Review

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Review

Differentiation Syndrome in Acute Myeloid Leukemia: Molecular Mechanisms, Clinical Spectrum, and Emerging Therapeutic Paradigms

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Abstract

Acute Myeloid leukemia (AML) is characterized by differentiation arrest, driving blast proliferation and abnormal blood formation. While differentiation therapy revolutionized acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), its extension into non-APL AML has been limited until recent targeted agents. This narrative review synthesizes preclinical and clinical evidence into differentiation-inducing therapy, with a focus on IDH1/2, FLT3 and menin inhibitors. Following SANRA guidelines, we searched pubmed (2010-sep,2025) for clinical trials and key preclinical studies, with particular attention to the molecular mechanism of differentiation induction, clinical efficacy and management of differentiation syndrome (DS). IDH1/2 inhibitors (ivosidenib, enasidenib, olutasidenib) yield overall response rate (ORR) of 30-94% in AML with DS in 10-19%. Menin inhibitors (revumenib, ziftomenib, enzomenib, bleximenib) achieve an ORR of 33-88% in KMT2A-rearranged or NPM1-mutated AML, with DS in 10-25% and QT prolongation as key toxicities. FLT3-inhibitors (gilteritinib, quizartinib) improve survival in FLT3-mutated AML with DS in 1-5%. Resistance mutations limit durability and combinations enhance efficacy. Differentiation therapy represents a paradigm shift towards non-cytotoxic AML management. Improved recognition of DS and rational combination approaches will be essential to maximize therapeutic benefit. Future research should address mechanisms of resistance and biomarkers to achieve cure beyond APL.

Keywords: acute myeloid leukemia; differentiation; differentiation syndrome; IDH1/2 inhibitors; FLT3 inhibitors; menin inhibitors

1. Introduction

Acute myeloid leukemia (AML) is a clonal malignancy of hematopoietic stem and progenitor cells characterized by uncontrolled expansion of immature blasts and failure of normal hematopoiesis [1]. At a biological level, AML is driven by disruption of genetic and epigenetic regulation that guide myeloid differentiation [2], resulting in persistent self-renewal and arrest of leukemic cells at immature developmental stage [3]. The paradigm of "differentiation therapy" was first established in acute promyelocytic leukemia (APL), an distinct AML subtype driven by the PML-RARA fusion oncoprotein which enforces transcriptional repression of myeloid differentiation [4].

The introduction of all-trans retinoic acid (ATRA) in the mid-1970s, demonstrated that pharmacological release of this block can induce terminal differentiation of leukemic promyelocytes into mature granulocytes, leading to high remission rates [4]. Subsequent combination of ATRA and arsenic trioxide (ATO) achieved durable remission and long-term cure rates exceeding 90-95% in APL, despite minimal reliance on conventional cytotoxic mechanisms 5. This paradigm-shifting

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success established differentiation therapy and raised the question of whether similar approaches could be extended into non-APL AML [5–8].

Early attempts to generalize differentiation therapy using ATRA were largely unsuccessful. Meta-analysis of five randomized controlled trials including more than 1,000 patients with non-APL AML, demonstrated no significant improvement in overall survival (OS) or remission rates [9]. While preclinical studies suggested certain molecular subsets might respond to ATRA [10,11], these findings have not translated into clear clinical benefit in non-APL AML, underscoring the molecular specificity underlying APL's unique sensitivity and highlighting the need for mechanism-driven approaches.

Historically, treatment for non-APL AML was predominantly based on intensive cytotoxic chemotherapy, primarily consisting of a backbone of cytarabine- and anthracycline- based regimens established in the 1970s, designed to eliminate proliferating leukemic blasts, without addressing the underlying differentiation blockade that drives disease pathogenesis. While these strategies achieve complete remission (CR) rates of 60-80% in younger adults and 40-60% in older patients [12,13], long term outcomes remained poor, particularly in older adults and those with adverse-risk disease, with five-year overall survival rates typically below 30%. The advent of next-generation sequencing (NGS) and large-scale genomic profiling has since revealed recurrent genetic and epigenetic mutations that directly contribute to differentiation arrest, enabling development of targeted agents designed to reverse these effects.

Differentiation has therefore re-emerged as a central focus of targeted therapy development in non-APL AML [14]. Preclinical evidence demonstrated that leukemic cells could be induced to undergo maturation through targeted modulation of oncogenic transcriptional network and epigenetic regulators [15]. More recently novel menin-KMT2A inhibitors have shown efficacy in mouse xenograft models harboring KMT2A-rearranged or NPM1-mutated AML, have shown robust differentiation-inducing activity [16], validating differentiation therapy as a viable strategy beyond APL.

In this article, we provide an overview of current mechanisms of differentiation arrest in AML and the ways in which emerging targeted treatments exploit this hallmark. We focus on the clinical development of differentiation-directed therapies, notably IDH1/2 inhibitors, FLT3 inhibitors, and menin inhibitors, as these agents have demonstrated the ability to induce blast differentiation in clinical trials. We focus on the clinical development, clinical efficacy, key clinical trials, differentiation-associated toxicities and the resistance pathways that limit their long-term success. Finally, we discuss future directions aimed at enhancing differentiation-based therapy through rational combination regimens and next-generation inhibitors to overcome resistance and improve durable remission rates.

2. Results

Targeting IDH1/2

IDH1/2 inhibitors are small molecules that induce differentiation by binding to the active site of the mutant isocitrate dehydrogenase enzyme. The bond also blocks the production of 2-hydroxyglutarate and restores normal levels of α-Ketoglutarate (α-KG), thereby reactivating epigenetic regulation and removing the differentiation block. Across clinical trials, DS has been reported in 12-19% of patients receiving IDH1/2 inhibitors [18], with a median time to onset of DS of 17-20 days. Most cases of DS related to IDH inhibitors have a mild to moderate severity and are usually manageable with steroids, supportive care, and temporary treatment interruption. Table 1 shows a summary of IDH1/2 inhibitors, their clinical efficacy incidence of major treatment related adverse events with a focus on differentiation syndrome.

Ivosidenib, a selective IDH1-inhibitor targeting the R132 mutation demonstrated meaningful activity in R/R AML. In the initial phase 1 dose-escalation and dose-expansion study of ivosidenib monotherapy in IDH1-mutated AML [19], the rate of overall response rate (ORR), complete remission

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or complete remission with incomplete hematologic recovery (CR/CRi), and CR rates were 41.6%, 30.4% and 21.6% respectively. Duration of response was highest in patients who achieved CR, with a median of 9.3 months. Among patients who achieved CR/CRi, 21% had no residual IDH1 mutation detected after therapy. Treatment-related adverse events (TRAEs) of grade 3 or higher that were defined to be of special interest were prolongation of the QT interval (7.8%, any grade 24%), DS (3.9%, any grade 10.6%), and leukocytosis (1.7%, any grade 36%). Median time to onset of DS was 29 (range 5 to 59) days. None were grade 4, and no patients discontinued the medication due to DS. Treatment for DS included glucocorticoids, diuretics, and (if accompanied by leukocytosis) hydroxyurea. With these interventions, the syndrome was resolved in 17 of 19 patients, and the remaining 2 patients had ongoing DS at the data-cutoff date. However, since this was a first-in-human experience where the signs and symptoms were not initially recognized as DS, and due to a lack of a codified adverse event term for DS outside of the context of APL or ATRA, the FDA suspected DS was underreported in this setting, and subsequently sought to perform a systematic analysis of DS cases based on adverse events terms, laboratory abnormalities, and vital sign results grouped per Montesinos criteria [20]. The algorithm identified potential DS in 40% (72/179) of patients treated with ivosidenib; however, subsequent review by the FDA showed that around half of these cases were DS secondary to ivosidenib (34/179, 19%) [18].

In the phase III AGILE trial [21], patients with newly diagnosed IDH1-mutated AML who were ineligible for intensive chemotherapy were randomly assigned to receive oral ivosidenib and subcutaneous or intravenous azacitidine or to receive a matched placebo and azacitidine. The primary endpoint was event-free survival (EFS), defined as treatment failure, relapse from remission, or death. In the intention-to-treat population (N=146), EFS was significantly higher in the ivosidenib-and-azacitidine group (HR 0.33; 95% confidence interval [CI], 0.16 to 0.69; P=0.002). The median overall survival (OS) was 24 months (95% CI, 11.3 to 34.1) and 7.9 months (95% CI, 4.1 to 11.3) in the ivosidenib-and-azacitidine and placebo-and-azacitidine groups, respectively (HR=0.44; 95% CI, 0.27 to 0.73; P=0.001). As for safety, the percentage of patients with DS of any grade was 14% with ivosidenib and azacitidine (no grade ≥4 events) and, interestingly, 8% with placebo and azacitidine (including one grade 4 event), with a median time to onset of 19.5 (3-33) days. No deaths due to DS were noted in either group.

Ivosidenib has also been evaluated as part of a triplet regimen in combination with azacitidine and venetoclax in patients with newly diagnosed (ND) IDH-mutated AML, not fit for intensive chemotherapy, or high-risk myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) (defined as ≥10% blasts or intermediate/high risk by IPSS, R-IPSS, or D-IPSS). The ORR was 94% with 93% achieving CRc within 5 cycles and 77% achieving minimal residual disease (MRD) negativity by flow cytometry. These responses translated into a 3-year OS for MDS or MPN (n=12), newly diagnosed AML (n=31), and R/R AML (n=13) subsets of 81.5% (95% CI: 61.1 - 100%), 71.4% (53.2 - 95.8%), and 52.1% (28.8 - 94.3%), respectively. Patients who received allogeneic stem cell transplant (allo-SCT) had a 3-year OS of 94.7% (95% CI: 85.2 - 100%) compared to 52.8% (25.6 - 78.2%) in those who did not [22,23].

Enasidenib an oral, selective inhibitor of mutant-IDH2 enzymes, has demonstrated efficacy in the management of R/R and ND IDH2-mutated AML. In a phase I/II study, enasidenib doses of 50 to 650 mg per day were evaluated, and a once-daily 100 mg dose was selected on the basis of pharmacokinetic and pharmacodynamic profiles, as the maximum tolerated dose was not reached. DS occurred in 23 (8%) patients with 15 having grade 3-4 DS. Median time to onset was 48 days (range 10-340 days). Enasidenib dosing was interrupted in 10 patients with DS, but permanent drug discontinuation was not required. Enasidenib was also associated with non-infectious leukocytosis in 17%, primarily within the first 2 cycles; however, these were not necessarily accompanied by DS. In regard to response, the ORR for all R/R AML was 40.3% with 19.3% of patients attaining CR. The median time to first response was 1.9 months (range, 0.5-9.4 months) with 87.3% of responding patients attaining a first response by cycle 5 [24]. In patients with newly diagnosed AML, the ORR was 30.8% with 21% achieving CR/CRi [25].

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In a randomized phase II trial, patients received enasidenib plus azacitidine or azacitidine only, in the enasidenib plus azacitidine arm, 7% achieved a response, compared with 36% in the azacitidine monotherapy group. Of note, the rate of DS in the enasidenib plus azacitidine arm was 10% [26].

Olutasidenib an structurally distinct allosteric non-competitive IDH1 inhibitor, that is is FDA-approved for the treatment of adult patients with R/R IDH1-mutated AML [27]. Olutasidenib has demonstrated clinically meaningful efficacy in a pivotal phase 2 trial involving 147 efficacy-evaluable patients with R/R IDH1-mutated AML [28,29]. The ORR was 48%, while the CR/CRi rate was 35% with a median duration of response of approximately 25.9 months. Median OS was 11.6 months, which included patients who had failed prior venetoclax-based regimens [30]. DS occurred in approximately 14% of patients, with grade ≥3 events in 9% and 1 fatal case reported. Olutasidenib has also been studied in combination with azacitidine in IDH1-mutated MDS, yielding an ORR of 59% and a CR/CRi rate of 27% with durable remissions and a tolerable safety profile, DS occurred in 3 patients (14%), including 1 (5%) with grade 3 severity [31,32].

Table 1. List of clinical trials evaluating IDH1/2 inhibitors.

Medication	Trial / ID (Ref)	Line of Therapy	Response Rate (ORR / CR / CRh)	Grade ≥ 3 Complications	Differentiation Syndrome (DS)
Ivosidenib	Phase 1 Expansion NCT02093559 (AG120-C-001)	R/R AML	ORR: 41.6% CR/CRh: 30.4% CR: 21.6%	QT Prolongation: 7.8% Leukocytosis: 1.7%	10.6% (Any grade) 3.9% (Grade ≥ 3) FDA review: 19%
Ivosidenib + Azacitidine	Phase 3 AGILE	Newly Diagnosed (Unfit)	ORR: 62.5% CR: 47.2%	Neutropenia: 28% Febrile Neutropenia: 28%	14% (Any grade) No Grade ≥ 4
Ivosidenib + Aza + Venetoclax	Phase 1b/2 Triplet (NCT03471260)	ND AML, R/R AML, or MDS/MPN	ORR: 94% CRc: 93%	Febrile Neutropenia: 28% Infection: 24%	11% (Any grade) No G4/5 reported
Enasidenib	Phase 1/2 Study NCT01915498 (AG221-C-001) (24, 25)	R/R AML	ORR: 40.3% CR: 19.3%	Hyperbilirubinemia: 12% Thrombocytopenia: 6%	12% (Any grade) 7% Grade ≥3
Enasidenib + Azacitidine	Phase 1b/2 Study NCT02677922 (Phase 2)	ND AML (Unfit)	ORR: 74% CR: 54%	Neutropenia: 37% Thrombocytopenia: 37%	18% (Any grade) 8% Grade ≥3
Olutasidenib	Phase 2 Pivotal 2102-HEM-101 (NCT02719574)	R/R AML	ORR: 48% CR/CRh: 35%	Transaminitis: 13% Febrile Neutropenia: 8%	14% (Any grade) 9% (Grade ≥ 3) 1 Fatal case
Olutasidenib + Azacitidine	NCT02719574 (Pivotal)	R/R AML	ORR: 59% CR/CRh: 27%	Thrombocytopenia: 37% Neutropenia: 24%	9% (Any grade) 5% (Grade 3)

Note: Data derived from clinical trials NCT02093559 (Ivosidenib monotherapy), NCT03173248 (AGILE), NCT03471260 (Triplet), NCT01915498 (Enasidenib monotherapy), NCT02677922 (Enasidenib combo), and NCT02719574 (Olutasidenib). **Abbreviations: AML**: Acute Myeloid Leukemia; **Aza**: Azacitidine; **CR**: Complete Remission; **CRh**: Complete Remission with partial hematologic recovery; **CRc**: Composite Complete Remission; **DS**: Differentiation Syndrome; **MDS/MPN**: Myelodysplastic Syndromes/Myeloproliferative Neoplasms; **ND**: Newly Diagnosed; **ORR**: Overall Response Rate; **R/R**: Relapsed/Refractory; **Ven**: Venetoclax. **Grade:** Adverse events

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graded per CTCAE criteria. Differentiation Syndrome rates include both Investigator-reported and FDA-adjudicated data where specified.

Targeting Menin

The menin and histone-lysine-N-methyltransferase 2A (KMT2A) protein complex is an essential epigenetic regulator of genes (eg, MEIS1 and the homeobox [Hox] gene family) essential for leukemic self-renwal [33]. This is particularly pronounced in NPM1-mutated AML (approximately 25%-30% of AML) as well as KMT2A-rearranged AML (5%-10% of AMLs) [34]. In these genetically defined subtypes, menin facilitates oncogenic transcriptional program leading to myeloid differentiation in preclinical models. Table 2 shows a summary of clinical studies evaluating menin inhibitors, their clinical efficacy incidence of major treatment related adverse events with a focus on differentiation syndrome.

Table 2. Menin Inhibitors.

Medication	Trial / ID	Line of Therapy	Response Rate (ORR / CR / CRh)	Grade ≥ 3 Complications	Differentiation Syndrome (DS)
Revumenib	AUGMENT-101	R/R AML (KMT2Ar/NPM1m)	KMT2Ar: ORR 64% NPM1m: ORR 47%	QTc Prolongation: 16% Febrile Neutropenia: 14%	16% (Any grade) All G2–3
Revumenib + Aza + Ven	Beat AML (NCT03013998)	ND AML (Older adults)	CR/CRh 81.4% ORR: 88.4%	QTc Prolongation: 12% (G3) Universal MRD- in responders	19% (Any grade) 5% (Grade 3)
Revumenib + Dec/Ced + Ven	SAVE Study	ND AML (NPM1m/KMT2Ar)	CR: 88% MRD-Rate: 100%	Infection: 53% Febrile Neutropenia: 37%	24% (Any grade) 12% Grade 3
Ziftomenib	KOMET-001	R/R NPM1m AML	CR/CRh: 22% mDOR: 4.6 months	Febrile Neutropenia: 26% Anemia/Thrombocytopenia: 20%	25% (Any grade) 15% Grade 3
Ziftomenib + 7+3	KOMET-007 (39)	ND AML (KMT2Ar/NPM1m)	NPM1m: CR 100% KMT2Ar: CR 83%	Febrile Neutropenia: 15% Thrombocytopenia: 15%	2% (Any grade) 1 Case G3 reported
Ziftomenib + Aza + Ven	KOMET-007 (40)	ND NPM1m AML	CRc: 84% MRD-Rate: 54%	QTc Prolongation: 3% (G3)	3% (Grade 2)
Ziftomenib + Aza + Ven	KOMET-007 (41)	R/R AML (KMT2Ar/NPM1m)	NPM1m: ORR 65%	Thrombocytopenia: 31% Anemia: 26%	1% (Grade 3)

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			KMT2Ar: ORR 33%		
Enzomenib	Phase 1/2 (Daver 2025)	R/R Acute Leukemia	KMT2Ar: ORR 72.7% NPM1m: ORR 47%	No ≥G3 QTc prolongation Sepsis: 25%	12.9% (Any grade) 7.7% Grade 3/4
Enzomenib + Aza + Ven	Phase 1 (Watts 2025)	R/R AML	CRc: 56% MRD-Rate: 83%	Thrombocytopenia: 44.4% Leukopenia: 38.9%	1 Case (Grade 2)
Bleximenib + Ven (+/- Aza)	ALE1002 (4.1, 4.4)	R/R AML (KMT2Ar/NPM1m)	ORR: 69%–79% CRc: 38.5%	Febrile Neutropenia: 37% Anemia: 46.7%	6% (Any grade) G5 reported at 50mg
Bleximenib + 7+3 Chemo	ALE1002 (4.2)	ND AML (KMT2Ar/NPM1m)	ORR: 95.8% CR: 87.5%	Thrombocytopenia: 79.5% Neutropenia: 72.7%	Low (Safety mitigation in place)

Data compiled from AUGMENT-101 (Revumenib), Beat AML/SAVE (Revumenib combos), KOMET-001/007 (Ziftomenib), and ALE1002 (Bleximenib). Abbreviations: 7+3: Cytarabine and Anthracycline induction; AML: Acute Myeloid Leukemia; Aza: Azacitidine; CR: Complete Remission; CRc: Composite Complete Remission (CR + CRh + CRp + CRi); CRh: Complete Remission with partial hematologic recovery; Dec/Ced: Decitabine/Cedazuridine; DS: Differentiation Syndrome; KMT2Ar: KMT2A rearrangement; mDOR: median Duration of Response; MRD-: Measurable Residual Disease negative; ND: Newly Diagnosed; NPM1m: NPM1 mutation; ORR: Overall Response Rate; QTc: Corrected QT interval; R/R: Relapsed/Refractory; Ven: Venetoclax. Safety: Adverse events graded by CTCAE. Differentiation syndrome (DS) rates reflect investigator-reported or trial-adjudicated events. G5 refers to fatal adverse events.

Revumenib

Revumenib is a first in class oral menin inhibitor. It demonstrated robust differentiation-driven activity in the phase I/II AUGMENT-101 trial involving R/R KMT2A-rearranged or NPM1-mutated AML. Among 161 patients enrolled, the ORR reached 64% in the KMT2A-rearrnaged cohort and 47% in the NPM1-mutated group. Rates of CR/CRi were identical between cohorts at 23%. MRD negativity among responders was achieved in 58% of KMT2A-rearranged patients and 64% of those with NPM1 mutations. 36% of responding KMT2A-reaarnaged patients and 17% of NPM1-mutant responders received allo-SCT [35,36].

Revumenib demonstrated a manageable and distinct safety profile; the most frequently reported TRAEs of any grade included nausea (28%), vomiting (18%), increased alanine aminotransferase (ALT) levels (18%), anemia (16%), febrile neutropenia (14%), and QT interval prolongation (16%). Among grade 3 or higher TRAEs, febrile neutropenia occurred in 14% of patients, and QTc prolongation ≥ grade 3 was observed in 16% of patients, including one case of dose-limiting QT prolongation beyond 500 ms. QTc prolongation typically peaked around day 8 of treatment but was not associated with any documented arrhythmia or treatment-related deaths, and it was managed with monitoring and dose adjustments. DS was reported in 16% of patients, all of which were grade 2 or 3 in severity. These cases responded to corticosteroids and/or hydroxyurea without the need for

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permanent treatment discontinuation or dose reduction, and no DS-related mortality occurred. Overall, 6% of patients discontinued therapy due to adverse events.

Revumenib has also been evaluated in combination with azacitidine and venetoclax in a phase I dose-escalation and expansion study at two dose levels (113 mg or 163 mg orally every 12 hours in combination with strong cytochrome P450 inhibitor azoles) in patients aged 60 years and older newly diagnosed with AML with NPM1 mutation or KMT2A rearrangement , 43 patients were enrolled and treated with a CR/CRi rate of 81.4% (NPM1-mutated: 79.4%; KMT2A-rearrnaged: 88.9%) with 84% of evaluable patients achieved remission within one cycle of therapy. There were no dose-limiting toxicities. DS occurred in 8 (19%) patients and QTc prolongation in 19 (44%) patients, however, neither required permanent discontinuation of revumenib.

Similarly, revumenib was evaluated in an all-oral combination with decitabine/cedazuridine and venetoclax in ND patients with NPM1-mutated, KMT2A-rearrnaged or NUP98-rearrnaged AML or mixed-lineage acute leukemia who were not candidates for high intensity chemotherapy. Among evaluable pts, the CR rate was 88% (14/16 pts, 95% CI, 59-94), with MRD negative rate by flow cytometry of 100%. At a median follow-up of 6 months (range, 1-14), the median OS and EFS were not reached. Allo-SCT has been performed in 5 (29%) pts; 2 (18%) NPM1-mutated and 3 (50%) KMT2A-reaarnaged AML. Relapse occurred in 2 pts (1 NPM1-mutated and 1 KMT2A-rearrnaged). Neither underwent allo-SCT in CR1 and both had detectable MEN1 M327I mutations at relapse. The most common TRAEs was infection in 9 patients (53%), all grade 3. QTc prolongation occurred in 8 (47%) patients; 3 were grade 2 (18%), the rest were grade 1 (29%). DS occurred in 4 (24%) patients; 2 patients had grade 3 DS which promptly resolved with steroids [37].

Ziftomenib

Ziftomenib another oral menin inhibitor, has shown activity across many preclinical and clinical settings. In the phase 1/2 open-label multicenter KOMET-001 trial, 92 patients with R/R NPM1-mutated AML were treated with ziftomenib 600 mg once daily, with a CR/CRi rate of 22% and a median duration of response of 4.6 months. In regard to TRAEs, 86 of 92 patients (93%) had grade ≥3 treatment-emergent adverse events, with the most common of these being febrile neutropenia (26%), anemia (20%), thrombocytopenia (20%), and QT prolongation (9%). DS occurred in 25% of patients, but grade ≥3 DS occurred in only 15% (all grade 3, no grade 4 or 5). Two patients (2%) discontinued treatment because of ziftomenib-related DS; one patient had resolved DS but stopped therapy because of other unrelated complications; the other died due to progressive AML.

Ziftomenib is also under evaluation in the ongoing KOMET-007 phase1a/1b, combining it with venetoclax/azacitidine, venetoclax alone, or cytarabine and daunorubicin (7+3) in NPM1-mutated or KMT2A-rearranged AML. In an interim analysis for the intensive chemotherapy arm (n=46 evaluable) [38]. CR rates were 88% (30/34) for NPM1-mutated and 83% (10/12) for KMT2A-rarrnaged; composite complete remission (CRc) rates were 94% (32/34) and 83% (10/12), respectively. The most common grade ≥3 TEAE) were febrile neutropenia (47%), thrombocytopenia (31%), anemia (22%), and neutropenia (20%). Importantly, there were no cases of DS, ziftomenib-associated QTc prolongation or drug-limiting toxicities (DLTs) with the 200 mg or 400 mg dose levels.

Ziftomenib was also evaluated in combination with azacitidine and venetoclax in ND and in R/R NPM1-mutated or KMT2A-rarranged AML. In the ND NPM1-mutated cohort , the recommended phase 2 dose (RP2D) of ziftomenib 600 was used (n=31, evaluable), CRc rate was 84% (26/31) after a median time to first CRc of 3.5 weeks (range 2.4–9.4), with local MRD-negativity rates among tested CRc responders of 54% (13/24) after a median time to first MRD-negativity of 8.4 weeks (range 2.9–17.4). DS occurred in 1 (3%) patient (grade 2), which successfully resolved with protocol-specified mitigation. One patient (3%) had investigator-assessed ziftomenib-associated QTc prolongation (grade 3); however, there were concomitant significant electrolyte abnormalities, and the event resolved with electrolyte repletion [39].

In the R/R AML cohort (n= 70 evaluable patients, NPM1-mutated = 43; KMT2A-rarrnaged= 27). With a median follow-up of 18.0 weeks for NPM1-mutated and 16.4 weeks for KMT2A-rearrnaged ,

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the ORR were 65% (28/43) for NPM1-mutated and 33% (9/27) for KMT2A-rearrnaged CRc rates were 49% (21/43) for NPM1-mutated and 22% (6/27) for KMT2A-rarrnaged after median time to first CRc of 4.9 wks (range 2.7–15.6) and 5.5 wks (range 2.6–18.9), respectively; MRD negativity rates among tested CRc responders were 50% (9/18) for NPM1-muated and 60% (3/5) for KMT2A-rearranged after median time to first MRD-negativity of 5.9 weeks (range 2.9–15.6) and 8.1 weeks (range 7.7–18.9), respectively. DS occurred in 1 (1%) NPM1-mutated patient (Grade 3), which lasted 1 day and successfully resolved with protocol-specified DS mitigation. No ziftomenib-related QTc prolongation was reported with the combination, and no DLTs were observed in Phase 1a [40].

Enzomenib

Enzomenib (DSP-5336), an oral menin-KMT2A inhibitor, intentionally designed with different physicochemical properties, such as a short half-life of 2-5 hours, low lipophilicity, and rapid drug clearance. In a phase1/2 trial in patients with R/R KMT2A-rearrnaged, NPM1-mutated, and other HOXA9/MEIS1-driven leukemias [41], 116 heavily pre-treated patients were enrolled; median of 2 prior treatment regimens, range (1-9); 36 (31%) patients had prior allo-SCT, 86 (74.1%) patients had prior venetoclax. KMT2A-rarrnagement was documented in 61 pts (52.6%), NPM1-mutation in 34 (29.3%), and other abnormalities in 21 (17.7%). TRAEs included nausea (16.4%), DS (12.9%, Grade 3 DS was reported in 8 pts (6.9%), grade 4 in 1 patient (0.8%), and vomiting (11.2%). There was no G3+ treatment-related QT prolongation. Grade 1/2 treatment-related QT prolongation was reported in 5 pts (4.3%), did not require discontinuation, and was complicated by underlying electrolyte abnormalities and concomitant medications. Outcomes were reported for patients without prior exposure to menin inhibitors. The ORR and CR+CRi rates at the recommended phase 2 dose (RP2D) for pts with KMT2A-rearrnaged (300 mg BID with strong CYP3A4 inhibitor azoles) were 72.7% (8/11) and 45.5% (5/11). Dose optimization for the NPM1 cohort is still ongoing.

Enzomenib was also evaluated in a phase 1 study in combination with venetoclax and azacitidine in patients with R/R AML [42]. among 18 enrolled patients (median age 50 (range: 21-76), median 2 prior regimens, 16.7% prior allo-SCT, 33.3% prior venetoclax exposure, 27.8% prior menin inhibitor exposure). KMT2A-rearrnagement and NPM1-mutation were documented in 7 (38.9%) and 11 (61.1%) pts, respectively. CRc rate was 56% of the 15 responders, 12 were assessed for MRD and 83% (10/12) were MRD negative by flow cytometry or NGS. Of patients with prior exposure to venetoclax, 67% (6/9) achieved a CRc.

Bleximenib

Bleximenib (JNJ-75276617) is another oral menin inhibitor which was evaluated in the phase 1 ALE1002 study, where it showed high rates of response at the bleximenib RP2D 100 mg BID in combination with venetoclax and azacitidine in patients with ND KMT2A-rearrnaged or NPM1-mutated AML. Bleximenib is currently being evaluated in cAMeLot-2 (NCT06852222), a phase 3, randomized, double-blind, placebo-controlled, global multicenter study that will evaluate the efficacy and safety of bleximenib with venetoclax + azacitidine in adults with ND KMT2A-rearrnaged or NPM1-mutated AML who are ineligible for intensive chemotherapy, and the HOVON 181 AML / AMLSG 37-25, a doble-blinded, phase 3 study of bleximenib or placebo in combination with standard induction and consolidation therapy followed by maintenance for the treatment of patients with ND KMT2A-rearranged or NPM1-mutated AML eligible for intensive chemotherapy.

Targeting FLT3

The incidence of DS with FLT3 inhibitors is less frequent than in IDH and menin inhibitors and is estimated to be in the range of 1-5% across various studies [43]. Patients who develop FLT3-associated DS tend to present with prominent dermatologic manifestations (rash, neutrophilic dermatoses), yet similar to IDH-DS, they tend to occur within days but can also be delayed,

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presenting weeks to months later. There have been no reports in the literature of DS occurring with midostaurin, likely related to the use of midostaurin in combination with intensive chemotherapy as outlined in the RATIFY trial thereby mitigating the risk of DS [44].

Gilteritinib

Gilteritinib is a highly selective, oral FLT3 inhibitor with activity against both FLT3 internal tandem duplication (ITD) and tyrosine kinase domain (TKD) and weak activity against c-Kit [45]. Gilteritinib was evaluated in the phase 3 ADMIRAL trial, where adults with R/R FLT3-mutated AML were randomized in a 2:1 ratio to receive either gilteritinib or salvage chemotherapy. Gilteritinib significantly improved overall survival and remission rates compared to salvage chemotherapy and retained clinical activity previously exposed to FLT3 inhibitors [46]. Gilteritinib induces two distinct marrow responses in FLT3-mutated AML: responses with and without differentiation. While responses with differentiation happen in around 50% of the cases, clinically significant DS occurs at a lower frequency of 3-5% in patients receiving monotherapy for R/R disease [47].

Quizartinib

Quizartinib is a type II FLT3 inhibitor that binds adjacent to the ATP-binding domain when the FLT3 protein is in its inactive conformation and, therefore, lacks activity against TKD-mutant FLT3. Quizartinib caused terminal myeloid differentiation of leukemic blasts with a surge in the number of FLT3-ITD-retaining neutrophils, and development of clinical DS [48]. Dermatologic manifestations including sweet's syndrome (acute febrile neutrophilic dermatosis) have also been reported with FLT3 inhibitors, including quizartinib [49]. Quizartinib is FDA-approved (since July 2023) in combination with standard induction/consolidation chemotherapy and as maintenance monotherapy for ND FLT3-ITD mutated AML in R/R setting. DS incidence is lower (1-5% in real-world and trial data), compared with IDH and menin inhibitors and usually presenting with dermatologic manifestations (Cite: Oncologic Drugs Advisory Committee (ODAC) Meeting, May 14, 2019, NDA 212166, Quizartinib, Applicant: Daiichi-Sankyo, Inc.)

3. Methods

This review was conducted and reported in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines [17]. The SANRA criteria guided the formulation of the research questions, the structured literature search strategy, the critical appraisal of included studies, and the organization of evidence into thematic sections relevant to this review. We conducted a structured literature search using the PubMed (MEDLINE) database to identify relevant English-language publications from 2010 through the present (September 2025). This timeframe was chosen to capture the modern era of differentiation-directed treatments in AML, as IDH1/2 inhibitors, FLT3 inhibitors, and menin inhibitors have entered clinical trials and practice mainly in the past decade 20. Search terms strategy employed combinations of keywords related to AML and differentiation therapy, including: "acute myeloid leukemia", "IDH1", "IDH2", "FLT3", "gilteritinib", "quizartinib", "menin inhibitor". Studies included phase I-III clinical trials and clinical studies evaluating differentiation-directed targeted therapy in AML. A limited number of preclinical or translational studies that were deemed mechanistically essential were also included. Editorials, commentaries and studies lacking relevance to differentiation mechanisms or clinical outcomes were excluded. Data from the included publications were extracted and synthesized through a qualitative, thematic approach. Evidence was first aggregated to define key biological mechanisms of differentiation blockade in AML and then grouped by therapeutic class. Within each group, we compared study results in terms of clinical efficacy and evidence of differentiation induction. We also extracted reported resistance mechanisms from both clinical studies. Finally, we summarized emerging research on therapeutic strategies to circumvent resistance.

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4. Conclusions

Differentiation arrest is a central pathogenic feature of AML and a tractable therapeutic target beyond APL. Molecularly targeted agents, including IDH1/2 and menin inhibitors and selective FLT3 inhibitors, restore leukemic maturation through transcriptional and epigenetic reprogramming, producing meaningful clinical response in genetically defined AML subset. Differentiation syndrome represents an on target inflammatory consequence of effective therapy and is manageable with early recognition and corticosteroids. However, incomplete remissions and acquired resistance limit single-agent efficacy. Rational combination strategies, biomarker-driven patient selection, and deeper mechanistic understanding are essential to fully integrate differentiation therapy into precision-based, non-cytotoxic AML treatment paradigms.

5. Future Directions

Future directions for differentiation-directed therapy AML increasingly center on the rational integration of menin and IDH1/2 inhibitors into frontline combination regimens, with an ongoing pivotal phase III trial (KOMET-017; NCT07007312) evaluating ziftomenib in combination with venetoclax and azacitidine or intensive chemotherapy, and early-phase data (BEAT AML sub-study) supporting advancement of revumenib-based triplets toward potential registrational studies , with the goal of establishing new standards of care for NPM1-mutated and KMT2A-rearranged AML. Parallel efforts focus on overcoming resistance through next-generation menin inhibitors and molecular surveillance for emerging MEN1 alterations, with expansion into R/R settings includes combination strategies with intensive salvage regimens and FLT3 inhibitors (KOMET-008; NCT06001788), exploiting transcriptional dependencies such as STAT5A signaling in co-mutated disease. Biomarker development beyond founding driver mutations, particularly HOXA/B and MEIS1 expression signatures, may enable broader patient selection, including NUP98-rearranged leukemias [50]. For IDH1/2 inhibitors, future studies emphasize optimized triplet regimens [51], investigation of epigenetic and metabolic resistance mechanisms, and evaluation of maintenance strategies to enhance response durability. Collectively, these approaches aim to extend differentiation-based, precision therapies across AML subsets beyond APL.

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Abbreviations

The following abbreviations are used in this manuscript:

7+3	Cytarabine plus anthracycline induction chemotherapy
α-KG	Alpha-ketoglutarate
ADMIRAL	Phase III trial of gilteritinib in relapsed/refractory AML
AGILE	Phase III trial of ivosidenib plus azacitidine
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia

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APL	Acute promyelocytic leukemia
ATRA	All-trans retinoic acid
ATO	Arsenic trioxide
Aza	Azacitidine
BID	Twice daily
CI	Confidence interval
CR	Complete remission
CRc	Composite complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete hematologic recovery
CTCAE	Common Terminology Criteria for Adverse Events
Dec/Ced	Decitabine/cedazuridine
DLT	Dose-limiting toxicity
DS	Differentiation syndrome
EFS	Event-free survival
FDA	U.S. Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
HOX	Homeobox gene family
HR	Hazard ratio
IDH1/2	Isocitrate dehydrogenase 1 / 2
IPSS	International Prognostic Scoring System
ITD	Internal tandem duplication
KMT2A	Lysine methyltransferase 2A
KMT2Ar	KMT2A-rearranged
MEIS1	Myeloid ecotropic viral integration site 1
MEN1	Menin gene
MDS	Myelodysplastic syndrome
MPN	Myeloproliferative neoplasm
MRD	Measurable residual disease
ND	Newly diagnosed
NGS	Next-generation sequencing
NPM1	Nucleophosmin 1
NPM1m	NPM1-mutated
ODAC	Oncologic Drugs Advisory Committee
ORR	Overall response rate
OS	Overall survival
PML-RARA	Promyelocytic leukemia–retinoic acid receptor alpha fusion
QTc	Corrected QT interval
R/R	Relapsed or refractory
RP2D	Recommended phase II dose
SANRA	Scale for the Assessment of Narrative Review Articles
STAT5A	Signal transducer and activator of transcription 5A
TEAE	Treatment-emergent adverse event
TKD	Tyrosine kinase domain
TRAEs	Treatment-related adverse events
Ven	Venetoclax

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