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REVIEW

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Menin inhibitors for the treatment of acute myeloid leukemia: challenges and opportunities ahead

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Abstract

The AML treatment landscape has significantly changed in recent years with the approval of targeted therapies in the front-line and relapsed/refractory settings, including inhibitors of FLT3 and IDH1/2 mutations. More importantly, approval of the combination of the BCI-2 inhibitor, venetoclax, and hypomethylating agents or low dose cytarabine provided unprecedented breakthrough for the frontline treatment of older, unfit AML patients. Even with all this exciting progress, more targeted therapies for AML treatment are needed. Recent development of menin inhibitors targeting AML with *KMT2A* rearrangements or *NPM1* mutations could represent a promising new horizon of treatment for patients within these subsets of AML. Our current review will focus on a summary and updates of recent developments of menin inhibitors in the treatment of AML, on the challenges ahead arising from drug resistance, as well as on the opportunities of novel combinations with menin inhibitors.

Keywords Acute myeloid leukemia, Menin inhibitors, Novel therapies

Background

Acute myeloid leukemia (AML) treatment paradigm is undergoing a much-needed breakthrough with dedicated research, technological advances, and clinical trials. Detection of novel molecular targets, sensitive tumor detection markers and, importantly, drug discovery, are augmenting the outcomes of AML. This transformation has been heralded by approval and availability of small molecule inhibitors, such as selective antagonists of the anti-apoptotic protein BCL-2 (B cell lymphoma-2) including Venetoclax in 2017, inhibitors of mutated FLT-3 (FMS Like Tyrosine kinase 3), and IDH 1/2 (Isocitrate Dehydrogenase), as well as antibody drug conjugates(ADC). A detailed review of these and other agents in development for AML has been published previously [1].

In recent years, one of the most exciting advancements in AML treatment has been the clinical development of menin inhibitors. Here, we review the clinical development of menin inhibitors for the treatment of AML harboring mutations in the Nucleophosmin (*NPM1*) gene (*NPM1*m) or rearrangements in the histone-lysine N-methyltransferase 2A (*KMT2A*) gene (*KMT2A*r), and for other rare genetic aberrations. Additionally, we discuss the challenges and opportunities that lie ahead in the clinical application of these compounds.

Biological basis of menin inhibition

Menin protein biology, structure, and interaction with other proteins:

The menin protein is a one-of-its kind, scaffold nuclear protein which is encoded by the tumor suppressor MEN*1*

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(Menin 1) gene. *MEN1* mutations are well known to be implicated in the causation of sporadic or autosomal dominant hereditary cancer syndromes which affect the endocrine system, known as the MEN1 syndrome. This demonstrates the tumor suppressor activity of the gene. [2, 3] While the biological basis of this phenomenon is being actively studied, loss of cell cycle regulation, and disruption of inhibition of transcription factors such as JunD resulting from MEN1 mutation and a truncated menin protein are a few proposed mechanisms [4, 5] On the contrary, the menin protein exerts a paradoxically different function in the hematopoietic pathological states, where it serves as an essential oncogenic cofactor for the maintenance and propagation of leukemogenesis initiated by the oncoprotein KMT2A, as well as the KMT2A fusion protein complexes [6–8].

Crystallographic studies and subsequent functional investigations revealed the detailed structure of menin. Its essential biological functions are diverse in nature, likely in a mutually exclusive manner, carried out through its interactions with various proteins—transcription factors, chromatin modification proteins, and other regulators of cell function [9]. [4, 5] Menin protein mediates and regulates several physiological cellular functions in a tissue or cell-specific manner by varying expression levels, influencing gene transcription or repression, cell signaling, DNA repair, chromatin modulation, and other vitals interactions. [5, 9] In turn, it is itself regulated by several factors such as prolactin, transforming growth factor beta (TGFB), etc [5, 9].

Menin has been likened to a "curved left-hand like structure", in which a centrally located deep pocket or groove (formed by the palm) forms an essential binding site for different proteins and by which physiological and pathological functions are mediated. For example, the N-terminal portion of the KMT2A wild type (WT) protein, and the oncogenic KMT2A fusion protein (FP) bind to this location. [4, 5] The groove also forms a hub for binding other essential proteins and regulators such as JunD, or (Lens epithelium derived growth factor (LEDGF) which plays a key role in *KMT2A-AF9* rearranged leukemogenesis [8].

Menin-KMT2A complex formation and interaction

Role of LEDGF/HOX/MEIS1

KMT2A is a complex chromatin modifying protein with histone-methyltransferase activity (HMT), and it is ubiquitous in cells and is necessary for normal development of neural, skeletal and hematopoietic elements [10]. Importantly, in vivo mouse studies showed that KMT2A is important for the maintenance of expression of homebox (HOX family cluster genes) in tissues. [10] Alteration of KMT2A function during chromosomal rearrangements or duplications, which results in the loss of essential Su(var)3–9, Enhancer-of-zeste, Trithorax (SET) domain and the HMT activity, has been associated with leukemogenesis and other malignancies through deregulation of normal cellular processes. [11] The KMT2A WT and KMT2A FP contain short, conserved sequences on the N-terminal called high-affinity menin binding motifs (MBM 1 and MBM 2) which bind to the central groove of menin [7, 12]. The consequence of these fusions is the upregulation of HOX family cluster genes and their cofactor, Meis homebox 1 (*MEIS1)*, also denoted as HOX/MEIS1 complex, leading to differentiation blockade, and transformation of hematopoietic progenitors to leukemic stem cell state.

Homebox gene family (HOX) are vital determinants of structural development of tissues and organs in embryogenesis and are also involved in hematopoietic progenitor propagation, development and differentiation. Consequently, aberrant activation and expression of these genes has been found to be associated with transformation of leukemic cells. While HOX cluster genes are capable or leukemic initiation, MEIS1 and other cofactors such as PBX Homebox3 (PBX3) are critically necessary to potentiate and accelerate the transformation to leukemic cells [13, 14], Together, the upregulation and maintenance of these complexes underlie the converging pathway for leukemogenesis in various genomic alterations.

Menin is crucial for recruitment, activation and maintenance of HOX expression, as demonstrated by in vitro studies where HOX/MEIS1 gene expression is dramatically reduced upon deletion of MEN1 or with the introduction of dominant negative KMT2A mutations which interfere with KMT2A -menin interaction in transformed cells [12, 15].

The KMT2A binding sites on menin are the targets of menin inhibitors, which block the interaction with the KMT2A fusion proteins [16, 17].

LEDGF is a chromatin protein which serves a vital anchoring function for the oncoprotein KMT2A, and menin complex. Like MBM, the N-terminal of KMT2A binds to LEDGF using a LEDGF binding motifs (LBM). This KMT2A- menin- LEDGF complex formation is essential for the leukemogenesis which distinguishes it from the other protein KMT2D which does not contain LBM and therefore lacks leukemogenic properties [8].

Menin-NPM1*m* interaction

Early, global gene expression studies of de novo AML samples from pediatric and adult populations shed light on the association between NPM1*m* and concurrent overexpression of HOXA cluster and MES1, showing similarities with KMT2A driven leukemias [18,

19]. NPM1*m* protein is translocated to the cytoplasm through nuclear export signals (NES) to exert the oncogenic functions [20–22]. Relocation of NPM1m to the nucleus through abrogation of NES does not only reverse the differentiation blockade and but also turns off HOXA expression indicating the direct upstream effect of NPM1m on HOXA genes. [23, 24], Additionally, KMT2A-WT and menin interaction remains critical for the NPM1*m* leukemic states. [25, 26] This was demonstrated by in vivo gene expression studies of NPM1*m* leukemia models in which rapid reduction of the MEIS1/PBX3 cofactors' expression and concurrent loss of self-renewal capacity of leukemic stem cells, and upregulation of differentiation markers was observed upon treatment with menin inhibitor VTP-50469 (a precursor of revumenib) [25, 26].

The collective insights gained from these and numerous other important studies led to the investigation of inhibition of menin—KMT2A protein interaction, and the downstream repressive effect on *HOX/MEIS1* gene expression as an important therapeutic strategy in AML involving *KMT2A*r or *NPM1m,* and multiple other novel rearrangements [25, 27, 28]. Of note, the menin biding sites are also vulnerable to the emergence of mutations that confer resistance to the inhibitors, as elaborated in a later Section [16, 17].

KMT2A re-arranged AML

The *KMT2A* gene (previously known as mixed lineage leukemia 1 or *MLL1*) is located on chromosome 11q23, and translocations involving the *KMT2A* locus are present in approximately 5% of adult AML cases. However, the *KMT2A*r incidence is higher in other contexts, for example, in up to 70% of infantile leukemias and approximately 50% of therapy related AML (t-AML) following etoposide exposure [29, 30].The translocation process is complex, with over 80 different partner genes identified, and research into the mechanisms and partner genes involved in *KMT2*r AML is ongoing [31]. *KMT2A*-r AML is typically associated with decreased sensitivity to chemotherapy, leading to high rates of relapse, and an overall poor prognosis [32, 33]. The 2022 European Leukemia Network (ELN) guidelines on AML classify *KMT2A*r AML in the adverse risk disease category except for AML harboring t (9;11)(p21.3;q23.3) which is classified as an intermediate risk [34]. The fusion proteins created by translocations involving the *KMT2A* locus yield an aberrant transcription program characterized by increased expression of developmental genes including *HOX* and *MEIS1*, thereby promoting leukemogenesis. [35, 36] Menin protein binds to the KMT2A-fusion partner protein complexes leading to nuclear localization of the fusion product and thereby facilitating an aberrant transcription program. Specifically, menin forms a hub and links KMT2A and its fusion protein with a chromatin protein LDGF which is essential for leukemogenesis. [8] The interaction between the menin and KMT2A proteins is therefore central to the pathogenesis of *KMT2A*r AML and forms a therapeutic target [12, 37].

NPM1 mutated AML

The *NPM1* gene is located on chromosome 5q35 and codes for a protein involved in many basic cellular processes. Mutations in the *NPM1* gene (*NPM1*m) are seen in approximately 30% of AML cases. [38] *NPM1* mutations are considered favorable and are often associated with a better prognosis. The 2022 ELN guidelines on AML classify *NPM1*m AML as favorable risk when not associated with internal tandem duplications in the FMS-like tyrosine kinase gene (*FLT3* ITD mutations) or other adverse risk cytogenetic abnormalities. [34] Approximately 80% of patients with *NPM1*m AML treated with intensive chemotherapy achieve remission. [39] However, approximately 50% eventually experience relapse, and prognosis is worse for patients over age 60 compared to younger patients. [40, 41] In *NPM1*m AML, the mutant NPM1 protein binds to chromatin targets that are shared by the KMT2A protein. The expression of *HOX* and other developmental genes is also upregulated in *NPM1*m AML. [25, 27, 38] The interaction between menin and wild type KMT2A therefore plays an important role in the pathogenesis of *NPM1*m AML [25, 42].

Menin inhibitors

Menin inhibitors are small molecule inhibitors that bind with high affinity to the KMT2A binding pocket of menin. These agents inhibit the interaction between menin and KMT2A which inhibits KMT2A-dependent transcription of downstream target genes. These agents thereby inhibit an important component of the pathogenesis of *KMT2A*r and *NPM1*m AML. Similarly, disruption and inhibition of the menin and KMT2A interaction is also being studied as a therapeutic strategy in leukemic states driven by other molecular rearrangements which result in increased *HOXA* gene transcription. [43–45] The mechanism of action of menin inhibitors is depicted in Fig. 1. The menin protein structure, and common mutation hotspots contributing to resistance to menin inhibitors are depicted in Fig. 2.

The binding of menin to KMT2A allows the KMT2A/fusion protein to promote downstream transcription of MEIS1, HOXA, and other leukemogenic proteins. Menin inhibitors block the interaction between menin and KMT2A and thereby inhibit this downstream transcription.

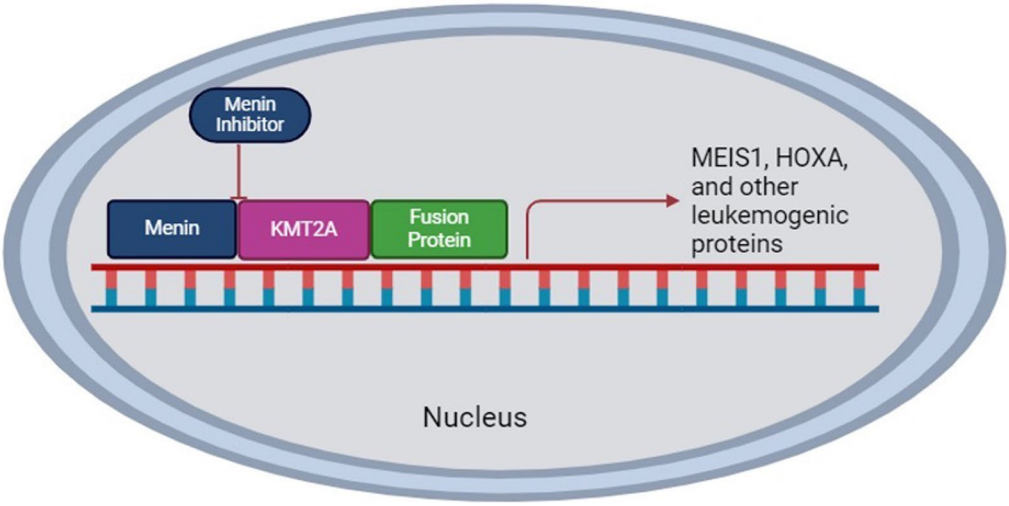

Fig. 1 Mechanism of action of Menin Inhibitors

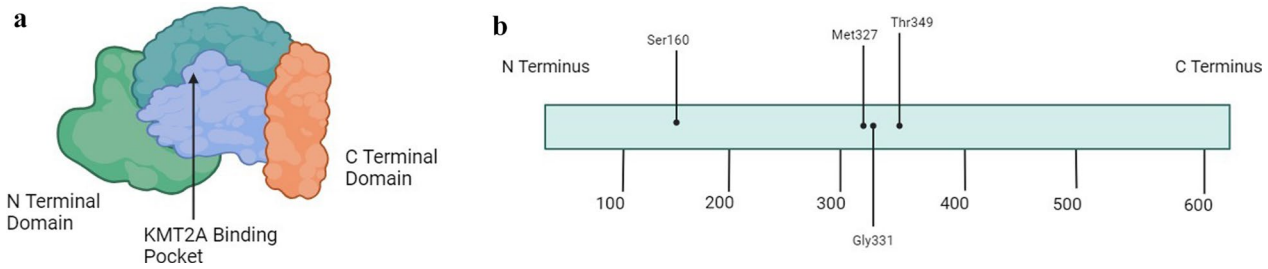

Fig. 2 The Menin Protein Amino Acid Map

1 Physical depiction of the menin protein structure including the N terminal domain, C terminal domain, and middle region. The crystal structure of the middle region is often likened to a palm, and the KMT2A binding pocket is in this region.
2 Amino acid map of the menin protein which is comprised of 610 amino acids. There are various mutational hotspots that contribute to acquired resistance to menin inhibitor therapy. These hotspots are depicted here and include Ser160, Met327, Gly331, and Thr349. These mutations interfere with the interaction between menin and menin inhibitors but do not affect the interaction between menin and KMT2A.

Preclinical and clinical data for menin inhibitors in development

There are currently six different menin inhibitors being evaluated in clinical trials that are at various stages of development. These menin inhibitors include revumenib (SNDX-5613), ziftomenib (KO-539), DSP-5336, Bleximenib (JNJ-7526617), DS-1594, and BMF-219, which will be reviewed in the following sections.

Revumenib

Revumenib, also known as SNDX-5613, is the first menin inhibitor to be studied in humans. VTP-5046 is a close analogue of revumenib that demonstrated promising results in pre-clinical studies. VTP-50469 was found to be active in vitro in *KMT2A*r AML cell lines. VTP-50469 was found to displace menin from KMT2A which impaired KMT2A binding to chromatin at select genes. This led to changes in gene expression with associated cellular differentiation and apoptosis. Similarly, xenograft models from patients with *KMT2A*r AML or *KMT2A*r acute lymphoblastic leukemia (ALL) treated with VTP-50469 demonstrated significant reduction in disease burden. [28] VTP-50469 was also found to induce loss of *MEIS1* gene expression and increased differentiation of *NPM1*m leukemic cells in vitro. This agent also inhibited growth and stimulated differentiation of leukemic blasts in patient-derived xenograft (PDX) models containing *NPM1*m cells [26].

These promising pre-clinical studies led to the development of a phase I/II trial of revumenib in patients with relapsed/refractory (R/R) *KMT2A*r or *NPM1*m acute leukemias including AML, ALL, and mixed phenotype acute leukemia (MPAL) (AUGMENT-101). This study included adult and pediatric patients aged 30 days or older. The phase 1, dose-escalation portion of the study enrolled patients not taking (arm A) or taking (arm B) strong CYP3A4 inhibitors. Revumenib was administered orally every 12 h (q12h) on days 1–28 per 28-day cycle. For arm A, four different dose levels were studied including 113 mg q12h, 226 mg q12h, 276 mg q12h, and 339 mg q12h. For arm B, three dose levels were studied including 113 mg q12h, 163 mg q12h, and 226 mg q12h. Overall, revumenib was well tolerated. Dose limiting toxicities in both arms of the phase 1 dose escalation portion included asymptomatic grade 3 QTc prolongation without any ventricular arrhythmias observed. Treatment with revumenib was found to downregulate key target genes involved in leukemogenesis and to upregulate the expression of genes involved in cellular differentiation. The revumenib doses of 226 mg q12h and 276 mg q12h in arm A and 113 mg q12 h and 163 mg q12h in arm B met the specified criteria for Recommended Phase 2 Dosing (RP2D) based on safety, tolerability and pharmacokinetic (PK) parameters. PK analysis found that drug exposure was dose-proportional in both arm A and arm B. The half-life of revumenib in arm A was approximately three hours on the 276 mg q12h dose level at the cycle 1, day 8 assessment. The half-life was approximately eight hours on the 163 mg q12h dose level in Arm B at the same assessment. The overall response rate (ORR) in the phase 1 portion was 53% and included patients with complete remission (CR), complete remission with partial hematologic recovery (CRh), complete remission with incomplete platelet recovery (CRp), and complete remission with incomplete count recovery (CRi). The median overall survival for the phase 1 population was 7 months [46].

Recently, results were reported from the phase 2 portion of the study involving patients with *KMT2A*r ALL, *KMT2A*r MPAL, and *KMT2A*r AML. Analysis is ongoing for the cohort of patients with *NPM1*m disease and has not yet been reported. In the phase 2 portion of the trial, patients with *KMT2A*r acute leukemias were treated with revumenib 163 mg (or 95 mg/m^2 for body weight < 40 kg) every 12 h with a concurrent strong CYP3A4 inhibitor. This was a recommended phase 2 dose determined for patients in Arm B of the phase 1 portion of the study. Patients continued treatment on the phase 2 study until they experienced unacceptable toxicity or failed to achieve a morphologic leukemia free state (MLFS) or better response by the end of cycle 4. A total of 94 patients with *KMT2A*r acute leukemias received at least one dose of study drug and were included in the safety analysis. The patient population was overall heavily pre-treated with 43.6% of patients receiving 3 or more lines of therapy prior to enrollment, and 50% having undergone prior allogeneic hematopoietic stem cell transplantation (alloHSCT). The most frequent adverse events related to treatment were nausea, differentiation syndrome (DS) seen in 26.6% of patients and QTc prolongation seen in 23.4% of patients. The most common grade 3 or higher treatment related adverse events were DS (16%), QTc prolongation (13.8%), and febrile neutropenia (13.8%). Despite the relatively high rates of DS and QTc prolongation, none of the patients discontinued study therapy because of these two adverse events. DS is an important adverse event associated with menin inhibitors that needs to be monitored. It can present in different ways with signs and symptoms including fever, hypotension, edema, weight gain, pleural effusions, pericardial effusions, dyspnea, radiographic changes on chest imaging, acute kidney injury, rash, and a rapid increase in white blood cell count. Treatment of DS includes immediate initiation of steroids and holding the menin inhibitor in cases of severe or progressive DS.

A total of 57 patients with *KMT2A*r acute leukemias were included in the interim phase 2 efficacy analysis. At a median follow up of 6.1 months, 22.8% of patients had achieved a CR + CRh which outperformed the pre-specified efficacy boundary for *KMT2A*r disease. The median duration of CR + CRh was 6.4 months. Composite complete response (CRc) for the phase 2 efficacy analysis was defined as CR + CRh + CRp + CRi and was 43.9%. ORR included CRc in addition to MLFS and partial remission and was reported to be 63.2%. Notably, MRD-negativity was achieved in 68.2% of patients with CRc who had MRD reported. A total of 38.9% of patients went on to transplant. Patients were allowed to resume revumenib after transplant, and it was resumed in 50% of patients. Based on this analysis, the *KMT2A*r portion of the study was terminated early for observed efficacy. [47] Notably, in the phase I/II AUGMENT-101 study of revumenib in R/R AML, 9 patients with AML, including one with detectable MRD, were able to resume revumenib following ASCT per protocol amendment. While 4 patients had progressive disease, the remaining 5 patients were able to continue therapy and maintained composite complete remission(CRc), including the patient with detectable MRD who later regained undetectable MRD status. Duration of therapy ranged between 23 and 588 days. Authors reported a tolerable safety profile with dose adjustments for cytopenia. These results sparked interest in the role of menin inhibitors in deepening responses in heavily pretreated patients. More clinical trials are

underway and are being designed to study MRD eradication and maintenance strategies [48].

Ziftomenib

Ziftomenib, also known as KO-539, is another small molecular inhibitor of the menin-KMT2A interaction. Preclinical studies found that ziftomenib induced differentiation and inhibited proliferation of leukemic cell lines containing a *KMT2A* rearrangement or *NPM1* mutation. [49] Ziftomenib was also found to lead to clearance of leukemia cells in mouse xenograft models derived from *KMT2A*r and *NPM1*m cells with 40% of surviving mice remaining free of detectable leukemia after four weeks [50].

These encouraging pre-clinical results led to the creation of a phase I/II study of ziftomenib in patients with R/R AML with a dose escalation phase followed by a dose expansion phase which specifically included patients with *KMT2A*r or *NPM1*m leukemias (KOMET-001). The phase 1a portion of this trial studied varying doses of ziftomenib ranging from 50 to 1000 mg daily in 30 patients with R/R AML regardless of cytogenetic or molecular profile. Clinical benefit with decreasing blast counts or decreasing hydroxyurea requirement were seen at all dose levels. The phase 1b portion of this study was a dose-validation study exploring two of the phase 1a doses (200 mg and 600 mg) in 24 patients with R/R *KMT2A*r or *NPM1*m AML to determine the optimal biologically active dose. The patient population in the phase 1b study was heavily pre-treated with a median of 2.5 prior lines of treatment in the patients receiving the 200 mg dose and a median of 4 prior lines of treatment in patients receiving the 600 mg dose. Treatment emergent adverse events of grade 3 or higher included neutropenic fever, neutropenia, anemia, and thrombocytopenia at 25% each, DS and leukocytosis at 17% each, sepsis and leukopenia at 13% each. The incidence and severity of DS initially prompted the FDA to place a hold on enrollment, but this was removed after the implementation of mitigation strategies. The severity of DS in this trial subsequently decreased. No QTc prolongation or other significant cardiac toxicity has been reported. The 200 mg dose notably yielded stable or decreasing blast counts but no overall responses. The 600 mg dose yielded a CR/CRh rate of 25%, a composite CR(CRc) of 33%, and an ORR of 41.7%. Among patients achieving CRc, 75% were MRD-negative. [51] Overall, these results are quite encouraging. PK studies of ziftomenib have determined that peak drug concentrations are seen between two and three hours after daily oral dosing and that the half-life is greater than 24 h. [52] Additional pharmacology studies involving ziftomenib have demonstrated a dose proportional exposure increase up to the RP2D of 600 mg with saturation occurring at this dose and higher doses. Ziftomenib is also not associated with clinically significant interactions with strong CYP3A4 inhibitors [53].

The phase 2 portion of this trial is ongoing, and patients with *NPM1*m R/R AML are being treated with ziftomenib 600 mg daily (NCT04067336). Ziftomenib is also being studied in newly diagnosed as well as relapsed AML patients in combination with conventional cytotoxic induction regimens as well with azacitidine, venetoclax and gilteritinib. These trials are elaborated in the subsequent sections.

DSP-5336

DSP-5336 is a small molecule inhibitor of the menin-KMT2a interaction. In pre-clinical studies, this agent has demonstrated inhibition of growth in human *KMT2A*r and *NPM1*m cell lines. [25, 54] This agent has also demonstrated decreased expression of *HOXA9* and *MEIS1* genes along with upregulated expression of the differentiation marker CD11b in *KMT2A*r AML cell lines. Treatment with DSP-5336 also yielded decreased leukemic cell burden in PDX models of *KMT2A*r and *NPM1*m AML [55].

A first in human phase I/II study of DSP-5336 is currently ongoing in patients with R/R AML, ALL, or acute leukemia of ambiguous lineage (ALAL) with a focus on patients with *KMT2A*r and *NPM1*m disease. Preliminary data was presented at the 2023 meeting of the American Society of Hematology (ASH) on the first 24 patients enrolled. This agent was well tolerated with no dose-limiting toxicities. One possible grade 4 differentiation syndrome was observed, but concurrent pneumonia and sepsis in this patient made attribution difficult. No other DS events have been reported, and no cardiac toxicities including QTc prolongation have been reported. Pharmacodynamic (PD) studies revealed rapid downregulation of menin-KMT2A target genes including *HOXA9* and *MEIS1* and an increase in the differentiation marker CD11b. The mean apparent half-life of this agent ranged from 2–5 h in patients not taking a concurrent strong CYP3A4 inhibitor and 3–7 h in patients taking a concurrent strong CYP3A4 inhibitor. The maximum serum concentration was observed within two hours of dosing this agent. A subset of patients achieved complete remission with incomplete count recovery (CRi), morphologic leukemia free state (MLFS), or stable disease. The study is ongoing to determine a recommended phase 2 dose along with additional efficacy and safety data. [56] Updated results from the study were presented at the recent EHA 2024 meeting. Of the 58 patients accrued and treated, doses ranged between 40 mg BID and 300 mg BID, with more responses noted at 140 mg BID doses. In the 140 mg BID cohort, ORR (CR + CRi + MLFS) was

45% (10/22) and the CR + CRh rate was 23% (5/22), while across all the dose levels, the ORR and CR + CRh were 32% (12/38) and 16% (6/38), respectively. No DLT were observed, and DS was reported in 3 patients, and grade 3 QTc in 1 patient [57].

Bleximenib

Bleximenib (JNJ-75276617) is a potent, highly selective inhibitor of menin-KMT2A binding. In *KMT2A*r and *NPM1*m AML cells, this agent has been demonstrated to inhibit the binding of menin to KMT2A, thereby down-regulating the expression of menin-KMT2A target genes including *MEIS1*. Treatment of these cell lines with this agent was also shown to increase expression of differentiation markers and to induce apoptosis. Exposure of pre-clinical animal AML models to Bleximenib also resulted in decreased leukemic cell burden and a dose-dependent survival benefit [58].

This promising pre-clinical data led to the development of a phase 1, open-label, dose-finding study in patients with R/R *KMT2A*r or *NPM1*m AML or ALL. Preliminary results from 58 patients were presented at the 2023 ASH annual meeting. Treatment emergent adverse events (TRAEs) were reported in 52% of patients with 29% experiencing a grade ≥ 3 adverse event. DS was notably seen in 14% of patients, with 5% of patients experiencing grade ≥ 3 DS. PD studies demonstrated down-regulation of menin-KMT2A target genes along with increased expression of markers of differentiation. Of the 41 patients with disease evaluation data, there were 12 responders across all dosing cohorts. The recommended phase 2 dose remains undetermined, and the dose escalation phase is ongoing. [59] There is another active phase 1b study assessing the efficacy and safety of Bleximenib in combination with venetoclax and azacitidine in patients with R/R *KMT2A*r or *NPM1*m AML, and preliminary results have been reported recently. The safety data set for these preliminary results included 45 patients. Grade ≥ 3 TRAEs occurred in 60% of patients with the most common being thrombocytopenia, leukopenia, and neutropenia. Notably, no DLTs were reported and cases of DS or QTc prolongation were seen. The efficacy dataset for these preliminary results included 21 patients who received doses of ≥ 50 mg bid of the drug. Composite CR rate (CR/CRh/CRi) was 48% with CR/CRh of 24% [60].

DS-1594

DS-1594 is another small molecule inhibitor of the menin-KMT2A interaction with promising pre-clinical results. Human AML and ALL cell lines with *KMT2A*r or *NPM1*m are highly sensitive to this agent. This agent was also found to be superior to cytarabine at eradicating leukemia-initiating *KMT2A*r cells in vitro. DS-1594 also demonstrated significant antileukemic activity in patient-derived xenograft models of *KMT2A*r or *NPM1*m acute leukemias in vivo [61].

This pre-clinical data led to the creation of a phase I/II trial of DS-1594 with or without mini-HCVD, azacitidine, or venetoclax in patients with R/R AML or ALL. This study is complete, but results are not yet reported (NCT04752163).

BMF-219

BMF-219 is a highly selective, covalent, irreversible inhibitor of the menin-KMT2A interaction which has demonstrated encouraging pre-clinical anti-leukemic activity in vitro and in vivo. Pre-clinical studies have also demonstrated activity of this agent in multiple myeloma (MM), chronic lymphocytic leukemia (CLL), and diffuse large B cell lymphomas (DLBCL). This is likely in part because the activity of the MYC oncoprotein is dependent on its interaction with menin, and BMF-219 has also been designed to inhibit MYC. [62] There is an ongoing phase 1 dose escalation and expansion study of this agent in patients with *KMT2A*r and *NPM1*m AML or ALL. This study also includes patients with DLBCL, MM, and CLL (NCT05153330). Preliminary results for the cohort of patients with acute leukemias have been reported. Among 26 patients, this agent was well tolerated overall with no DLTs, and no treatment discontinuations due to adverse events. Common TRAEs occurring in 10% or more of patients included DS in 13% and vomiting in 13%. The efficacy evaluable patient population for this analysis included patients receiving doses at or near those predicted to demonstrate efficacy and who had completed at least one response assessment or seven doses of therapy. This included five patients, of whom 1 experienced a CR and 1 experienced a CRi. [63] This agent has also interestingly demonstrated the ability to regenerate insulin-producing beta cells and is currently being studied in the treatment of type 1 diabetes mellitus.

A summary of characteristics and preliminary results associated with menin inhibitors in the treatment of R/R Acute Leukemias is presented in Table 1.

Clinical development of menin inhibitors in combinations

Preclinical studies indicate plausible synergy between menin blocking agents and various other approved and investigational cytotoxic and small molecule inhibitors, resulting in enhancement of antileukemic activity. Unlike the other targeted agents such as FLT3 inhibitors, IDH-1 and 2 inhibitors, which are specific to the presence of the mutated protein for their activity, menin inhibitor activity converges on modifying *HOXA/MES1* gene expression which appears to be the common pathway of

Table 1 Key Features of Menin Inhibitors with Reported Clinical Trial Results in R/R Acute Leukemias

	Significant CYP3A4 Inhibition	Differentiation Syndrome	QTc Prolongation	ORR (CR + CRh + CRp + CRi)
Revumenib [46, 47](SNDX-5613)	Yes	26.6% in phase 2	23.4% in phase 2	53% in phase 1 (*KMT2A*r and *NPM1*m) 43.9% in phase 2 (*KMT2A*r)
Ziftomenib [51](KO-539)	No	29% in phase 1b	0% phase 1a or 1b	33% at 600 mg dose of phase 1b (*KMT2A*r and *NPM1*m)
DSP-5336[56]	Yes	Possibly 1/24 (4%) in phase 1, but attribution difficult	0% in phase 1	33% among 6 patients treated on phase 1 at doses projected to be effective (*KMT2A*r and *NPM1*m)
Bleximenib (JNJ-75276617) [59]	No	14% in phase 1	1% reported in phase 1	35% in patients treated at higher dose levels in phase 1 (n = 20) (*KMT2A*r and *NPM1*m)
BMF-219[63]	Yes	13% in phase 1	0% reported in phase 1	2 out of 5 efficacy evaluable patients in phase 1 (40%) (*KMT2A*r and *NPM1*m)

CYP3A4, cytochrome P450 3A4; QTc, QT interval corrected for heart rate; ORR, overall response rate; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRp, complete remission with incomplete platelet recovery, Cri, complete Remission with incomplete count recovery; KMT2A, histone-lysine n-methyltransferase 2A; NPM1 Nucleophosmin 1

leukemogenesis and maintenance. The function of menin as a hub for chromatin regulators and gene transcription factors provides a potential for broader application and an essential target for menin inhibition, and combination therapies in the treatment of AML.

Menin inhibitors with chemotherapeutic agents

Conventional intensive induction therapy for fit, eligible patients includes a combination of cytarabine infusion and an anthracycline (7 + 3 or DA) which has been the standard of care (SOC) for several decades. Though historically CR (complete remission) rates have ranged around 80%, long term survival and cure without transplant have remained poor. [64] Persistent efforts to optimize SOC with the introduction of newer agents such as Gemtuzumab ozagomycin, or the FLT3 inhibitors (midostaurin and quizartinib) in combination with the standard induction and consolidation regimens led to improved PFS and OS for specific molecular sub-groups, such as core binding factor AML, or *FLT3*-ITD mutated AML, respectively [65–67].

As previously discussed, though *NPM1*m AML is considered as favorable risk by conventional classifications, and high CR rates and potential cures are achievable with intensive induction therapies, relapses are still quite common, approaching around 50%, particularly in older patients. [40, 68, 69] Similarly, long-term overall survival outcomes remain poor with *KMT2A*r AML even with intensive chemotherapy, due to early relapses, and there remains a huge unmet need to improve survival in these cohorts. With the encouraging results of clinical efficacy of menin inhibitors demonstrated in the phase I trials of relapsed/refractory AML with *NPM1*m or *KMT2A*r, it is imperative that these agents are tested in combination with the intensive and non-intensive induction regimens for newly diagnosed AML to improve long term survival and cures. Phase I dose escalation and expansion study KOMET-007 is actively investigating the safety and efficacy of ziftomenib in combination with 7 + 3 in newly diagnosed AML harboring *NPM1*m or *KMT2A*r. Concurrently, another phase I dose escalation and expansion study KOMET-008 is investigating the combination of ziftomenib and alternative intensive and non-tensive chemotherapy regimens Fludarabine, cytarabine and Idarubicin(FLAG-Ida), or low dose cytarabine(LDAC), respectively, for R/R AML.

It is inevitable that all the other menin inhibitor compounds will be tested in combinations with intensive and non-tensive SOC regimens in frontline as well as for R/R AML, and such trials are underway.

Combining menin-KMT2A Inhibition with BCL2 Inhibition:

Combination of menin inhibitors with Bcl-2 inhibitor in newly diagnosed or relapsed refractory AML is also an active area of investigation.

BCL-2 family proteins are anti-apoptotic proteins that inhibit cancer cell death by binding to the BH3 domain of pro-apoptotic proteins, thereby sequestering them. Venetoclax is a BH3 mimetic which blocks this interaction thereby allowing the pro-apoptotic proteins to stimulate apoptosis through cytochrome C activation in the mitochondria. [70] Venetoclax is currently approved in combination with azacitidine or low dose cytarabine for the treatment of newly diagnosed AML in patients who are ineligible for intensive chemotherapy. [71, 72] Venetoclax is also under active investigation in combination with multiple other agents in the treatment of AML. In pre-clinical studies, revumenib was found to decrease the

level of BCL-2 proteins in AML cell lines, and combined exposure to revumenib and venetoclax yielded synergistic lethality in these cells. [44] Similarly, apoptotic priming using ziftomenib also induced more potent activity of venetoclax in preclinical studies. [73] Another important observation from the study is that menin inhibitor ziftomenib could potentially re-sensitize leukemic cells to BCL2 inhibition. [73] This latter observation is particularly exciting given the emerging challenge of venetoclax-refractory AML. We await validation of these study findings. Ziftomenib is being studied in combination with venetoclax + azacitidine, venetoclax, or 7 + 3 in patients with newly diagnosed or R/R AML in KOMET-007 study (NCT05735184).

Revumenib is also being investigated in combination with venetoclax and azacitidine as frontline therapy in patients aged 60 and older with newly diagnosed *NPM1*m or *KMT2A*r AML as part of the BEAT-AML master trial. [74] Another study involving this triplet combination is being created for pediatric and young adult patients with R/R AML or acute leukemia of ambiguous lineage (ALAL) with *NPM1*m, *KMT2A*r, or other defined cytogenetic and molecular abnormalities (NCT06177067).

Combining menin-KMT2A Inhibition with FLT3 Inhibition

Mutations in the FMS-like tyrosine kinase 3 gene (*FLT3*) are present in approximately 30% of newly diagnosed AML cases. Most of these mutations are internal tandem duplication mutations affecting the juxtamembrane domain of the protein (ITD mutations) or point mutations in the tyrosine kinase domain (TKD mutations). *FLT3* ITD mutations are known to be an adverse prognostic factor while the prognostic significance of TKD mutations remains less certain. [75, 76] The FLT3 inhibitors midostaurin and quizartinib are approved in combination with intensive chemotherapy as frontline treatment for patients with *FLT3*-mutated AML. [66, 77] The FLT3 inhibitor gilteritinib is approved as monotherapy for patients with R/R *FLT3*-mutated AML. *FLT3* and *NPM1* mutations frequently co-occur in AML with one study finding concurrent *NPM1* mutations in 61% of *FLT3*-mutated AML cases. [78] *FLT3* mutations can also be seen in *KMT2A*r AML with one study of *KMT2A*r AML finding concurrent *FLT3* TKD mutations in 8% of cases and *FLT3* ITD mutations in 4% of cases. [79] The *FLT3* gene is notably a putative transcription target of the MEIS1 protein. [25, 80] In the phase 1 AUGMENT-101 trial, menin inhibition with revumenib was found to downregulate *FLT3* expression from screening through the end of cycle 1 of treatment. [81] Pre-clinical studies have also demonstrated synergy of combined menin and FLT3 inhibition in AML models harboring *NPM1* mutations and *KMT2A* rearrangements. The combination of menin inhibition and FLT3 inhibition demonstrated a greater decrement in cell viability than monotherapy with menin or FLT3 inhibition alone in human AML cell lines harboring co-mutations in *NPM1* and *FLT3*. Similarly, combination therapy with a menin inhibitor and FLT3 inhibitor was found to yield superior survival compared to monotherapy with either agent alone in mouse xenograft models of *KMT2A*r AML harboring a concurrent *FLT3* mutation. [80] Combined menin and FLT3 inhibition may therefore have the potential to improve survival outcomes in patients with *FLT3*-mutated AML harboring a concurrent *NPM1* mutation or *KMT2A* rearrangement. Early phase combination studies are currently being developed in this patient population. A phase 1 trial of revumenib combined with gilteritinib in patients with R/R *FLT3*-mtuated AML harboring a concurrent *NPM1* mutation or *KMT2A* rearrangement has recently opened to accrual (NCT06222580). Similarly, the KOMET-008, phase 1 trial also has an arm testing the combination of ziftomenib and giltertinib for FLT3-ITDm R/RAML.

Composite results and experience of all the above studies are expected to lead to yet another change in the landscape of treatment of *NPM1*m and *KMT2A*r AML towards improved outcomes.

Potential combinations with menin inhibitors for future development

DOT1L and menin inhibitors

DOT1L (disruptor of telomeric silencing 1-like) is an enzyme that catalyzes methylation of histone H3 lysine 79 (H3K79) and performs various key functions such as telomeric silencing, cell-cycle regulation, transcription, differentiation and is necessary for normal functional hematopoiesis. [82–84] The DOT1L- H3K79 methyltransferase complex interacts with the fusion partners of KMT2A to promote and maintain leukemogenesis and increased activity levels of H3K79 were observed in correlation to gene expression because of KMT2A fusion. [82, 85, 86] This observation led to preclinical and clinical investigation of DOT1L as a therapeutic target. [87] The first-in-class compound Pinometostat (formerly EPX5676) only showed modest activity in phase 1 study with 2 out of 51 patients responding, showing proof of concept, although the maximum tolerated doses could not be reached, and further dose expansion studies were not pursued. [88] Subsequent efforts and optimization led to drug discovery of second generation, novel compounds that showed more potent activity in early preclinical and PDX model studies. [89] In these studies, the novel compounds were effective in reducing leukemic cell burden and recovery of normal hematopoiesis and exhibited good safety profile. On target efficacy was

demonstrated by significant reduction of *MEIS1* and *HOXA* gene expression, as well as the H3K79 activity levels. These compounds are now in clinical trials. Additionally, due to their activity being independent of menin displacement from the chromatin, potential combinations of DOT1L and menin inhibitors and other demethylating agents are critically necessary [89].

XPO1 inhibition with menin inhibitors

Mutant *NPM1* is characterized by its aberrant translocation to the cytoplasm (*NPM1*c) upon acquisition of nuclear export signals (NES) at the c-terminus. [20] The nuclear exporter, or exportin-1 XPO1(also known as CRM1) assists in the nucleocytoplasmic shuttling of various molecules and plays a key role in the pathobiology of *NPM1*m AML whereby its interaction with XPO1 results in dislocation to cytoplasm, [38] and consequently persistent overexpression of *HOXA* cluster genes. [38] While menin inhibitors are actively being investigated in *NPM1*m leukemias, there has also been interest in interrupting the XPO1- *NPM1m* interaction utilizing XPO1 inhibitors. Selinexor is the first clinically tested XPO1 inhibitor, currently FDA approved for treating relapsed multiple myeloma, and diffuse large B cell lymphoma. However, results from the preliminary trials of selinexor monotherapy in AML were disappointing due to suboptimal efficacy and due to its intolerable adverse effects, such as anorexia. Based on these observations, a preclinical study of ziftomenib and selinexor was completed, which reported significant synergy and improved survival of combination compared to the individual agents alone, in the PDX models. [90] Other important observations from a recent preclinical study revealed that persistent XPO1 inhibition was essential for activity, and eltanexor, a second generation XPO1 inhibitor was found to be more tolerable and raised excitement for future clinical development [91].

Other potential combinations and indications

In addition to the above, drug compound screening studies in leukemia cell lines revealed that various other small molecular inhibitors are likely to have a synergistic antileukemic effect with menin inhibitors in NPM1m and KMT2Ar AML. [44, 73] Some of the notable prospective compounds include inhibitors of epigenetic regulation (LSD1 inhibitors), cell-cycle regulation (CDK4/6 inhibitors). Interestingly, all trans retinoic acid (ATRA) was also found to have a synergistic differentiating effect. [73] More validating preclinical and clinical studies are needed to test these combinations.

There is currently a clinical trial in development of revumenib in combination with venetoclax in patients with *NPM1*m, *KMT2A*r, or *NUP98*r AML in morphologic remission but with MRD ≥ 0.1% by MFC. This trial allows for patients in first remission following intensive chemotherapy or at least 2 cycles of non-intensive therapy. It will also include patients in second remission following any therapy (NCT06284486).

A summary of ongoing or upcoming trials combining menin inhibition with other therapies is presented in Table 2.

Opportunities for menin inhibitors in future clinical development

In addition to the activity of menin inhibition in the *NPM1*m and *KMT2A*r cohorts as depicted above, multiple preclinical studies and a few clinical observations point towards a much wider application of menin inhibitors in rare molecular alterations where dysregulation of *HOXA* genes and transcription is the essential component of leukemic development and progression.

NUP98 rearranged AML

Recurrent translocations resulting in the fusion of nucleoporin NUP98, present on chromosome 11p15, with histone proteins such as histone methyltransferase nuclear receptor-binding SET domain protein 1 (NSD1), are found to be sufficient to induce AML in vivo, through over expression of *HOX* genes. [92] Several other fusion partners including HOXA9 (NUP98-HOXA9), HOXA 13(NUP98-HOXA13) have also been identified. [93] These leukemias are overrepresented in pediatric populations, frequently co-occur with *FLT3*-ITD or *WT1*(Wilms tumor 1) mutations and are associated with poor survival. [93] Preclinical studies demonstrate that these leukemias are dependent on KMT2A and could be interrupted by inhibition and inactivation of KMT2A through menin inhibitors. [93–96] Similarly, other rare translocations involving NUP98 have been identified which are associated with poor prognosis and are likely susceptible to menin inhibition [97–103].

Clinical trials are now actively incorporating leukemias with *NUP98*r, along with the *NPM1*m and *KMT2A*r (NCT05326516; NCT06376162, testing revumenib and ziftomenib, respectively).

DEK-NUP214 AML

DEK is a nucleophosphoprotein which binds to the DNA and chromatin. It has been identified as an oncogene, particularly with its fusion partner NUP214, in t(6;9) AML. [104, 105] The fusion protein modulates aberrant *HOX* gene expression and is implicated in leukemogenesis. Similarly, SET-NUP214 fusion product also influences *HOX* cluster region and results in aberrant transcription. Menin inhibitors have potential therapeutic role in these rare leukemias with recurrent translocations through its

Table 2 Summary of select ongoing or planned trials evaluating menin inhibitors combined with standard of care therapies

Age	Phase	Agent	Indication and line of therapy	Combination regimen	Results
Adults > 18 years	I	Ziftomenib (KO-539) KOMET-007 (NCT05735184)	Upfront and R/R AML with *KMT2A*r and *NPM1*m	7 + 3; (Daunorubicin cytarabine); Venetoclax. Azacitidine, and Venetoclax	In accrual
Adults > 18 years	I	Ziftomenib (KO-539) KOMET-008 (NCT06001788)	R/R AML with *NPM1*m and *KMT2A*r, FLT3m	FLAG-IDA; LDAC; Gilteritinib	In accrual
Adults > 18 years	Ib	Revumenib (SNDX-5613) (NCT05886049)	Upfront AML with *NPM1*m and *KMT2A*r	7 + 3 (Daunorubicin cytarabine)	In accrual
Adults > 18 years	I/II	Revumenib (SNDX-5613) SAVE trial (NCT05360160)	Upfront AML with *NPM1*m and *KMT2A*r	ASTX (oral Decitabine-Cedazuridine)	In accrual
Pediatric and young adults 1–30 years	I	Revumenib (SNDX-5613) (NCT06177067)	Upfront AML, ALAL *KMT2A*r *NUP98*r, *NPM1*m or fusion, *PICALM::MLLT10*, *DEK::NUP214*, *UBTF*-TD, *KAT6A::CREBBP*, or *SET::NUP214*	Azacitidine and Venetoclax	In accrual
Children > 12 years, and adults	I/II	Revumenib (SNDX-5613) (NCT06284486)	CR1 or CR2 with detectable MRD *NPM1*m, or *KMT2A*r, or *NUP98*r AML	Venetoclax	Not yet open
Adults > 18 years	Ib	Revumenib (SNDX-5613) BEAT-AML[74] (NCT03013998)	Upfront AML with *NPM1*m and *KMT2A*r		Composite CR(cCR) of 100% (95% CI: 75.3–100)
Adults > 18 years	I	Revumenib (SNDX-5613) (NCT06222580)	R/R AML with *NPM1*m or *KMT2A*r, and FLT3m	Gilteritinib	In accrual
Adults > 18 years	I	Bleximenib (JNJ-75276617(60) (NCT05453903)	R/R AML with *NPM1*m or *KMT2A*r	Azacitidine and Venetoclax	Composite CR(CR/CRh/CRi) of 48% and CR/CRh of 24%

R/R, relapsed/refractory; AML, acute myeloid leukemia; ALL, Acute Lymphoblastic Leukemia; KMT2A, histone-lysine N-methyltransferase 2A; NPM1, nucleophosmin 1; ALAL, acute leukemia of ambiguous lineage; MRD, measurable residual disease; HMA, hypomethylating agent; FLAG-Ida, fludarabine, cytarabine, granulocyte colony stimulating factor-idarubicin; LDAC, low dose cytarabine; ORR, overall response rate; CR, complete remission; Ccr, composite complete remission; CRh, complete remission with partial hematologic recovery; Cri, complete remission with incomplete count recovery; FLT3m, FLT3-ITD and TKD gene mutations

negative modulation of the HOX pathway as aforementioned [106].

UBTF-TD AML

UBTF-TD (tandem duplication of upstream binding transcription factor) located on exon 13, has been found to be the third most common recurrent molecular aberration in relapsed and/or refractory pediatric AML, accounting for about 9% of the relapsed cohorts in one study, which is associated with very poor prognosis. [107]*UBTF*-TD shares similar transcriptional changes with those of *NPM1*m and *NUP98*-R AML sub-types. Importantly, *HOX* cluster genes are overexpressed across all these subtypes [108, 109]. Due to frequent associations with *FLT3*-ITD or *WT1* mutations, responses to conventional chemotherapy are sub-optimal. In a study by Barajas et al., *UBTF*-TD was found to colocalize on *HOXA/B* cluster along with the KMT2A/menin complex and contributed to the transcriptional dysregulation and leukemogenesis. In this model, primary leukemia cells were shown to be susceptible to menin inhibition (SNDX-5613). [110] This provides the proof of concept for further clinical study of menin inhibitors in these rare, yet molecularly defined subgroups of refractory adult and pediatric leukemias.

Challenges and resistance mechanisms to menin inhibitors

Limitations to the long-term durability and efficacy of most targeted therapies is the inevitable emergence of resistance mechanisms and pathways making the drugs or molecules ineffective, and disease relapses clinically.

Somatic mutations arising in the *MEN1* gene, contributing to resistance to the menin inhibitors have been identified and reported.

Important insights were obtained in a study which demonstrated for the first time in a comprehensive manner the nature of acquired, somatic *MEN1* mutations and their functional consequences. Using CRISPR-Cas9 base editing, authors identified hotspot mutations at the T349, G331, and s160 residues as the most common candidate drivers of development of resistance [16].

Targeted next generation sequencing analysis of pre- and post-treatment samples indicated development of *MEN1* mutations as the leading cause. Assessment

of archival bone marrow samples from the FIH phase I revumenib AUGMENT-101 trial revealed that resistance causing mutations were noted at an average of 2 cycles of treatment exposure [16] Mutations were found in 12 of 31 samples analyzed (38.7%), following revumenib exposure but none in the pre-exposure group. [16] In preclinical studies invitro and on PDX models, disruption of the binding affinity of revumenib is the most likely mechanism observed with the mutations at the residues. Of note, this change did not disrupt the interaction with the normal ligand of the MLL1 protein and only affected the interactions with revumenib. This led to abrogation of displacement of menin from the chromatin that was induced by the inhibitors. They observed that the target genes for menin inhibition were not adequately repressed in the mutant cases, when compared to the *MEN1*-WT cells. Also, these hotspot mutations were thought to be a class effect as they demonstrated similar effect of decreased binding affinity to other compounds, KO-539, and DS-25, etc. Continuous exposure to revumenib may lead to an increased selection of the fitter clones carrying the mutations, further driving resistance and leukemic progression.

Interestingly, an analysis of a relapsed AML patient sample without detectable *MEN1* mutation revealed distinct transcriptional programming, with attenuated expression of the KMT2A target genes *MES1* and *HOXA* at baseline, indicating existence of alternate mechanisms of resistance to menin inhibition. These mutations had similar effect on both the *KMT2A*r and *NPM1*m leukemias [16].

Second generation inhibitors that could overcome the effects of mutations and binding mechanisms, need to be developed to circumvent this emergent challenge. Combination strategies using other small molecule inhibitors, and conventional cytotoxic therapies in upfront treatment, as shown in Table 2. may likely delay or overcome some resistance pathways. [17] Clinical trials are also underway using menin inhibitors in R/R AML patients who were previously exposed to other menin inhibitor compounds and relapsed. These trial observations should answer the important question of efficacy of re-exposure to menin blockade.

Combination with IKAROS degraders

The concern about emergence of resistance mechanisms to menin inhibitor needing immediate attention is met with concerted efforts to unravel genetic vulnerabilities that could mitigate or overcome resistance pathways. Armstrong, Bourgeoius and colleagues, [111, 112] in their extensive preclinical work, demonstrated that IKAROS occupies a key component of transcriptional complex that mediates KMT2A/menin fusion driven overexpression of *HOX* family along with *MES1* genes, in an independent manner separate from the menin cofactor activity. Mezigdomide, the new generation cerebrelon E3 ubiquitin ligase modulator (CELmod) is an IKAROS degrader and retains more potent (nearly 1000-fold) single agent activity than the currently approved agents Lenalidomide, or Iberdomide, in the *KMT2A*r or *NPM1*m AML PDX models. Mezigdomide synergized with menin inhibitors resulting in prolonged survival in the preclinical studies. Interestingly, the combination therapy showed apoptosis as the predominant means of anti-leukemic activity, rather than differentiation which was the prominent mechanism of action of menin inhibitors.

IKAROS degradation with Mezigdomide when combined with revumenib delayed *MEN1* resistance mutation emergence and resensitized menin inhibitors to pre-existent *MEN1* hotspot mutations. Aside from transient leukopenia, dominated by lymphopenia, no other safety concerns were observed. Mezigdomide is already being tested in a phase III clinical trial for multiple myeloma and the findings of the current study lay compelling groundwork for combination clinical trials of menin inhibitors and Mezigdomide in *KMT2A*r and *NPM1*m AML patients both in upfront and relapsed setting, particularly following prior menin inhibitor exposure [112].

Conclusions

With the expansion of targeted treatment options for AML, we are entering a new era to provide better care of AML patients with improved efficacy, fewer toxicities, and more convenience for patients with oral compounds, essentially leading to a better quality of life. The clinical development of menin inhibitors is entering the mature stage, and these agents will change the treatment landscape for the patients with *KMT2A* re-arrangements, *NPM1* mutations, and patients with other rare genetic changes as discussed in the preceding sections. Further, combination of menin inhibitors with chemotherapy and other small molecules or targeted therapies might provide new hopes for some selected AML patients. While emergence of menin resistance is inevitable, it is also encouraging to note the development of novel pathways and compounds that can overcome and/or prevent the resistance development. The ongoing clinical development of novel targeted therapies might still have long way to go, but the future of the treatment of AML remains promising.

Abbreviations

Allo-SCT	Allogeneic hematopoietic stem cell transplantation
AML	Acute Myeloid Leukemia
BSC	Best supportive care
CI	Confidence interval
CR	Complete remission
CRc	Composite CR (includes CR, CRi, and CRp)

CRi	CR with incomplete hematologic recovery
CR_{MRD}	CR with absence of minimal residual disease
CRp	CR with incomplete platelet counts
DLT	Dose limiting toxicities
DFS	Disease-free survival
EFS	Event-free survival
FDA	US Food and Drug Administration
HR	Hazard ratio
KM	Kaplan–Meier
MDS	Myelodysplastic Syndrome
MLFS	Morphological leukemia-free state
MRD	Minimal (measurable) Residual Disease
OS	Overall survival
RFS	Relapse-free survival
SCT	Stem cell transplantation
TTE	Time-to-event
ATRA	All-Trans Retinoic Acid
CLL	Chronic lymphocytic leukemia
mCR	Bone marrow CR
HiDAC	High dose cytarabine (AraC)
HMA	Hypomethylating agent
LDAC	Low dose cytarabine
ITD	Internal tandem duplication
TKD	Tyrosine kinase domain
ORR	Overall response rate
RP2D	Recommended phase 2 dose

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