to the approval of midostaurin, thus a placebo control arm was included. If this study is positive for survival, it will be interesting to speculate how clinicians will decide which FLT3 inhibitor option to use. Midostaurin will have the advantage of being useful for patients with *FLT3*-TKD, in contrast to quizartinib. Among patients with *FLT3*-ITD, comparative differences in efficacy between midostaurin and quizartinib will be hard to prove, as the agents were not randomized against each other. Differences in tolerability profile, health economic factors and perceived differences in the magnitude of clinical benefit may ultimately determine which FLT3 inhibitor becomes the standard of care therapy for this patient population.

Other FLT3 inhibitors undergoing frontline evaluation include crenolanib, a type 1 FLT3 inhibitor active against both *FLT3*-ITD and *FLT3*-TKD mutant AML[19] and gilteritinib, a type 1 FLT3/AXL inhibitor.[20] Phase 1b/2 studies have been conducted and show promising activity and tolerability for either crenolanib (NCT02283177) or gilteritinib (NCT02236013) in combination with chemotherapy in patients with *FLT3* mutant AML. Crenolanib in combination with chemotherapy resulted in CR/CRi rates of 24/25 (96%) among *FLT3* mutant subjects,[21] and were able to overcome poor prognostic impact of co-occurring driver mutations (eg, *FLT3*-ITD, *NPM1*, and *DNMT3A* mutations).[22] Gilteritinib at ≥80 mg/day gilteritinib (n = 27) also produced CR/CRi rates of 89%.[23] At first glance, these CR/CRi rates appeared significantly higher than that achieved using midostaurin, however, the RATIFY study reported only rates of CR (59%) and was not inclusive of CRi.

Registration opportunities remain for positioning FLT3 inhibitors in maintenance post-allogeneic HSCT. Although the RATIFY study incorporated maintenance midostaurin or placebo postchemotherapy, the value of maintenance midostaurin after HSCT remains uncertain.[24] Another FLT3 inhibitor, sorafenib, has been used as maintenance in *FLT3*-ITD mutated AML (nonrandomized study) after HSCT (n = 214) and shown to improve 2-year progression-free survival (82% in the maintenance arm and 45% in the control arm) and OS (100% vs 60%).[25] Another randomized study also showed that sorafenib post-HSCT significantly improved 2-year relapse-free survival from 53% to 85%.[26] Mechanistically, it has been shown that sorafenib facilitates the secretion of IL-15 from *FLT3*-ITD positive AML cells, which promotes an increase in alloreactive $CD8^+CD107a^+IFN\text{-}\gamma^+$ T cells and eradication of residual leukemia in the post-HSCT setting.[27] Various other FLT3 inhibitors are also being examined as maintenance in first remission (eg, gilteritinib [NCT02927262] and quizartinib [NCT02668653]) and in the post-HSCT setting (eg, midostaurin [NCT0188336], crenolanib [NCT02400255], and gilteritinib [NCT02997202]).

3 | CHALLENGING STANDARD INDUCTION CHEMOTHERAPY IN NON-*FLT3* MUTANT AML

Gemtuzumab ozogamicin (GO [MYLOTARG]; Pfizer Inc.) was reapproved by the FDA on September 1, 2017 after withdrawal from the market in 2010, based on new data showing improved tolerability and efficacy with a fractionated dosing schedule for treatment of newly diagnosed[28–31] and R/R CD33-positive AML.[32] The ALFA-0701 study, conducted in patients with *de novo* AML aged between 50 and 70 years, demonstrated that GO delivered as a fractionated dose of 3 mg/m^2 on D1,4,7 in combination with induction with daunorubicin 60 mg/m^2 D1-3 and cytarabine 200 mg/m^2 D1-7 improved median EFS from 12 to 20 months and OS from 19 to 34 months.[30] A recent correlative analysis showed that EFS was only improved among patients with high levels of AML blast CD33+ expression (>70%).[33] The major safety concern with GO is the risk of veno-occlusive disease, which occurred in 3/139 (2.2%) patients receiving GO, of which two were fatal.[30] Avoiding HSCT within 90 days of GO administration may reduce the risk of this serious complication. In practice, GO may find its most acceptable place in patients with core-binding factor AML, who are less likely to be subjected to HSCT in first remission. Indeed, a meta-analysis of five randomized studies, including 3325 patients with AML concluded that the benefit of GO was limited to patients with favorable and intermediate-risk karyotype.[34]

Another new drug recently approved by the FDA in the first-line AML setting is CPX-351 (VYXEOS; Jazz Pharmaceuticals), a liposomal formulation encapsulating cytarabine and daunorubicin at a fixed synergistic 5:1 M ratio. Approval was based on a pivotal phase 3 study in 309 patients aged 60 to 75 years with a history of prior cytotoxic treatment, antecedent myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML), or AML with WHO-defined MDS-related cytogenetic abnormalities. Prior exposure to HMAs for CMML or MDS was also allowed. This study demonstrated a higher CR rate (47.7% vs 33.3%, $P = 0.016$) and OS (median 9.56 vs 5.95 months, HR = 0.69, one-sided $P = 0.003$) for CPX-351 over 7 + 3 (60 mg/m^2 daunorubicin).[35] This led to FDA approval on August 3, 2017 for the treatment of adults with t-AML or AML-MRC. In subgroup analyses, CPX-351 was not shown to be superior to standard chemotherapy among patients with prior HMA agent exposure. CPX-351 has also not been shown to overcome the negative prognostic impact of *TP53* mutation.[36–38]

4 | CHALLENGES IN VALIDATING POSTREMISSION MAINTENANCE THERAPY IN AML

Despite achieving CR in ~70% of patients with AML, 30% to 80% relapse within the first 2 years depending on age and disease characteristics,[39] representing the commonest cause of mortality in AML. The use of maintenance therapy to eradicate residual leukemic and/or preleukemic clones is theoretically sensible, considering significant proportions of patients have persistently detectable leukemia-associated mutations after induction chemotherapy.[40–42] However, the role of maintenance therapy in AML remains controversial (see review by Rashidi et al.).[43] Clinical trials seeking to evaluate the

efficacy of maintenance therapy are hampered by the small fraction of patients typically enrolled onto maintenance studies (~25%).

Several trials have focused on evaluating maintenance therapy in older patients with AML. In a phase 3 study conducted by the GOELAMS AML cooperative group, patients with AML age ≥60 years were randomized to receive maintenance with norethandrolone (an androgen) or no maintenance for 2 years, after the completion of induction therapy and six courses of conventional chemotherapy alternating with methotrexate and mercaptopurine. Although disease-free survival (DFS) was improved with norethandrolone maintenance, separation of the Kaplan-Meier survival curve only occurred after 1 year. Interestingly, the OS curve for norethandrolone only crossed into superior territory after ~2.5 years.[44]

Azacitidine has been evaluated in several phase 3 studies in the elderly patients with AML as a postremission maintenance therapy. The HOVON group recruited 116 patients age ≥60 years with AML or MDS (refractory anemia with excess blasts) in CR/CRi after at least two cycles of intensive chemotherapy (HOVON-97 study), randomized to azacitidine (50 mg/m^2 days 1-5 every 4 weeks) or observation. The 12-month DFS was significantly improved with azacitidine (64% vs 42%) but this did not translate into a significant improvement in OS (84% vs 70%).[45] In another ongoing phase 3 trial of older patients (>60 years) with AML in first remission, 149 patients were randomized to azacitidine or observation after completing two courses of 7 + 3 induction and one cycle of consolidation with intermediate-dose cytarabine (800 mg/m^2 bid days 1-3). Interim analysis of 54 patients showed DFS and OS benefit in patients >73 years of age.[46]

4.1 | Clinical utility of MRD to guide postremission therapy

MRD has become increasingly important as a prognostic indicator in AML and as a monitoring tool for the early detection of preclinical relapse. The ELN MRD Working Party have recently published guidelines on the methodology, use and interpretation of multiparametric flow cytometry and molecular-based MRD testing.[47] With the emergence of novel and targeted therapies, the use of MRD as a clinical endpoint is likely to become more important in the future. This is already considered routine for patients with APL receiving ATRA and arsenic-based therapy. Future possibilities include enhanced MRD eradication of *IDH* mutant disease with IDH inhibitors,[48] *FLT3*-ITD/TKD with FLT3 inhibitors[49] and core-binding factor AML with GO,[50] as all these therapies have been reported to result in MRD negative responses in certain patients treated in prior clinical trials.

5 | CHALLENGING THE NOTION THAT TREATING OLDER PATIENTS WITH AML IS FUTILE

The management of AML in the older patients remains challenging, with medical comorbidities and adverse cytogenetic and molecular risk factors more common in older patients and associated with poorer outcomes after intensive chemotherapy.[51,52] The median age at the time of AML diagnosis is ~70 years.[53] With progressive age, response rates fall with intensive chemotherapy, whereas the risk of early death rises (Figure 1).[54] There is a prevailing view that outcomes in older patients are extremely poor, with only modest clinical responses achievable with current treatment options, including azacitidine (28%), decitabine (26%), or LDAC (11%-18%).[55–57] Consequently, approximately one-third of patients >75 years with AML appear to be palliated without active therapy.[58] Therefore, the need for more effective and less toxic treatment options is paramount.

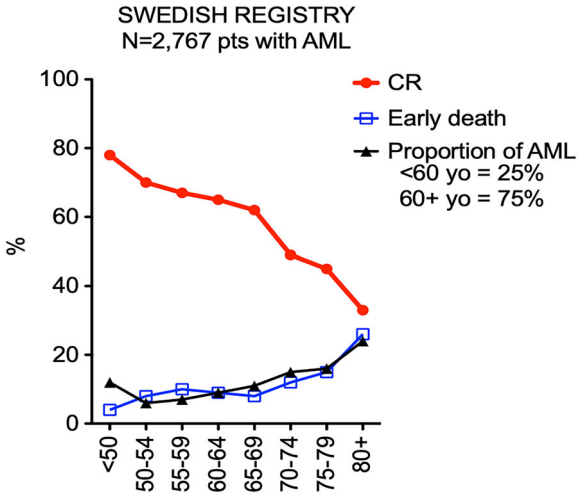

FIGURE 1 The outcomes (red line = complete remission [CR] rates; blue line = early death rates) of 2767 patients with acute myeloid leukemia (AML) diagnosed in 1997 to 2005 on Swedish Acute Leukemia Registry. Black line represents proportion of all AML cases according to different age groups. Figure produced based on publication by Juliusson et al.[54]

5.1 | The rise of the BH3-mimetics

Venetoclax is a selective BH3-mimetic that targets BCL-2, releasing pro-apoptotic BH3-only proteins, such as BIM and activating downstream BAX and BAK. Activated BAX/BAK facilitates release of mitochondrial intermembrane molecules, such as cytochrome c, resulting in activation of the caspase cascade and programmed cell death.[59] Increased expression of pro-survival BCL-2 relative to pro-apoptotic protein BAX is associated with inferior outcomes in patients receiving intensive chemotherapy for AML.[60] Targeting BCL-2 in AML represents an attractive approach, as preclinical studies have indicated the potential for venetoclax to synergistically enhance the activity of a broad range of anti-leukemic drugs such as HMA,[61,62] cytarabine, idarubicin,[63] and MDM2 antagonists.[64]

In clinical studies, although the selective BCL-2 inhibitor venetoclax has modest activity as monotherapy in R/R AML,[65] more impressive results have been observed in two phase 1b/2 studies using venetoclax in combination with either HMA or LDAC in older (≥65 years) patients with newly diagnosed AML unfit for intensive chemotherapy. In a study of 145 patients, venetoclax plus azacitidine or decitabine produced a CR/CRi in 67%, median OS lasting 17.5 months and 46% were alive at 2 years.[66] Similarly, in study of 82 patients (prior HMA exposure allowed), venetoclax plus LDAC (20 mg/m^2 subcutaneous daily d1-10) produced a CR/CRi in 54%, median OS lasting 10.1 months and 44%

were alive at 1 year.[67] Importantly, responses were achieved rapidly (median ~1 month), with virtually no clinical tumor lysis syndrome and low early (30-day) mortality (3%-6%). Based on these highly promising outcomes, venetoclax in combination with azacitidine, decitabine, or LDAC for previously untreated patients with AML older than 75 years or unfit for intensive chemotherapy was approved by the FDA on November 21, 2018. Phase 3 randomized placebo-controlled registration studies are currently underway to validate the benefit of venetoclax in combination with standard therapies in unfit elderly AML: venetoclax (400 mg/d) plus azacitidine vs azacitidine alone (NCT02993523) and venetoclax (600 mg/d) plus LDAC or LDAC alone (NCT03069352).

5.2 | The challenge of TP53 mutant AML

TP53 mutations are more common in the elderly AML patients (10%-18%) compared with younger patients (<5%).[51,68,69] Responses to cytotoxic therapy among patients with *TP53*-mutated AML are particularly poor. Even among patients who achieved CR following intensive chemotherapy, mutant clones frequently persist in remission samples (~70%).[40,41] Long-term outcomes among patients with *TP53* mutation treated with venetoclax in combination with either HMA or LDAC do not appear substantially improved, suggesting this subpopulation remains clinically challenging.[70] Extended 10-day regimens of decitabine have been proposed to be effective in *TP53*-mutant AML.[71] A randomized study examining 71 newly diagnosed patients age >60 years with AML showed no additional benefit of the 10 vs 5-day approach in terms of clinical response (CR/CRi 40% vs 43%) or OS (median 6 vs 5.5 months), including the subgroup with *TP53* mutations (CR/CRi 8/17 [47%] vs 2/7 [29%], $P = 0.40$).[72]

APR-246 is a PRIMA-1 (p53 re-activation and induction of massive apoptosis) analogue aimed at restoring a normal conformation of mutant p53. A phase 1b/2 study combining APR-246 with azacitidine in patients with *TP53*-mutant MDS and oligoblastic AML is ongoing (NCT03072043). So far, 12 patients have been enrolled (three AML and nine MDS), with CR achieved in 82% and morphologic leukemia-free state (MLFS) in 18%. With a median follow-up time of 7 months, median OS has not been reached.[73]

5.3 | Other low-intensity therapeutic approaches in late stage development for older patients with AML

Glasdegib (DAURISMO [PF-04449913]; Pfizer Inc.) is a potent oral selective inhibitor of the smoothened receptor, which is part of the Hedgehog signaling pathway. Hedgehog signaling has been implicated in mediating AML chemoresistance.[74–76] In a phase 2 study (BRIGHT AML1003, NCT01546038), 115 patients with newly diagnosed AML either ≥75 years or unfit for intensive chemotherapy were randomized to LDAC 20 mg subcutaneously twice daily on days 1 to 10 plus glasdegib 100 mg daily (n = 77) or LDAC alone (n = 38). Despite the modest CR rate (18.2% in patients receiving glasdegib compared to 2.3% for LDAC alone), median OS was significantly improved from 4.3 to 8.3 months (HR 0.46, 95% CI 0.30-0.71).[77–79] On November 21, 2018, the FDA approved glasdegib in combination with LDAC for newly diagnosed AML either age ≥75 years or with comorbidities precluding intensive induction chemotherapy. A phase 3 randomized study (BRIGHT AML1019) comparing glasdegib/placebo plus azacitidine in 320 patients with AML not suitable for intensive chemotherapy is also underway (NCT03416179).

Inhibition of both DNA hypermethylation and histone deacetylation is proposed to synergistically induce reexpression of silenced genes in cell lines and in MDS/AML primary patient cells.[80,81] The histone deacetylase inhibitor pracinostat has been combined with azacitidine in patients ≥65 years with previously untreated AML. CR/CRi was observed in 23/50 (46%) patients, 60-day mortality 10%, median OS 19.1 months, and 1 and 2-year OS of 62% and 45%, respectively.[82] This is a promising preliminary efficacy in elderly AML despite the lack of superiority of combination therapy over azacitidine alone in higher-risk MDS.[83] A phase 3 randomized study of pracinostat (or placebo) in combination with azacitidine is currently underway in patients unfit for standard induction chemotherapy (NCT03151408).

Guadecitabine (SGI-110) was designed as a next-generation DNA methyltransferase inhibitor resistant to degradation by cytidine deaminase. As a dinucleotide of decitabine and deoxyguanosine, pharmacokinetic studies showed the half-life was improved 4-fold to 12 hours, permitting prolonged exposure of tumor cells to the active metabolite, decitabine.[84] A phase 1/2 study in treatment-naïve AML patients age ≥65 years unfit for chemotherapy determined the 5-day (60 mg/m^2/d) guadecitabine schedule to be optimal, producing a CR/CRi rate of 54% and median OS 10.5 months.[85] A multinational randomized phase 3 study was performed in 815 patients with treatment naïve AML unfit to receive intensive chemotherapy (ASTRAL-1).[86] The study, however, did not meet its co-primary endpoints of CR ($P > 0.04$) and OS ($P > 0.01$), compared with the control arm of physician's choice of azacitidine, decitabine, or LDAC.

5.4 | Will lower intensity therapies challenge intensive chemotherapy in older patients with AML?

The recent approval of venetoclax in combination with lower-intensity regimens will likely create interest in whether a lower intensity regimen can be used in place of standard intensive chemotherapy in older patients with AML, as several nonrandomized studies have suggested that outcomes with HMA are comparable to intensive chemotherapy.[87–89] The phase 3 AZA-001 trial had only 16 patients with low blast count (20%-30%) AML preselected for intensive chemotherapy, precluding any meaningful conclusion.[90,91] Another phase 3 study (AZA-AML-001 trial) compared azacitidine against conventional care regimen among elderly (age ≥65 years) patients with AML >30% blasts. Subgroup analysis demonstrated similar 1-year OS between patients receiving azacitidine (n = 43) and intensive chemotherapy (n = 44).[56] An EORTC Intergroup study (AML 21) is currently randomizing 600 patients with AML fit for intensive chemotherapy ≥60 years to either 10-day course of decitabine (Dacogen; inDACtion) vs conventional "3 + 7" induction chemotherapy [NCT02172872]. If this study is positive, it may encourage future randomized studies examining the role of venetoclax plus low-dose chemotherapy in place of intensive chemotherapy in fit older patients with AML. The response rates and OS of venetoclax in combination with low-intensity therapies in elderly AML appear promising relative to outcomes reported with intensive chemotherapy (Table 2).[35,92] Lower-intensity approaches may be associated with reduced early mortality, less severe

toxic complications, and reduced time in hospital. These potential advantages, however, require randomized validation. Molecular correlative studies have attempted to identify subgroups of patients with particularly favorable outcome. Although patients with *NPM1* and *TP53* mutation/aneuploidy appear to have the best and worst survival outcomes, respectively, these observations remain preliminary.[70]

6 | THE CHALLENGE OF RELAPSED AND REFRACTORY (R/R) AML

R/R AML represents a formidable challenge for treating clinicians. Primary resistance to intensive chemotherapy occurs in 7%-12% of younger adults[93,94] and 14%-34% of older adults.[92,95] The risk of AML relapse occurs in 30%-80%, with higher risk associated with adverse cytogenetic and molecular risk factors, secondary and t-AML.[4,39] Cytotoxic therapies for R/R AML are generally ineffective and the benefits short-lived, particularly for relapses occurring within several months of achieving remission. More recently, however, novel noncytotoxic approaches have started to re-shape the therapeutic landscape of chemoresistant AML.

6.1 | IDH1/2 inhibitors

First identified by whole genome sequencing of an index patient with AML in 2009,[96] recurrent hotspot mutations affecting the catalytic domains of *IDH1* (Arg132) and *IDH2* (Arg140 and Arg172) have been found in ~8% and ~12% of AML cases, respectively,[69,97–99] and are more common in the elderly (25%-28%).[68,97,99] Mutations in *IDH1* or *IDH2* lead to the production of the oncometabolite 2-hydroxyglutarate (2-HG), which results in epigenetic perturbation and arrested myeloid differentiation.[100–104] Enasidenib (IDHIFA [AG-221]; Celgene) and ivosidenib (TIBSOVO [AG-120]; Agios) are small-molecule inhibitors of IDH2 and IDH1, respectively, and have been shown to block 2-HG production and induce myeloblast differentiation.[105,106] Other IDH inhibitors are also in clinical development, such as FT-2102 (Forma Therapeutics), which targets IDH1 (NCT02719574);[107] and AG-881 (Agios), which is a brain-penetrant combined IDH1/2 inhibitor (NCT02492737).

Both enasidenib (approved August 1, 2017)[108] and ivosidenib (approved July 20, 2018)[109] were approved on the basis of nonrandomized studies showing promising response rates (enasidenib CR/CRi 26.6% and ivosidenib 30.4%) in patients with R/R AML. Approximately, 35%-43% of patients have also demonstrated transfusion independence, including those with non-CR/CRi responses.[48,109] For responding patients, molecular MRD eradication rates of 35% and 23% for enasidenib (12/35 CR) and ivosidenib (7/31 CR or CR with partial hematologic recovery [CRh]), respectively, have been reported, suggesting the potential for marked suppression of *IDH* mutant clones in some patients.[48,109] Response to IDH inhibitors appears greater among patients with fewer concomitant mutations, which may explain the trend for higher response rates when patients are treated at earlier stages of disease. Interestingly, late relapses have been reported in association with rising 2-HG and noncatalytic second site mutations located at the homodimer interface.[110]

In the frontline AML setting, enasidenib produces CR/CRi of 21%-43%[111,112] and ivosidenib produces CR/CRh of 41%.[113] The median time to first response and CR to IDH inhibitors are approximately 1.9 months and 2.8 to 3.7 months, respectively, which can be challenging for patients with active disease needing to sustain therapy for several months without certainty of an eventual response. Combining IDH inhibitors with HMAs has been explored in newly diagnosed patients ineligible for intensive treatment. Preliminary results indicate high-response rates are possible for enasidenib (8/11; including 4 CR and 1 CRi, 1 partial remission [PR], and 2 MLFS) or ivosidenib (4/6; 2 CR, 1 PR, and 1 MLFS) in combination with azacitidine.[114] It remains to be determined whether combination therapy will lead to shorter time to response and higher overall response rate, compared with monotherapy. Translation of IDH inhibitors into the frontline setting in combination with intensive chemotherapy has also been shown to be feasible,[115] leading to development of randomized registration studies seeking to incorporate IDH inhibitors into the continuum of induction, consolidation, maintenance, and post-HSCT maintenance for patients with AML (HOVON 150 AML, NCT03515512, and NCT03728335).

6.2 | FLT3 inhibitors

The landscape of R/R AML is also set for change with the recent approval of the FLT3 inhibitor gilteritinib (XOSPATA; Astellas Pharma US Inc.) on November 28, 2018, for the treatment of adult patients who have R/R AML with a *FLT3* mutation as detected by an FDA-approved test. Approval of gilteritinib was based on the interim analysis of phase 3 ADMIRAL trial (NCT02421939), which included 138 adults with R/R AML with *FLT3* ITD, D835, or I836 mutation detected by the LeukoStrat companion diagnostic assay (Invivoscribe Technologies, Inc.), randomized to either oral gilteritinib 120 mg daily vs investigators' choice of LDAC, azacitidine, or salvage chemotherapy (mitoxantrone, etoposide, and cytarabine [MEC], or fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin [FLAG-IDA]). After a median follow-up time of 4.6 months (range: 2.8-15.8), composite CR was 21% (CR 11.6% and CRh 9.4%), median duration of remission 4.6 months, and transfusion independence 31%.[116] Full data presentation is eagerly anticipated.

Positive phase 3 (QuANTUM-R trial, NCT02039726) results have also been reported for the FLT3 inhibitor quizartinib (AC220, Daiichi-Sankyo), which randomized (2:1) 367 patients with an *FLT3*-ITD allelic burden of ≥3% to either single-agent quizartinib (n = 245; 60 mg, with a 30-mg lead-in of 15 days) or standard salvage chemotherapy (n = 122; investigators' choice of LDAC [n = 29], MEC [n = 40], or FLAG-IDA [n = 53]). Median OS was improved by 1.5 months (from 4.7 to 6.2 months), with higher responses (composite CR 48% vs 27%) achieved in the quizartinib arm, lasting a median of 12.1 months. The subsequent SCT rate was also higher for patients receiving quizartinib (32% vs 12%).[117] Unlike gilteritinib, quizartinib is a type 2 inhibitor and is ineffective against *FLT3*-TKD mutant AML. In relapsing cases, drug resistant *FLT3*-TKD and gatekeeper *FLT3* mutations have been observed.[118] Both quizartinib and gilteritinib are being explored for clinical utility in diverse AML settings, including frontline combination with intensive and nonintensive chemotherapy, maintenance therapy,

TABLE 2 Comparison of approved low-intensity regimens and intensive chemotherapy in elderly patients with acute myeloid leukemia

	Venetoclax + HMA[a]	Venetoclax + LDAC[b]	Glasdegib + LDAC[c]	CPX-351[d]	7 + 3[e]
No. of patients	145	82	77	153	813
Median age (range)	74 (65-86)	74 (63-90)	77 (64-92)	Mean 68 (60-75)	67 (60-83)
Secondary AML (%)	25	49	51	73	21
Prior HMA (%)	Excluded	29	14	41	Not reported
CR/CRi (%)	67	54	24	48	59
De novo	67	71	-	-	62
Secondary	67	35	-	48	47
Median OS (months)	17.5	10.1	8.3	9.6	~12.0
De novo	12.5	16.9	-	-	-
Secondary	Not reached	4.0	-	9.6	-
30-day mortality (%)	3	6	-	6	11

[a]Venetoclax + HMA: median follow up 15.1 months.[66]
[b]Venetoclax + LDAC: Among patients without prior HMA exposure, CR/CRi was 62%, median duration of remission 14.8 months, and median OS 13.5 months.[67]
[c]Glasdegib + LDAC: full publication not available; results based on the submitted data within prescribing information.[79]
[d]CPX-351: median age not reported; 41 (27%) patients have de novo AML with MDS karyotype.[35]
[e]7 + 3: subjects were randomized to either 45 or 90 mg/m^2 of daunorubicin; hematological recovery was not required for protocol-defined CR; 64% patients receiving 90 mg/m^2 achieved CR; median OS was estimated from the published figure.[92]

post-transplant maintenance, and in novel combination with non-cytotoxic drugs in R/R AML.

6.3 | Microenvironment for example, E-selectin

The bone marrow microenvironment ("niche") is increasingly recognized to play an important role in AML. E-selectin, an adhesion molecule expressed constitutively in bone marrow endothelium, interacts with leukemic blasts, supporting leukemic cell dormancy and activating cell survival pathway, contributing to chemoresistance.[119–121] Leukemic cells in patients with relapsed AML have higher expression of the E-selectin ligand than those with newly diagnosed AML, suggesting that these cells may contribute to the likelihood of relapse.[120] E-selectin also plays a major role in chemotherapy-induced mucositis, which could be therapeutically inhibited.[122] Uproleselan (GMI-1271), a selective E-selectin antagonist disrupting the leukemia-stroma interaction, has been combined with salvage mitoxantrone, etoposide, cytarabine [MEC] chemotherapy (n = 19 and 47 in phase 1 and 2, respectively) in R/R AML and in combination with 7 + 3 induction (n = 25) for newly diagnosed older (≥60 years) patients (NCT02306291).[123] In R/R AML, responses (CR/CRi) have been reported in 41%, remission duration 9.1 months, and median OS 8.8 months. Grade 3/4 mucositis was observed in only 2%. Responders have higher E-selectin ligand expression on leukemic stem cells.[124] Phase 3 trials are underway (NCT03616470 and NCT03701308).

6.4 | Immunologic approaches

The three immune-based approaches showing most potential in AML currently are T cell-recruiting antibody constructs (eg, bispecific T-cell engager [BiTE] and dual-affinity retargeting [DART]), chimeric-antigen-receptor (CAR) T cells and checkpoint inhibitors in combination with HMAs. T cell-recruiting antibody constructs and CAR-T cell approaches are being developed to target a growing spectrum of surface expressed leukemic antigens, including CD33, CD123, CLL-1, and FLT3. Preliminary results show these approaches to have positive anti-leukemic activity in heavily treated patients, with cytokine release syndrome (CRS) a frequent and challenging issue, impeding more rapid clinical development.

Flotetuzumab, a CD123 x CD3 bispecific DART molecule, produced CR/CRi in 5 (19%) of 27 patients with R/R AML in phase 1 study at cohort expansion.[125] AMG 330, a CD33 x CD3 BiTE antibody construct, is being tested in an ongoing phase 1 first-in-human dose escalation study (range 0.5-480 μg/d). To date, 4 CR/CRi have been observed at target doses of 120 and 240 μg/d.[126] Case reports of CAR-T therapies producing robust responses in patients with chemorefractory AML and acting as a bridge to HSCT have been reported.[127,128] The main challenges for CAR-T cell approaches in AML, however, center around target specificity, toxicities related to CRS and central nervous system complications, durability of CAR-T cells in vivo, and the formidable logistical and economic challenges in making such complex technologies widely available.

Checkpoint inhibitors have been most actively explored in combination with HMAs, with the goal of leveraging the potentially beneficial effect of epigenetic therapy on immune effector function. Azacitidine combined with nivolumab (to target PD-1) in 70 patients with R/R AML, produced a CR/CRi rate of 22%. The median OS among patients achieving response (including stable disease) was 16.1 months. Grade 3/4 immune-related adverse events (irAEs) were observed in 11% patients.[129] In another cohort of 14 patients with R/R AML receiving triple combination azacitidine, nivolumab, and ipilimumab (to target CTLA-4), CR/CRi rates were 43% and projected 1-year OS 58%. However, grade 3/4 irAEs were noted in 26% of patients.[130] Promising CR/CRi rates of 5/9 (56%) have been observed in a cohort of elderly unfit AML receiving frontline azacitidine and nivolumab.[131] Nivolumab has also been combined with intensive chemotherapy in younger patients with newly diagnosed AML: CR/CRi 77%, median OS 18.5 months, grade 3/4 irAEs 14%. Post-transplant severe graft-vs-host disease was not significantly increased and was manageable.[132] Other checkpoint targets being explored in combination with HMA include PD-L1, TIM3, and KIR (see review by Daver et al.).[133]

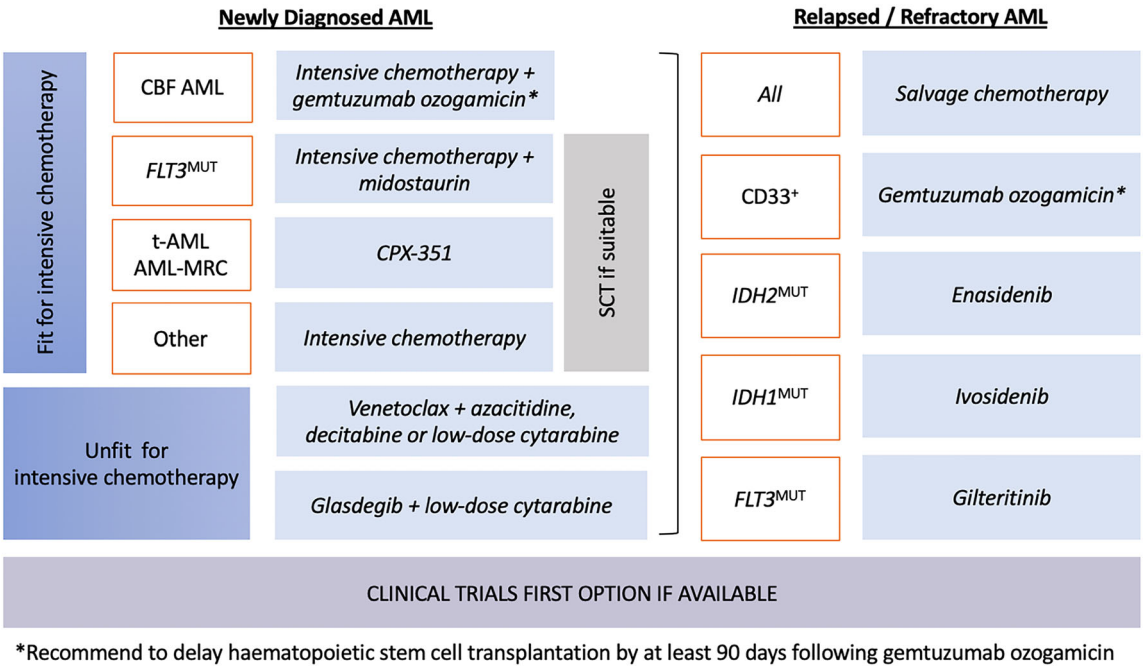

FIGURE 2 Current approach and standard therapies in newly diagnosed and relapsed/refractory acute myeloid leukemia

7 | CHALLENGES IN CLINICAL TRIAL DEVELOPMENT IN THE CURRENT CLINICAL LANDSCAPE

With eight new drug approvals in the past 2 years offering treating physicians unprecedented therapeutic options in AML, future drug developments have also become more complex than ever before. In the frontline AML setting, new drugs must consider how they might exceed drugs with established efficacy, such as GO in core-binding-factor AML, midostaurin in *FLT3* mutant AML, CPX-351 in t-AML and AML-MRC, and venetoclax and glasdegib in elderly unfit AML. In the R/R AML setting, drugs must now show superiority to enasidenib, ivosidenib, gilteritinib, and quizartinib within small molecularly defined AML subgroups (Figure 2). The rapidly evolving landscape will likely require greater cooperation between pharma and academic groups to better coordinate the effectiveness and efficiency of their clinical development strategies in light of the restricted pool of clinical patients. The FDA appears to have taken a far more aggressive and pro-active stance on drug approvals than in the past, accepting promising single arm data (eg, enasidenib, ivosidenib, and venetoclax) prior to completion of pivotal phase 3 studies. There is a strong need for platform studies with greater flexibility to rotate new drugs in and out of clinical development within molecularly defined disease strata. Greater international cooperation is also required to enable sufficiently large cohorts of patients to be screened to achieve meaningful patient numbers within increasingly narrow disease subgroups. Despite AML being in the therapeutic wilderness for so many decades and lagging behind the rapid progress seen in genetic characterization, the field of AML is now entering a golden phase in clinical development that will radically reshape the standard of care paradigm over the coming years.

CONFLICT OF INTEREST

I. S. Tiong: None; A. H. Wei: Consultancy: AbbVie, Celgene, Roche, Janssen, Astellas, Novartis, Amgen, MacroGenics, and Servier.

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