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Combination therapy with novel agents for acute myeloid leukaemia: Insights into treatment of a heterogenous disease

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Summary

The treatment landscape of acute myeloid leukaemia (AML) is evolving rapidly. Venetoclax in combination with intensive chemotherapy or doublets or triplets with targeted or immune therapies is the focus of numerous ongoing trials. The development of mutation-targeted therapies has greatly enhanced the treatment armamentarium, with FLT3 inhibitors and isocitrate dehydrogenase inhibitors improving outcomes in frontline and relapsed/refractory (RR) AML, and menin inhibitors showing efficacy in RR *NPM1*^{mut} and *KMT2A*-rearranged AML. With so many new drugs approved, the number of potential combinatorial approaches to leverage the maximal benefit of these agents has increased dramatically, while at the same time introducing clinical challenges, such as key preclinical and clinical data supporting the development of combinatorial therapy, how to optimally combine or sequence these novel agents, how to optimise dose and duration to maintain safety while enhancing efficacy, the optimal duration of therapy and the role of measurable residual disease in decision-making in both intensive and low-intensity therapy settings. In this review, we will outline the evidence leading to the approval of key agents in AML, their on-label current approvals and how they may be optimally combined in a safe and deliverable fashion to further improve outcomes in AML.

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AUTHOR CONTRIBUTIONS

W-YJ wrote the manuscript. NGD conceptualised the review and revised the manuscript. All authors revised and approved the manuscript.

CONFLICT OF INTEREST STATEMENT

W-YJ, MY and GB declare no relevant conflicts of interest.

Keywords

acute myeloid leukaemia; novel agents; novel combinations; targeted treatment

INTRODUCTION

For decades, combination chemotherapy with an anthracycline and cytarabine has formed the backbone of therapy for acute myeloid leukaemia (AML), for example, the 3 + 7,[1,2] fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin (FLAG-Ida)[3] or daunorubicin, cytarabine and cladribine (DAC)[4] regimens. In patients under 60 years of age, intensive chemotherapy (IC) offers complete remission (CR) or complete remission with incomplete count recovery (CRi) rates of 70%–80% and cure rates of 35%–55%.[5,6] In older patients (>65 years of age), the prognosis remains dismal due to an inability to tolerate IC,[7,8] ineligibility for allogeneic stem cell transplantation (SCT)[9] and inherently adverse disease biology, leading to cure rates of 10%–15%.[10]

The year 2017 marked a therapeutic turning point in AML therapy. In the last 6 years, 13 drugs have been approved by the United States Food and Drug Administration (FDA) for the treatment of AML. A number of these have since been approved by the European Medical Agencies (EMA) and other national regulatory agencies, thereby becoming accessible in many regions of the world. Key novel agents and their recommended dose schedules are presented in Table 1. In particular, the incorporation of venetoclax into frontline doublets with azacitidine (HMA-VEN)[13] or low-dose cytarabine (LDAC)[14] has improved the treatment of older adults with AML, with composite complete remission (CRc, CR + CRi) rates increased from 28% to 66% and 13% to 48% and overall survival (OS) from 9.6 to 14.7 months (hazard ratio [HR] for death, 0.66; 95% confidence interval [CI] 0.52–0.85; $p < 0.001$) and 4.1 to 8.4 months (HR 0.70; 95% CI, 0.50–0.99; $p = 0.04$), for HMA-VEN and LDAC-VEN, respectively. However, long-term follow-up has confirmed that these responses are not as durable as initially hoped, with continuous drop-offs in survival curves and 3-year OS of 23% with the HMA-VEN combination.[15,16] Mechanisms of relapse in patients treated with venetoclax doublets include upregulation or mutations in other B-cell lymphoma 2 (BCL2) family proteins, mutations in activating kinases such as FMS-like tyrosine kinase 3 (FLT3), RAS and mitogen-activated protein kinases (MAPK), emergent *TP53* mutations (*TP53*^{mut}) and monocytic clone expansion, among others.[17]

Acute myeloid leukaemia is a heterogenous disease, with clonal heterogeneity that evolves dynamically and differentially in response to the specific therapy implemented.[18–20] Advances in molecular diagnostic techniques have enabled the identification and characterisation of diverse genomic alterations and chromosomal aberrations driving leukaemogenesis.[21–23] Consequently, several novel agents have been approved or are in development to target these aberrations. Personalised, patient-specific combinations targeting specific aberrations are likely to be required for attainment of deeper and more durable remissions, and to mitigate primary and secondary resistance to venetoclax-based therapies (Figure 1). Understanding the unique molecular and cytogenetic architecture, including potentially relevant fusions, distinguishing driver mutations from clonal

haematopoiesis and anticipating patterns of relapse are essential for up-front selection of combinations versus sequencing therapies to optimise outcomes (Figure 2). In this review, we will discuss the data leading to the approval of novel agents in AML, how they might be combined with current established therapies or with each other to eventually improve cure rates while maintaining safety, and practical prescribing and monitoring considerations when designing and delivering such combinations. As most novel agents are targeted agents, we will first address actionable targets, then mutation agnostic combinations.

FLT3 MUTATIONS

FLT3 is a transmembrane tyrosine kinase receptor which plays a role in downstream cell survival and signalling pathways when activated by an extracellular ligand (FLT3 ligand). Mutations in the *FLT3* (*FLT3*^{mut}) gene are unstable and present in approximately 30% of newly diagnosed AML (ND AML)[24] and up to 20% of patients at relapse (RR AML).[25,26] Approximately 80% of *FLT3*^{mut} are internal tandem duplications (ITD), which are associated with high relapse rates,[27] with mutations in the tyrosine kinase domain (TKD) being the next most common. Patients with *FLT3*^{mut} tend to be very proliferative at presentation and, although they respond to initial therapy, are frequently associated with a shorter duration of remission and early relapse. The dynamic kinetics of *FLT3*^{mut} highlights the importance of screening for *FLT3*^{mut} not just at initial diagnosis but throughout the disease continuum. Major studies of FLT3 inhibitors in AML are outlined in Table 2.

Current options: Frontline

The incorporation of FLT3 inhibitors (FLT3i) to frontline therapy was evaluated in the pivotal RATIFY trial, which randomised 717 ND AML patients aged <60 with *FLT3*-ITD and TKD mutations to 3 + 7 backbone combined with midostaurin or placebo.[28] Midostaurin is a multikinase type 1 inhibitor with activity against *FLT3* TKD and ITD.[40] The addition of midostaurin significantly improved OS from a median of 25.6 months (95% CI, 18.6–42.9) to 74.7 months (95% CI, 31.5–not estimable [NE]), with 4-year OS of 44.3% versus 51.4% (HR for death, 0.78, 95% CI, 0.63–0.96, $p = 0.009$).

The efficacy of incorporating FLT3i in the frontline setting was confirmed in the QuANTUM-First trial, which randomised 539 patients with *FLT3*-ITD mutations aged 18–75 to 3 + 7 backbone combined with quizartinib, a highly potent, selective, second-generation type 2 FLT3i active against *FLT3*-ITD,[41] or placebo.[29] Patients in the quizartinib arm had a significantly longer OS of 31.9 months (95% CI, 21.0–NE) compared with 15.1 months (95% CI, 13.2–26.2) in the placebo arm (HR 0.78, 95% CI, 0.62–0.98, $p = 0.032$).

A crucial difference between RATIFY and QuANTUM-First is that the former enrolled patients only up to the age of 60 years, whereas the latter enrolled patients up to 75 years (40% of the patients on QuANTUM-First were aged 60–75) and the RATIFY enrolled patients with both ITD and TKD mutations, whereas QuANTUM-FIRST enrolled only those with ITD mutations. The FLT3-ITD mutation tends to be associated with shorter remission durations and inferior OS; the prognostic impact of FLT3-TKD is less clear. The proportion of patients with a TKD mutation in RATIFY (23%) was also substantially higher than the incidence in de novo AML (5%–15%). On subset analysis of RATIFY, patients who derived

the most benefit were those with *FLT3*-TKD mutations.[28] This suggests that the patient population treated on QuANTUM-First was likely a more challenging population, despite which the combination was able to demonstrate an improved OS and reasonable tolerability. Also, in our experience, quizartinib has been better tolerated than midostaurin, especially from a taste and gastrointestinal perspective.

Current options: Relapsed/refractory

In the relapsed/refractory (RR) setting, both gilteritinib, a highly selective, type 1 FLT3i with activity against both ITD and TKD subtypes, and quizartinib demonstrated improved OS in RR FLT3-mutated AML. For RR AML, Gilteritinib is approved as a single agent by the US FDA, EMA and other regions, while quizartinib is approved in Japan. The ADMIRAL trial randomised 247 patients with ITD or TKD mutations in a 2:1 ratio to receive gilteritinib monotherapy or investigator choice salvage chemotherapy (mitoxantrone, etoposide and cytarabine [MEC], FLAG-Ida, LDAC or azacitidine). Prior midostaurin or sorafenib was allowed. Patients who received gilteritinib had a median OS of 9.3 months versus 5.6 months for salvage chemotherapy (HR for death 0.64; 95% CI, 0.49–0.83, $p < 0.001$), with subgroup analysis suggesting that the benefit was regardless of treatment intensity or prior SCT.[12] A post hoc analysis demonstrated similar CRc rates in patients who had received prior FLT3i compared to those who had not (52% vs. 55%).[42] Real-world data corroborate this with CRc rates of 58% with single-agent gilteritinib in patients relapsing after midostaurin-based induction.[43]

QuANTUM-R randomly assigned 245 patients with ITD mutations in a 2:1 ratio to receive quizartinib or investigator-choice chemotherapy (MEC, FLAG-Ida or LDAC). Prior midostaurin was allowed; sorafenib was initially allowed but was excluded after a protocol amendment. Patients with exposure to other FLT3i were excluded. Median OS was longer in the quizartinib group at 6.2 months (95% CI, 5.3–7.2) versus 4.7 months (95% CI, 4.0–5.5, HR 0.76, 95% CI, 0.58–0.98, $p = 0.02$). Forty-eight per cent of patients in the quizartinib arm achieved a CRc (CR, CRi and CR with incomplete platelet recovery) compared with 27.0% in the chemotherapy arm, enabling SCT in 32% and 11% in the two arms, respectively.[30] This is important as a post hoc analysis demonstrated that being able to proceed with SCT was the most important factor associated with longer OS (SCT vs. no SCT: 12.2 months vs. 4.4 months; HR, 0.32, 95% CI, 0.233–0.427) in patients with relapsed *FLT3*^{mut} AML.[44]

Maintenance options in *FLT3*^{mut} AML

It is likely that persistent FLT3 inhibition may be required to continually suppress *FLT3*^{mut} clones after attainment of remission and after SCT to further prevent relapses. In the SORMAIN trial, 83 patients with *FLT3*-ITD in complete haematological remission after SCT were randomised to sorafenib or placebo maintenance for 24 months. The study was prematurely terminated due to slow recruitment and a growing body of data supporting the use of FLT3i maintenance post-SCT, making physicians less inclined to randomise patients to placebo versus sorafenib. Nevertheless, at a median follow-up of 41.8 months, the median relapse-free survival (RFS) was not reached in the sorafenib group, compared with 30.9 months in the placebo group (HR 0.39, 95% CI, 0.18–0.85, $p = 0.013$). The estimated

probability of survival at 24 months was 90.5% (95% CI, 77%–96%) with sorafenib versus 66.2% (95% CI, 49%–79%) for placebo.[35] However, only nine patients received FLT3i with their pre-SCT frontline induction therapy, limiting generalisability in the current era of widespread FLT3i use during induction.

The MORPHO trial was a double-blind study which randomised 356 patients with *FLT3*-ITD AML to gilteritinib or placebo for 24 months post-SCT.[45] The RFS was higher in the gilteritinib group (HR 0.68, 95% CI, 0.46–1.01), but not statistically significant ($p = 0.052$). However, there was a clear benefit for gilteritinib in a prespecified subgroup analysis of patients positive for measurable residual disease (MRD), using a high-sensitivity *FLT3* next-generation sequencing (NGS) assay (sensitivity of 10^{-6}), immediately prior or immediately post-SCT (HR for relapse 0.52, 95% CI 0.32–0.84, $p = 0.0065$).[46] Approximately half the patients were positive for MRD peritransplant using this assay. Furthermore, depth of MRD was closely associated with OS, with an improved OS noted with each log improvement in MRD clearance, demonstrating the powerful prognostic value of high-sensitivity *FLT3* MRD assessments.[46]

Emerging combinatorial approaches in clinical trials

The improvements in survival for *FLT3*^{mut} patients have been so significant that it has been re-classification from an adverse prognostic marker by the European LeukemiaNet (ELN) to an intermediate one.[47] Despite this, it has become increasingly apparent that FLT3 inhibition alone is insufficient to cure *FLT3*^{mut} AML. Patients relapsing after treatment with type 1 FLT3i frequently lose *FLT3*^{mut} at relapse and gain signalling mutations, especially RAS/MAPK and *BCR::ABL1*,[48,49] or have on-target resistance through the emergence of gatekeeper F691L *FLT3*^{mut}.[50] Patients relapsing after type 2 inhibitor treatment often gain *FLT3*-TKD mutations at relapse[51,52] (Figure 3A). This suggests that combination therapy will be required to prevent emergence of parallel pro-survival clones to prolong remissions and improve survival. For frailer frontline patients, although *FLT3*^{mut} were included in VIALE-A, evidence suggests that despite CRc rates of 63.3% with HMA-VEN in *FLT3*^{mut}, this was one of the molecular subsets that did not benefit as much as some of the other molecular subtypes, with a median OS of only 12.5 months. The HR for death in patients with *FLT3*^{mut} was 0.63 (95% CI, 0.35–1.13) for treatment with HMA-VEN versus azacitidine.[53,54] This was more apparent among *FLT3*-ITD treated with HMA-VEN ($n = 30$), with median OS of only 9.9 months, compared with *FLT3*-TKD ($n = 13$) who had a median OS of 19.2 months. In addition, emergence of activated kinase signalling (including RAS/MAPK mutations) and selection of *FLT3*-ITD has been shown to be a mechanism of resistance to HMA-VEN.[55] Thus, urgent improvement in the frontline treatment of *FLT3*-ITD-mutated patients not eligible for IC beyond that achieved with HMA-VEN is needed.

Preclinical studies have demonstrated synergism when venetoclax is combined with FLT3i through FLT3 inhibitor-mediated downregulation of myeloid leukaemia 1 (Mcl-1) and BCL-extra-large (Bcl-xL), two major mechanisms of resistance to venetoclax therapy.[56,57] These data led to further clinical studies. In a phase 1b open-label single-arm trial, 61 patients failing ≥1 prior line of treatment (median salvage 2) were treated with the combination venetoclax and gilteritinib[33] (ClinicalTrials.gov identifier: NCT03625505). Prior exposure to

venetoclax and/or FLT3i was allowed. The modified CRc (mCRc, CR + CRi + morphologic leukaemia-free state) was 75%, comparing favourably to a response rate of about 45%–50% achieved with gilteritinib single agent in first salvage patients in the ADMIRAL study. Furthermore, about 65% of the patients treated in the venetoclax and gilteritinib combination study had prior FLT3i exposure, in line with contemporary practice, compared with only about 10% who had prior FLT3i in the ADMIRAL study. The response rate was similar with venetoclax with gilteritinib in prior FLT3i-exposed and naive patients. Thus, despite a more advanced salvage population, and more prior FLT3i exposure, the venetoclax and gilteritinib combination demonstrated striking mCRc rates, albeit with cumulative myelosuppression, warranting frontline evaluation of addition of gilteritinib to HMA-VEN in dose-optimised fashion to improve marrow reserve and recovery capacity.

Gilteritinib was added to azacitidine and venetoclax to address the issue of potential *FLT3*^{mut}-driven relapses with HMA-VEN alone (ClinicalTrials.gov identifier NCT05520567, Table 3). Fifty-two patients with ND (n = 30) or RR (n = 22) AML were treated in a phase 1/2 study.[34] The mCRc rate was 100% and 73% in ND and RR AML, respectively, with 93% and 45% achieving MRD negativity by flow cytometry.[67,68] In the ND patients, the median OS was not reached, with a 1-year OS of 83%. A day 14 bone marrow was performed to guide the duration of venetoclax and gilteritinib, owing to concern for myelosuppression with the combination. Ninety-four per cent attained either mCRc or had an aplastic marrow on day 14, allowing venetoclax and gilteritinib to then be safely held for count recovery.[68] A triplet combination of decitabine, venetoclax and quizartinib has been trialled in ND (n = 10) or RR (n = 40) AML (ClinicalTrials.gov identifier NCT03661307). In the RR cohort, 85% had received prior FLT3i, including 78% with prior gilteritinib exposure. The CRc rate was 68%, with 7/24 patients achieving MRD negativity by flow cytometry (sensitivity 10^{-4}). There were no early mortalities, and the median number of cycles to response was 1. In the frontline setting, all 10 of 10 patients have achieved a CR/CRi but follow-up is short and enrolment is ongoing.[31]

Practically, when prescribing triplets, dosing schedules need to be considered to avoid prolonged and profound myelosuppression.[69] Initial experience with the triplets yielded time to neutrophil >1 × 10^9/L and platelet >50 × 10^9/L in cycle 1 of 44 and 34 days, respectively.[69] It is critical to perform early disease assessments on day 14 of induction for patients on triplet regimens. Patients who are in remission or marrow aplasia can stop venetoclax and their FLT3i to allow for marrow recovery. With this approach, the ANC and platelet recovery times are now shorter, ranging from 34 to 38 days.[31,68] Adjustment of venetoclax duration in subsequent cycles is also essential to improve tolerability of the regimen.[11] In our opinion, adequate antimicrobial prophylaxis must also be instituted for both HMA-VEN and triplets. We recommend that all patients uniformly receive antifungal prophylaxis with an azole, or echinocandin if an azole is contraindicated, antibacterial prophylaxis with levofloxacin or cefpodoxime and prophylaxis against herpes simplex virus with valacyclovir or acyclovir. Drug interactions between venetoclax, gilteritinib and CYP3A4 inhibitors such as azole antifungals should also be considered and relevant-dose adjustments made.[11,70,71]

IDH MUTATIONS

Isocitrate dehydrogenase (IDH) 1 and 2 are enzymes in the citric acid cycle. Approximately 20% of AML patients harbour *IDH1* (*IDH1*^{mut}) and *IDH2* (*IDH2*^{mut}) mutations, 8% and 12% respectively.[72,73] These mutations lead to accumulation of the oncometabolite 2-hydroxyglutarate (2-HG), which promotes differentiation block, BCL2 dependence and altered hypoxic responses.[74] *IDH*^{mut} may be acquired at progression from an underlying myelodysplastic syndrome or myeloproliferative neoplasm (MPN),[75] and can be seen in up to 20%–30% of patients with MPN transforming to AML.[76] Patients with *IDH*^{mut} are often older and tend to present with preserved platelet counts.[77]

Current options

The IDH inhibitors ivosidenib, olutasidenib and enasidenib decrease intracellular levels of 2-HG and relieve differentiation block.[78] They have modest single-agent activity in ND AML, with CRc rates of 42.4%[79] and 22%[80] for *IDH1*^{mut} and *IDH2*^{mut} AML respectively. The phase 3 AGILE trial randomised 146 ND *IDH1*^{mut} AML patients ineligible for IC 1:1 to azacitidine with either ivosidenib or placebo.[81] The trial was stopped early due to a benefit in the ivosidenib arm. Both event-free survival (EFS) and OS were significantly longer in the ivosidenib arm compared with placebo (HR for treatment failure, relapse or death 0.33, 95% CI, 0.16–0.69, $p = 0.002$ and HR for death 0.44, 95% CI, 0.27–0.73, $p = 0.001$). The CRc rate and CR rates were also significantly higher with ivosidenib (53% vs. 18%, $p < 0.001$ and 47% vs. 15%, $p = <0.001$, respectively), with a median duration of response (DOR) of 22.1 months. Forty-six per cent of patients achieved transfusion independence. At an updated median follow-up of 28.6 months, the median OS was a robust 29.3 months (95% CI, 13.2–NE) in the ivosidenib arm versus 7.9 months (95% CI, 4.1–11.3) for placebo.[82] This study led to the global approval of azacitidine with ivosidenib in frontline *IDH1*^{mut} AML not suitable for intensive induction. The combination of enasidenib and azacitidine also outperformed azacitidine in a randomised phase 2 study of ND *IDH2*^{mut} AML, with an overall response rate (ORR) of 74% (95% CI, 61–84) versus 36% (95% CI, 20–55, $p = 0.0003$)[83]; however, median EFS (15.9 months vs. 11.9 months, $p = 0.11$) and median OS were not improved (22.0 months vs. 22.3 months, respectively, $p = 0.97$), likely due to availability of salvage venetoclax-based therapies that are effective in RR *IDH2*^{mut} AML.

Although patients with *IDH*^{mut} have an excellent response to HMA-VEN, with CRc rates of 66.7% and 86.0% for *IDH1*^{mut} and *IDH2*^{mut}, respectively,[84] the haematological toxicity of the regimen can be significant with febrile neutropenia rates of 45%–50%.[11] Furthermore, the median DOR and OS with HMA-VEN in *IDH1*^{mut} AML were 21.9 and 15.2 months, respectively, on a subset analysis of the pooled population of the phase IB and phase III VIALE-A patients.[84] Hence, for ND older patients with *IDH1*^{mut}, if limited to doublets, it is our opinion that consideration should be given to ivosidenib and azacitidine given its excellent tolerability. For ND *IDH2*^{mut} AML, we continue to use HMA + VEN due to impressive median DOR and OS (not reached for both).[84] The reasons for differential responses between *IDH1*^{mut} and *IDH2*^{mut} AML are unclear but may be related to differing intracellular localisation. IDH1 is located in the cytoplasm, whereas IDH2 is located in the mitochondria,[85] the site of action of venetoclax.

Emerging combinatorial approaches in clinical trials

Relapse following azacitidine with ivosidenib induction is typically characterised by emergent *IDH2*^{mut} and alternative *IDH1*^{mut}[39,86] (Figure 3B). Given the dependence of *IDH*^{mut} AML on BCL2[74] and the improved responses with *IDH2*^{mut} with HMA-VEN,[87] a triplet of azacitidine, venetoclax and ivosidenib was developed[58] (Table 3, ClinicalTrials.gov identifier NCT03471260). This has shown encouraging efficacy, with CRc at 93% and MRD negativity by flow cytometry at 60% in 14 ND AML patients, a subset of 31 patients treated on a phase 1b/2 study of the triplet. With a median follow-up of 24 months, the median OS has not been reached in the frontline patients, with a projected 2-year OS of 67%. Of interest, patients relapsing after triplets appear to have emergent signalling mutations and transcription factor mutations. Second site and *IDH2*^{mut} have yet to be identified with triplet regimens.

As with FLT3i triplets, myelosuppression remains a consideration, with the median cycle length for patients treated with ivosidenib, venetoclax and azacitidine significantly longer than that for patients treated with a doublet of ivosidenib and venetoclax (38 vs. 28 days respectively, $p < 0.001$). Dose reductions were also more common with the triplet compared with the doublet (47% vs. 17%). The most common dose reduction was a reduction in venetoclax duration to 7–10 days in the second cycle or later in the absence of marrow disease, an appropriate mitigating strategy for myelosuppression.

A trial of an all-oral triplet of decitabine–cedazuridine, venetoclax and ivosidenib or enasidenib is currently ongoing[59,88] (ClinicalTrials.gov identifier NCT04774393). To date, 57 patients have been treated with the combination, 27 ND and 30 RR AML. Eighty-two per cent were classified as ELN adverse risk, many due to the presence of splicing mutations. In ND AML, impressive CRc rates of 96.2%, with 85% achieving MRD negativity, were observed. The median OS and DOR were not reached. In RR AML, the CRc rate was again robust at 56.6%, with 70.5% achieving MRD negativity. The median OS was 13.8 months with a median DOR of 17.7 months for *IDH1*^{mut} AML, and 16.1 and 10.4 months, respectively, for *IDH2*^{mut} AML, both of which are numerically higher than the 8- to 9-month median OS achieved with single-agent IDH inhibitors in RR *IDH*^{mut} AML. This triplet combination trial is our preferred treatment option for *IDH*^{mut} AML.

Practically, when prescribing IDH inhibitors, it is important to have a high index of suspicion for differentiation syndrome (DS), which may occur in up to 20%–30% of patients treated with IDH1 and IDH2 inhibitors.[89] The most frequent manifestations are dyspnoea, fevers and pulmonary infiltration, with or without hypoxia. Prompt recognition and treatment with corticosteroids are required to minimise the risk of fatal DS.[90] DS may sometimes be confused with disease progression, so a high index of suspicion is important. Interestingly, rates of DS were lower when IDH inhibitors were combined with venetoclax (10%) or other cytotoxic agents,[58] likely due to dampening of the differentiation process by promoting rapid apoptosis or cytotoxic cell death of the differentiated cells, an additional potential ancillary benefit of the combinatorial approaches. Ivosidenib is metabolised by CYP3A4 and is an inducer of CYP enzymes, indicating it can accelerate metabolisation of venetoclax. Venetoclax dose adjustments are hence necessary when given together with

ivosidenib and/or azole antifungals.[91] In our triplet combinations incorporating venetoclax and ivosidenib, the recommended phase 2 (RP2D) dose of venetoclax was 600 mg.[88]

KMT 2A REARRANGEMENTS AND *NPM1* MUTATIONS

Lysine methyltransferase 2A (*KMT2A*), previously known as *mixed-lineage leukaemia* (*MLL*), is a gene located on chromosome 11q23. *KMT2A* rearrangement (*KMT2Ar*) is seen in paediatric (10%) and adult AML (5%–10%), acute lymphoblastic leukaemia (ALL) (5%) and mixed phenotype acute leukaemia (8%).[92] Acquired genetic and chromosomal aberrations result in fusion of *KMT2A* to over 100 different partners,[93] with most conferring a poor prognosis.[47] *KMT2Ar* may be cryptic, necessitating complementary molecular methods such as f luorescence in situ hybridisation,[94] NGS,[95,96] optical genome mapping[97,98] or whole-genome sequencing[21] for detection. Mutations in *nucleophosmin 1* (*NPM1*^{mut}) are present in up to 30% of ND AML[23] and 12% of RR AML, including first salvage (64%) and salvage 2 and beyond (36%).[99] Unlike their favourable prognostic impact in frontline AML, *NPM1*^{mut} appears to have no impact on prognosis in salvage 2 and beyond. *NPM1*^{mut} patients in salvage 2 or later have a median OS of 4–6 months, similar to that seen in *NPM1*^{WT} AML. *NPM1*^{mut} results in defective shuttling and cytoplasmic persistence of NPM1.[100] One of the mechanisms by which both *NPM1*^{mut} and *KMT2Ar* drive leukaemogenesis is through constitutive activation of subordinate transcriptional homeobox (*HOX*) genes and their co-factor *MEIS1*, which regulate cell proliferation and differentiation.[101–103] Menin is a scaffold protein that interacts with transcription factors and chromatin regulators, including KMT2A, to regulate gene expression.[92] *NPM1*^{mut} AML has also been demonstrated to be menin-dependent through interactions with wild-type KMT2A.[104] Menin inhibitors target the transcriptome complex by inhibiting the interaction between menin and KMT2A and are active in preclinical models of *NPM1*^{mut}[105] and *KMT2Ar* AML.[106]

Menin inhibitors in clinical development for AML include revumenib,[107] ziftomenib,[108] BMF-219,[109] JNJ-75276617[110] and DSP-5336,[111] with revumenib being furthest along in clinical development. Sixty-eight patients with RR *NPM1*^{mut} and *KMT2Ar* acute leukaemia (82% AML) were treated with single-agent revumenib in a phase 1 dose-escalation study[107] (ClinicalTrials.gov identifier NCT04065399). The only dose-limiting toxicity was asymptomatic QTc prolongation over 500 ms. All-grade QTcF prolongation was seen in 52.9% and grade ≥3 QTcF was seen in 13.4% of patients. The ORR was 53%, with CR or CR with partial haematological recovery (CRh) in 30% (95% CI, 18.8–43.2). Seventy-eight per cent of patients who attained CR/CRh also became MRD negative by f low cytometry. Responses were seen in both *KMT2Ar* (ORR 59%, CR/CRh 33%) and *NPM1*^{mut} (ORR 36%, CR/CRh 21%). The median time to CR/CRh was 1.9 months (range 0.9–4.9), with a median DOR of 9.1 months (95% CI, 2.7– NE) and median OS of 7 months (95% CI, 4.3–11.6) at a median follow-up of 14.3 months. Of interest, transcriptional suppression of FLT3 was observed following menin inhibition, which could have therapeutic implications for cases of AML with *NPM1* and *FLT3* co-mutations.

Like IDH inhibitors, DS can also be seen with menin inhibition. With revumenib, all-grade DS was seen in 16% of patients; no grade ≥3 DS events were noted. The median time to

DS onset was 18 days (range, 5–41) and all cases responded to corticosteroids. Five of 11 patients required addition of hydroxyurea for associated leucocytosis.[107] Revumenib is also a substrate of CYP3A4, necessitating dose adjustments when prescribed with strong CYP3A4 inhibitors. Lastly, given the mechanism of action is to induce differentiation, response assessment should consider that morphologic and phenotypic responses are attained before molecular clearance, as observed in acute promyelocytic leukaemia.

Mechanisms of relapse after menin inhibition are an area of active investigation. Mutations in *MEN1* which affect drug-target binding likely mediate resistance in a proportion of patients.[112] Other possible mechanisms of relapse under investigation include the emergence of mutations in epigenetic or parallel, pro-survival pathways, such as RAS mutations or *FLT3*-ITD. (Figure 3C). Studies investigating revumenib in combination with IC (AUGMENT-102, ClinicalTrials.gov identifier NCT05326516) and decitabine–cedazuridine and venetoclax (SAVE, ClinicalTrials.gov identifier NCT05360160) are ongoing. The first results of SAVE were recently presented, demonstrating response in 9/9 RR AML patients with a *KMT2Ar* or *NPM1*^{mut} (median salvage number, 3), including CR/CRh in 7/9 and MRD negativity in all responding patients.[60] In this study, decitabine–cedazuridine is given on days 1–5, with venetoclax on Days 1–14. A cycle 1 day 14 marrow is performed on all patients to stop venetoclax after Day 14 if the marrow shows <5% blasts or marrow aplasia/insufficiency. Revumenib is being evaluated in this combination at two dose levels. Myelosuppression was noted with febrile neutropenia in 63% of patients but was manageable with a 60-day mortality of 0.

Ziftomenib has been evaluated in 10 RR *KMT2Ar*[108] and *NPM1*^{mut}[113] patients, with 35% demonstrating CRc (ORR 45%, ClinicalTrials.gov identifier NCT04067336). The median DOR was 8.2 months, with potentially less resistance emergence via known menin gatekeeper mutations. The most common adverse events were diarrhoea in 45%, hypokalaemia in 40% and nausea in 30%; none of these were grade 3 or higher. Ziftomenib is being evaluated in combination with azacitidine and venetoclax and 3 + 7 chemotherapy for patients with ND or RR AML (KOMET-007, ClinicalTrials.gov identifier NCT05735184).[114] JNJ-75276617 (ClinicalTrials.gov identifier NCT04811560) and DSP-5336 (ClinicalTrials.gov identifier NCT04988555) are other menin inhibitors in clinical development. An ongoing phase 1 trial of JNJ-75276617 presented data on 58 patients, 57% with *KMT2Ar* and 43% with *NPM1*^{mut}.[110] Grade ≥3 adverse events were neutropenia (10%), anaemia (7%), thrombocytopenia (7%), DS (5%) and transaminitis (3%). At higher dose levels, the ORR was 40%. DSP-5336 has been administered to 24 patients in an ongoing phase 1 dose-escalation trial, with no dose-limiting toxicities observed thus far. Grade ≥3 adverse events include anaemia (22%), pneumonia (19%), sepsis (11%) and hypokalaemia (11%), all deemed unrelated to the study drug. Activity was noted with three of five patients treated at the most recent dose level of 200 mg BID achieving a CR/CRi. Dose escalation continues. No QTcF prolongation or clinical DS has been documented.

TP53 MUTATIONS

Mutations in the tumour suppressor gene *TP53* (*TP53*^{mut}) are found in 10%–15% of ND AML and confer a dismal prognosis, regardless of induction regimen.[53,115,116] Cases of

secondary AML and therapy-related AML are particularly enriched for *TP53*^{mut} with up to 20%–30% harbouring this mutation.[117,118] Although they are frequently associated with a complex karyotype, they do not always co-occur, and the negative prognostic effects of a complex karyotype, or other adverse cytogenetic categories, and *TP53*^{mut} are additive.[23,119] In the 2022 ELN classification, *TP53*^{mut} is an adverse prognostic factor when the variant allele frequency (VAF) is ≥10%.[47] However, emerging data suggest that the survival of patients with *TP53*^{mut} VAFs between 5% and 10% is similar to those with higher VAFs.[119] The optimal cut-off for *TP53*^{mut} VAF which defines poor-risk disease is the subject of active investigation, with studies suggesting that >40% are associated with higher cumulative incidence of relapse[120] and >23% in monoallelic *TP53*^{mut} having similar biology to biallelic *TP53*^{mut}.[121] Patients with *TP53*^{mut} and poor-risk cytogenetics have a particularly dismal prognosis; although they have higher response rates to HMA-VEN than azacitidine alone (CRc 40.7% vs. 16.7%), they have shorter durations of remission and equivalent OS (5.2 months vs. 4.9 months).[122] Thus, for patients in whom consolidation with SCT, which represents the best chance to improve long-term outcomes,[123] is feasible, we prefer HMA-VEN due to the higher response rates with the addition of VEN. In patients who are not candidates for SCT, the added myelosuppression and toxicity from venetoclax should be considered and the pros and cons of single-agent HMA versus HMA + VEN should be discussed.

Magrolimab is an anti-CD47 monoclonal antibody that causes T-cell-mediated cytotoxicity.[124] Preclinical data suggested that magrolimab in combination with azacitidine and venetoclax could potentiate phagocytosis of *TP53*^{mut} AML cells resistant to venetoclax.[125] Early studies suggested promising activity in AML; in a phase 1b study, 72 *TP53*^{mut} AML patients were treated with azacitidine and magrolimab with an ORR of 48.6%, CR rate of 33.3%, DOR of 8.7 months and median OS of 10.8 months.[126] The ENHANCE-2 and ENHANCE-3 trials were randomised phase 3 trial comparing magrolimab plus azacitidine to HMA-VEN or IC and HMA-VEN with magrolimab or placebo. Unfortunately, both were terminated after independent data monitoring committee review determined that the doublet was unlikely to demonstrate a survival benefit[127] and increased risk of death with the triplet.[128] The failure of magrolimab underscores the persistent gap in treatment options for *TP53*^{mut} AML. It is hoped that the ongoing intense preclinical and clinical efforts in *TP53*^{mut} myeloid disease will culminate in breakthroughs in the near future.

MUTATION AGNOSTIC EMERGING OPTIONS AND VENETOCLAX COMBINATIONS

High-intensity backbones in frontline AML

The incorporation of venetoclax into IC or low-intensity regimens containing a purine analogue has shown promising efficacy in both fit[63,129] and unfit[64] patients. Monocytic leukaemias have distinct transcriptomic profiles and rely on Mcl-1, which may explain emergence of monocytic clones at relapse.[130] Critically, it appears that monocytic leukaemia stem cells are reliant on purine metabolism, and are hence exquisitely sensitive to cladribine.[131] In fit patients, venetoclax combined with purine analogue-based IC regimens

such as FLAG-Ida (ClinicalTrials.gov identifier NCT03214562) or cladribine, idarubicin and cytarabine (CLIA, ClinicalTrials.gov identifier NCT02115295) has yielded CRc rates of 90%–95%, with median EFS and OS not reached in two separate phase 2 studies (Table 3).[62,63] In a post hoc propensity score-matched analysis of ND patients treated with venetoclax in combination with IC (IC + VEN), compared with IC alone, the MRD-negative CRc rate was 86% versus 61% (odds ratio 3.2, 95% CI, 1.5–6.7, $p = 0.0028$). This translated to higher rates of SCT and better EFS in the IC + VEN group (79% vs. 57% and not reached vs. 14.3 months, respectively), but OS was not statistically different. There was no difference in outcomes between patients treated with FLAG-Ida + venetoclax and CLIA + venetoclax.[65] The upper age limit for both trials was 65, owing to tolerability of IC in older adults. IC + VEN are demanding regimens associated with profound myelosuppression. The median time to count recovery was 31, 60, 42 and 42 days for cycles 1, 2, 3 and 4, respectively, in patients treated with FLAG-Ida and venetoclax. The shorter count recovery in cycles 3 and 4 was likely due to protocol-mandated dose adjustments made for haematological toxicity.

Other studies have also demonstrated similar efficacy with IC + VEN. The Italian AML1718 study evaluated venetoclax in combination with f ludarabine, cytarabine and idarubicin (V-FLAI) in RR AML, with CRc observed in 75% after the first cycle.[132] Sixty-five per cent achieved MRD negativity, with the median OS being 22.4 months (95% CI, 13.4–NE) and a 1-year OS of 64%. In Germany, the combination of high-dose cytarabine, mitoxantrone and venetoclax (HAM-Ven) was evaluated in 52 RR AML patients, of whom 38 were evaluable for response at the time of presentation. Forty-five per cent were adverse risk per ELN 2022 criteria. Grade ≥3 events occurring in >10% of patients included febrile neutropenia, pneumonia, sepsis and gastrointestinal disorders. The CRc rate was 81.6% with 6/8 (75%) patients with available MRD data achieving MRD negativity. A retrospective review of 35 patients treated with IC + VEN at a single centre in the USA demonstrated CRc rates of 76% in ND AML and 80% in RR AML.[133] The median OS was 16.5 and 8 months for ND and RR AML respectively. In adults aged ≥65, the combination of cytarabine for 5 days and idarubicin for 2 days (5 + 2) with venetoclax was evaluated in a phase 1b study. The CR/CRi rate was 72%, with an induction mortality of 6%.[134]

The significant myelosuppression, and myelosuppression-related infectionswhich can occur with increased frequency with IC + VEN requires specific expertise, and patients should be referred to academic centres for this treatment whenever possible. The duration of venetoclax when given with IC should not exceed 7 days. Rigorous supportive care, including prophylactic antimicrobials, frequent laboratory assessments and streamlined access to speciality support services such as Infectious Disease, Blood Bank and Critical Care are essential to optimise and replicate the published outcomes with IC + VEN. At present, these regimens are implemented primarily as part of clinical trials. However, reports of regimens incorporating IC + VEN are proliferating in numerous centres around the world, as outlined. As we transparently share our experiences and continue to optimise the dosing and schedule of IC + VEN, we hope these approaches will lead to evolution and improvement in AML treatment.

Lower-intensity backbones in frontline AML

Given the intensity associated with IC + VEN, alternative options are needed in older adults and those unfit for intensive treatments. In a phase 2 study of 60 patients aged ≥60 years or unfit patients with ND AML, the combination of cladribine, LDAC and venetoclax alternating with HMA-VEN was investigated[64] (ClinicalTrials.gov identifier NCT03586609, Table 3). The CRc rate was 93%, with 34% proceeding to SCT. Responses were preserved across high-risk subgroups, with a CRc rate of 89% in patients with ELN 2017 adverse risk disease, and 4/4 patients with *TP53*^{mut} attaining a CRc. Responses appeared to be durable, with the median DOR not reached at a median follow-up of 22.1 months and estimated 24-month DOR of 75.9% (95% CI, 63.8–90.3). Median OS was not reached. The regimen was well tolerated, with only one induction death; the median time to neutrophil recovery was 27 days.

Relapsed/refractory AML

Options in RR AML for patients without mutational targets remain limited, especially if they have received frontline regimens containing venetoclax. Idasanutlin is an inhibitor of murine double minute 2 (MDM2), a crucial regulator of p53. MDM2 inhibition leads to p53 stabilisation and activation. MDM2 overexpression is demonstrated in up to 50% of AML patients.[135] As a single agent, idasanutlin is tolerable, with mostly grade 1/2 adverse events and CRc rates of 18.9%.[136] A phase 3 trial of cytarabine and idasanutlin versus cytarabine and placebo enrolled 447 RR AML patients.[137] The primary end point, OS, was not met (8.3 vs. 9.1 months in the study and control groups respectively). In a multicentre phase 1b trial, the safety and efficacy of the combination of venetoclax and idasanutlin were assessed in 56 RR or secondary AML patients with a median of 1 (range, 1–4) prior line of treatment[138] (ClinicalTrials.gov identifier NCT04029688). The population included 10 patients with *TP53*^{mut}. The most common treatment-related adverse events were gastrointestinal (87.3% diarrhoea, 74.5% nausea and 52.7% vomiting), hypokalaemia (50.9%), which were largely grades 1–2, and febrile neutropenia (45.5% grade 3 or 4). The diarrhoea resulted in a protocol amendment mandating anti-diarrhoeal prophylaxis. None of the adverse events resulted in treatment discontinuation. The CRc rate was 26%, with a median time to CRc of 1.4 months and a median DOR of 3.9 months. Other MDM2 inhibitors include milademetan and siremadlin. Milademetan has been evaluated in combination with LDAC, with or without venetoclax[139] (ClinicalTrials.gov identifier NCT03634228). Sixteen patients (14 RR, 2 ND secondary AML) were enrolled with a median age of 70. The median number of cycles administered was 1, with gastrointestinal toxicity being significant and dose limiting (grade ≥3 in over 50% of patients). Two patients (13%) achieved CRi. A triplet regimen of azacitidine, venetoclax and siremadlin, another MDM2 inhibitor, is currently being investigated in a phase 1b/2 study (ClinicalTrials.gov identifier NCT05155709).

A possible reason for the modest activity of MDM2 inhibitors is the induction of a feedback loop which paradoxically increases MDM2 levels and represses p53 activity.[140] MDM2 degraders, such as KT-253, may overcome this feedback loop by suppressing p53-dependent MDM2 protein upregulation. In AML patient-derived xenograft (PDX) models, KT-253

administered in vivo achieved significant tumour regression. A phase 1 trial of KT-253 is currently underway (ClinicalTrials.gov identifier NCT05775406).

FUTURE DIRECTIONS AND EMERGING TARGETED THERAPIES AND IMMUNOTHERAPIES TO LOOK OUT FOR

The treatment landscape of AML is evolving rapidly. However, there are clearly areas of unmet need. Compounds in development may address these areas, and, if found to be effective, may help improve outcomes in combination with established treatments. Drugs under active investigation include CD123 antibody-drug conjugates (ADCs), ADCs with novel toxins such as BET inhibitor proteins (ABBV-787, ClinicalTrials.gov Identifier: NCT06068868), kinase inhibitors, chimeric antigen receptor T (CAR-T) cells and natural killer (NK) cell-based approaches with NK engagers. Newer CD123 ADCs are adopting innovative strategies to mitigate myelosuppression and hepatotoxicity associated with earlier constructs. These include VIP935 (ClinicalTrials.gov identifier NCT06034275)[141] and pivekimab sunirine (ClinicalTrials.gov identifier NCT04086264), which has a novel indolinobenzodiazepine pseudo-dimer payload which alkylates deoxyribonucleic acid and causes single-strand breaks without cross-linking.[142,143]

Tuspetinib (ClinicalTrials.gov identifier NCT03850574) is an oral myeloid kinase inhibitor of SYK, FLT3, Janus kinase (JAK) 1/2, ribosomal S6 kinase (RSK) 1/2, mutant KIT and TAK1-TAB1 kinases which mediate dysregulated cellular proliferation in AML. To date, 123 patients have been treated with tuspetinib, either alone or in combination with venetoclax.[144] The drug was well tolerated, with no dose-limiting toxicities. Clinical responses were seen at all dose levels, including CRc in two of five included *TP53*^{mut} patients. Among RR AML patients (median salvage 2) treated at the RP2D of 80 mg daily, the CRc rate was 36%, including CRc 50% in *FLT3*^{mut} and 25% in *FLT3*^{WT} patients, with a very good safety profile.

Chimeric antigen receptor T cells have induced durable remissions and are potentially curative in ALL, B-cell lymphomas and multiple myeloma. Their application to AML has thus far been limited by targets uniquely expressed on AML cells. Several CAR-T constructs for AML are in active development. These include KITE-222, an autologous CAR directed against C-type lectin-like molecule-1 (CLL-1), expressed in up to 90% of AML cells (ClinicalTrials.gov identifier NCT04789408), CB-012, an allogeneic construct directed against CLL-1, and ACLX-002, directed against CD123. Both CB-102 and ACLX-002 are currently in preclinical development. Finally, SAR443579, a trifunctional anti-CD123 NKp46xCD16 NK cell engager which promotes tumour killing via endogenous NK cells, has been trialled in 42 RR AML patients.[145] These patients had a median of two prior lines of treatment (range 1–10), 30.2% with prior SCT and 83.7% with prior venetoclax exposure. Sixty-five per cent of patients experienced grade ≥3 adverse events, with none leading to permanent treatment discontinuation. The CRc rate was 12.0%, which increased to 33.3% at the highest dose level. These novel approaches are leveraging pathogenic and therapeutic pathways which have not been successfully trialled in AML before. These pathways may be

complementary to existing therapeutic targets and provide rationale for more combinations in the future.

Although the number of novel agents for AML has increased dramatically over the last decade, the importance of consolidation with SCT must still be underscored. Allogeneic SCT is the consolidative regimen of choice for AML patients with a relapse risk exceeding 30%–40%.[47] Even when given in combination, novel agents do not result in durable remissions in the absence of SCT.[15,44] However, there is some hope that the calculus of which patients may benefit from SCT may change in the future, especially as MRD techniques and sensitivity improve. It has now been demonstrated that attainment of undetectable MRD with the use of a high-sensitivity *NPM1* real-time quantitative polymerase chain reaction assay is highly prognostic in *NPM1*^{mut} AML[146] and that the benefit of SCT, even in patients with co-occurring *FLT3*-ITD, appears to be limited to patients who were *NPM1* MRD positive after induction.[146,147]

CONCLUSION

Progress in AML treatment is being made at an unprecedented pace. A deepened understanding of the pathophysiology and drivers of AML has led to the approval of several targeted agents. These are being combined to maximise synergistic potential and eradicate emergent clones, especially in older adults where the prognosis has typically been dismal. Patients with actionable mutations should have those preferentially targeted, ideally in a triplet regimen to reduce the risk of disease escape. Future directions for clinical research include identification of personalised combinations for remission induction, followed by investigation into reduced number of combination treatment days or drug taper to maintain remission while reducing treatment burden and maximising quality of life.

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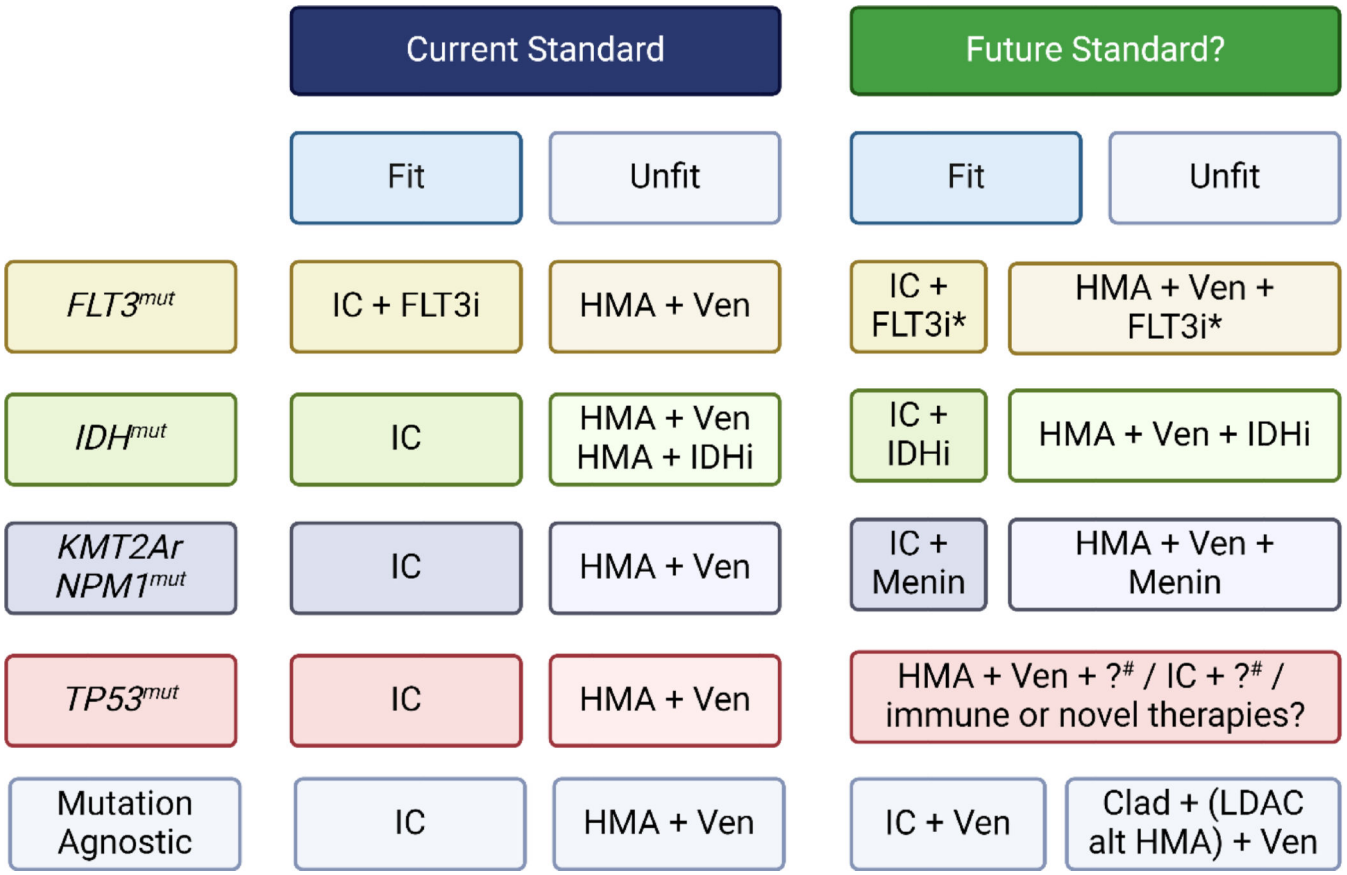

FIGURE 1.

Current and future options for newly diagnosed AML. Key targetable mutations are presented along the left. The middle block of two columns represents current approved treatments, while the right-most block of two columns represents future combinatorial approaches currently under investigation. AML, acute myeloid leukaemia; Clad, cladribine; FLT3i, FLT3 inhibitor; HMA, hypomethylating agent; IC, intensive chemotherapy; IDHi, IDH1/2 inhibitor; LDAC, low-dose cytarabine; LDAC alt HMA, low-dose cytarabine alternating with hypomethylating agents; maint, maintenance; menin, menin inhibitor; Ven, venetoclax. *FLT3i may be used for maintenance remission in the future. #The optimal agent for *TP53*^{mut} AML remains to be identified. It is hoped that one will be in the coming years given the intensive preclinical and clinical research into *TP53*^{mut} myeloid disease.

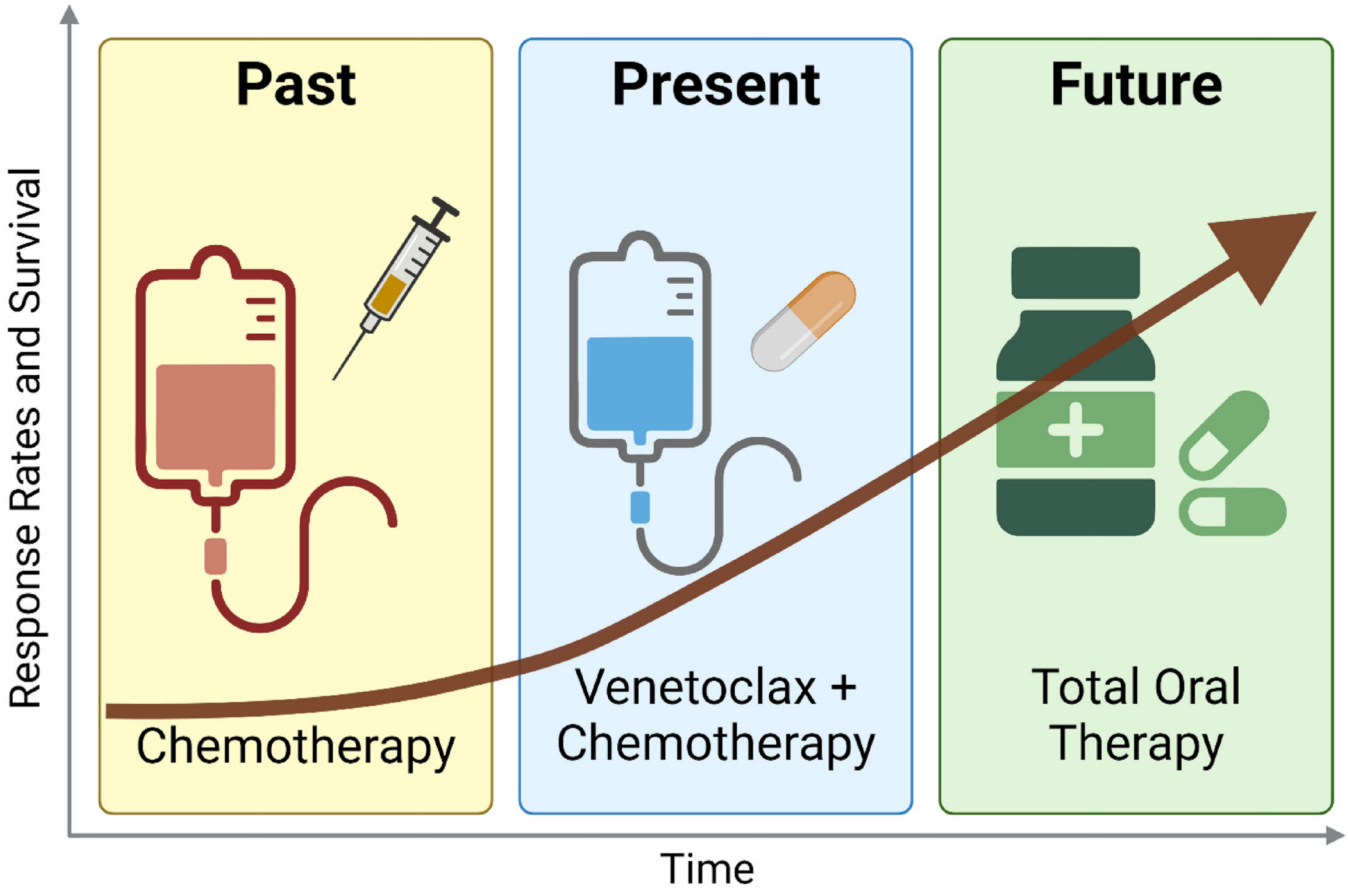

FIGURE 2.

Future directions in AML. For decades, chemotherapy administered parenterally was the standard of care for AML (left panel). The introduction of venetoclax has revolutionised outcomes, especially for older, frail adults (middle panel). As more agents become available, including targeted therapies and oral formulations of agents previously administered parenterally, novel triplet combinations may help to further improve outcomes and allow AML treatment to be administered orally in the convenience of the patient's home (right panel). The brown arrow symbolises improved response rates and survival with novel approaches. AML, acute myeloid leukaemia.

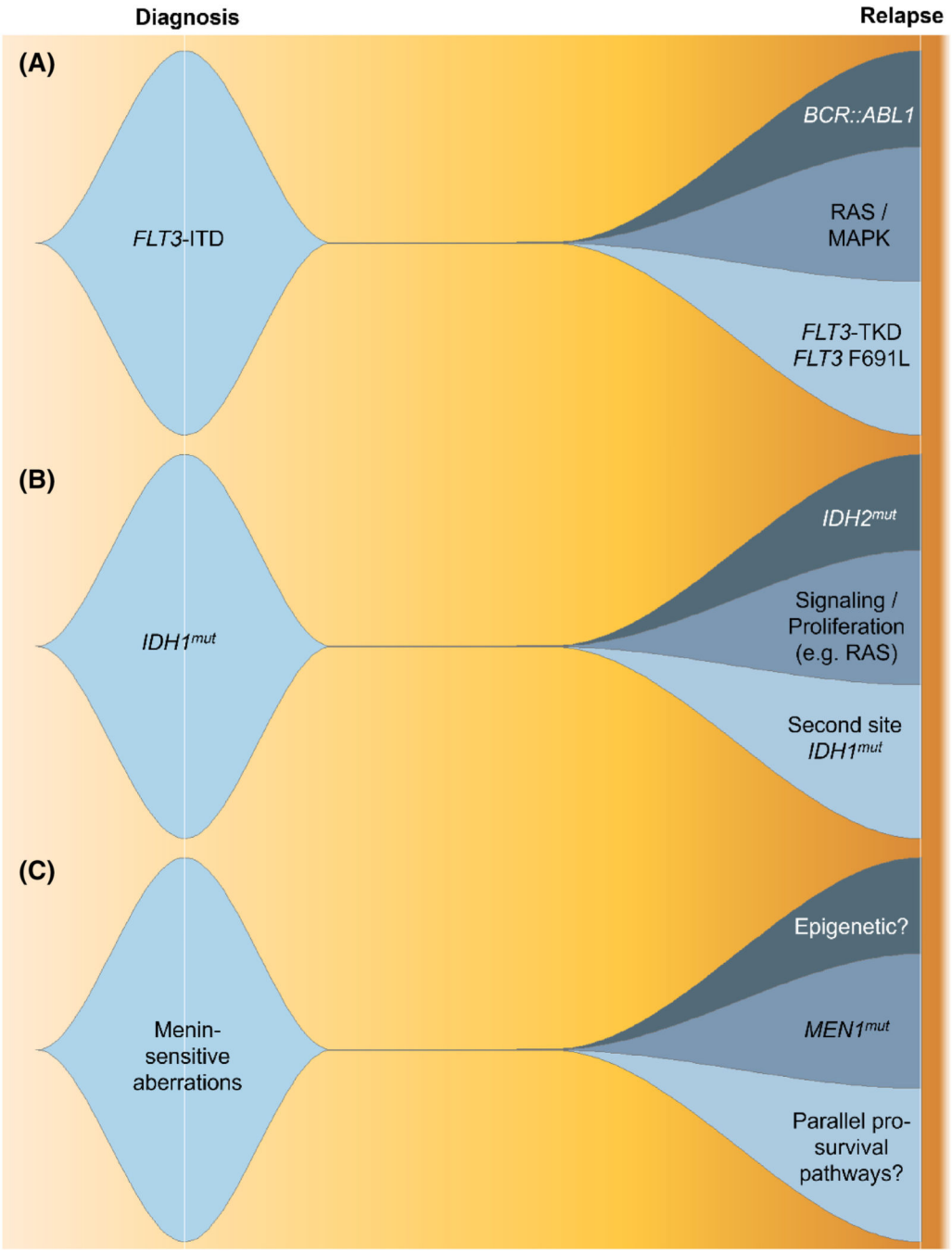

FIGURE 3.

Mechanisms of relapse with standard therapies. (A) Patients with *FLT3*-ITD AML treated with type 1 FLT3 inhibitors may have emergent *BCR::ABL1* or RAS/MAPK pathway mutations at relapse. They may also have on-target F691L mutations in *FLT3*. Patients treated specifically with type 2 FLT3 inhibitors (such as quizartinib and sorafenib) may have emergent *FLT3*-TKD at relapse. (B) Patients with *IDH1*^{mut} AML may show 'isoform switching' with *IDH2* at relapse or alternative *IDH1* mutations. Emergent signalling mutations in the RAS pathway have been observed at relapse. (C) Patients treated with some

menin inhibitors have been known to gain mutations in *MEN1*, which attenuates the drug-target binding. Other mechanisms of resistance are under investigation, but we postulate these may include emergent mutations in epigenetic or parallel, pro-survival pathways. AML, acute myeloid leukaemia; FLT3i, FLT3 inhibitor.

TABLE 1

Selected novel agents in AML.

Class	Drug	Dosing schedule	Indication
BCL2 inhibitor	Venetoclax	400 mg OD PO D1-28[a]	ND AML with HMA
		600 mg OD PO D1-28[a]	ND AML with low-dose cytarabine
		600 mg OD PO D1-14[b]	In combination with ivosidenib[c]
		400 mg OD D1-14[d]	In triplet combinations[c]
FLT3 inhibitor	Midostaurin	50 mg BD PO D8-21	ND AML induction and consolidation
		50 mg BD PO D1-28	Maintenance (12 cycles)[c]
	Quizartinib	40 mg OD PO D8-21	ND AML induction
		40 mg OD PO D6-19	ND AML consolidation
		60 mg OD PO D1-28[e]	Maintenance (36 cycles)
		60 mg OD PO D1-28[e]	RR AML (till progression)[c]
		30 mg OD PO D1-28	ND or RR AML with HMA + VEN[c]
	Gilteritinib	120 mg OD PO D1-28[f]	RR AML (till progression)
		80 mg OD PO D1-28	ND or RR AML with HMA + VEN[c]
	Sorafenib	400 mg BD PO D1-28[g]	Maintenance (24 cycles)
	Crenolanib	100 mg TDS PO D9 onwards[h]	ND AML induction and consolidation[c]
IDH1 inhibitor	Ivosidenib	500 mg OD PO D1-28	ND AML or RR AML (till progression)
	Olutasidenib	150 mg BD PO D1-28	RR AML (till progression)
IDH2 inhibitor	Enasidenib	100 mg OD PO D1-28	RR AML (till progression)
Menin inhibitor	Revumenib	276 mg 12H PO D1-28[i]	RR AML (till progression)[c]
	Ziftomenib	600 mg OD PO D1-28[j]	RR AML (till progression)[c]

Abbreviations: AML, acute myeloid leukaemia; BD, bis in die (twice daily); FLT3i, FLT3 inhibitor; HMA, hypomethylating agent; ND, newly diagnosed; OD, omne in die (once daily); PO, per os (by mouth); RP2D, recommended phase 2 dose; RR, relapsed/refractory; TDS, ter die sumendum (three times daily); VEN, venetoclax.

[a]Venetoclax should be ramped up over 3–4 days per the product label to minimise the risk of tumour lysis syndrome. It requires dose modification if co-administered with CYP3A4 inhibitors (200 mg daily if co-administered with ciprofloxacin, fluconazole or isavuconazole, 100 mg daily if co-administered with voriconazole and 50–70 mg daily if co-administered with posaconazole). The duration of venetoclax in subsequent cycles should be adjusted to minimise myelosuppression based on the duration of count recovery in the antecedent cycle.[11]

[b]Venetoclax levels are decreased by co-administration of ivosidenib. Venetoclax should be increased to 600 mg daily when co-administered with ivosidenib. It should be reduced to 300 mg if co-administered with ivosidenib and fluconazole or isavuconazole, 150 mg with voriconazole and 100 mg with posaconazole.

[c] Not approved by the United States Food and Drug Administration for this indication.

[d] If used in a triplet combination (especially with an FLT3i: HMA + VEN + FLT3i), a cycle 1 day 14 bone marrow is recommended with the intent to stop venetoclax on day 14 after confirming marrow remission, aplasia or insufficiency to minimise cumulative myelosuppression. If ivosidenib is used as part of the triplet, dosing advice outlined above (in footnote "b") applies.

[e] Quizartinib starts at a dose of 30 mg OD and is escalated to 60 mg OD if the patient's QTc (Frederica correction) interval is ≤450 ms on cycle 1, day 15.

[f] Dose escalation to 200 mg OD was allowed in the ADMIRAL trial for non-responders.[12]

[g] Sorafenib starts at 400 mg OD for 2 weeks, then 600 mg OD for 2 weeks before reaching target dose.

[h] Crenolanib is continued till 72 h before the next cycle.

[i] Revumenib requires dose adjustment to 163 mg 12H PO for concomitant strong CYP3A4 inhibitors. Doses are RP2D doses for *NPM1*^{mut} or KMT2A-rearraged RR AML when given as monotherapy.

[j] No dose adjustment for concomitant strong CYP3A4 inhibitors. Doses are RP2D doses for *NPM1*^{mut} RR AML only, when given as monotherapy.

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TABLE 2

Major studies of FLT3 inhibitors (FLT3i).

			mOS (months)	
Drug	**Population**	**Arms**	**Study**	**Control**
Midostaurin	ND AML age 18–60 *FLT3*-ITD and TKD[28]	3 + 7 + midostaurin vs. 3 + 7 + placebo	74.7	25.6
Quizartinib	ND AML age 18–75 *FLT3*-ITD only[29]	3 + 7 + quizartinib vs. 3 + 7 + placebo	31.9	15.1
	RR AML *FLT3*-ITD only[30]	Quizartinib vs. chemotherapy	6.2	4.7
	ND or RR *FLT3*-ITD AML[a],30,31	Quizartinib + decitabine + venetoclax[b]	ND: Not reached, 7.1 (RR cohort)	
Gilteritinib	RR AML *FLT3*-ITD and TKD[12]	Gilteritinib vs. chemotherapy	9.3	5.6
	FLT3-ITD AML in remission after SCT[32]	Gilteritinib vs. placebo	Not published, RFS HR 0.846, $p = 0.0518$	
	RR *FLT3*^{mut} AML[33]	Gilteritinib + venetoclax[b]	10.0	
	ND or RR *FLT3*-ITD or TKD AML[a],34	Gilteritinib + azacitidine + venetoclax[b]	ND: Not reached, 18-month OS 72%; RR: 5.8	
Sorafenib	*FLT3*-ITD AML in remission after SCT[35]	Sorafenib vs. placebo	NR (mRFS)	30.9 (mRFS)
	RR AML *FLT3*-ITD only[a],36	Azacitidine + sorafenib	6.2	
	ND AML age ≤65 *FLT3*-ITD only[a],37	CLIA + sorafenib	NR	
Crenolanib	ND AML age <60 *FLT3*-ITD and TKD[a],38,39	3 + 7 + Crenolanib	NR	

Abbreviations: 3 + 7, cytarabine for 7 days and daunorubicin or idarubicin for 3 days; AML, acute myeloid leukaemia; CLIA, cladribine, idarubicin and cytarabine; mOS, median overall survival; mRFS, median relapse-free survival; ND, newly diagnosed; NR, not reached; SCT, stem cell transplant.

[a]Single-arm phase 2 trial, combinations under evaluation in ongoing clinical trials.

[b]Of note, a majority (65%–80%) of patients on these doublet (VEN + Gilt) or triplet (DAC + VEN + QUIZ, AZA + VEN + GILT) regimens had received a prior FLT3i, and a large proportion had received prior venetoclax-based therapy, so this would be considered a more refractory and heavily treated population compared with the single-agent Gilteritinib (ADMIRAL) and single-agent Quizartinib (QUANTUM-R) studies, which were done prior to the approval of frontline midostaurin or venetoclax for AML.

TABLE 3

Major emerging combinations.

Target	Combination	CRc/MRD negative rate	NCT ID/reference
FLT3	Gilteritinib + azacitidine + venetoclax	96%/93% (ND) 73%/45% (RR)	NCT05520567 [34]
FLT3-ITD	Quizartinib + decitabine + venetoclax	100%/90% (ND) 68%/33% (RR)	NCT03661307 [31]
IDH1^{mut}	Ivosidenib + azacitidine + venetoclax	93%/60% (ND)	NCT03471260 [58]
IDH1^{mut} and *IDH2*^{mut}	Ivosidenib (*IDH1*^{mut}) or enasidenib (*IDH2*^{mut}) + decitabine-cedazuridine + venetoclax	96%/85% (ND) 57%/71% (RR)	NCT04774393 [59]
Menin	Revumenib + decitabine-cedazuridine + venetoclax	100%/43% (RR)	NCT05360160 [60]
Agnostic	FLAG-IDA + venetoclax	89%/93% (ND) 53%/71% (RR)	NCT03214562 [61,62]
	CLIA + venetoclax	96%/90% (ND)	NCT02115295 [63–66]
	Cladribine + low dose cytarabine + venetoclax alternating with azacitidine + venetoclax	93%/84% (ND)	NCT03586609 [64]

Note: Major emerging combinations under evaluation at The University of Texas MD Anderson Cancer Center are summarised in this table.

Abbreviations: CLIA, cladribine, cytarabine and idarubicin; CRc, composite complete remission; FLAG-IDA, fludarabine, cytarabine, idarubicin and filgrastim; MRD, measurable residual disease; ND, newly diagnosed; RR, relapsed/refractory.