SPOTLIGHT REVIEW ARTICLE

Revumenib for patients with acute leukemia: a new tool for differentiation therapy

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Received: June 18, 2024.
Accepted: July 25, 2024.
Early view: August 1, 2024.

https://doi.org/10.3324/haematol.2022.282621

Abstract

Treatment of acute leukemia is gradually moving away from a "one-size-fits-all" approach, as scientific and clinical advances expand the arsenal of available targeted therapies. One of the recent additions is the group of menin inhibitors; oral, selective, small molecules that disrupt the interaction between the chromatin adapter menin, and an epigenetic regulator, the lysine methyltransferase 2A (KMT2A) complex. Two susceptible leukemia subtypes have been identified: (i) acute myeloid leukemia with a mutation in nucleophosmin 1 (*NPM1*), and (ii) any acute leukemia, myeloid or lymphoid, with a translocation resulting in the rearrangement of *KMT2A*. These leukemias share a distinct genetic expression, maintained by the KMT2A-menin interaction. Together they account for approximately 40% of patients with acute myeloid leukemia and 10% of patients with acute lymphoblastic leukemia. This spotlight review follows the journey of revumenib, as a representative of menin inhibitors, from bench to bedside. It focuses on the pathophysiology of leukemias sensitive to menin inhibition, delineation of how this understanding led to targeted drug development, and data from clinical trials. The important discovery of resistance mechanisms is also explored, as well as future directions in the use of menin inhibitors for treating leukemia.

Introduction

Patients with acute leukemia, whether myeloid or lymphoid, commonly have recurrent cytogenetic and molecular abnormalities that lead to a block in hematopoietic differentiation with persistence and expansion of leukemic blasts. Over the past 40 years preclinical studies have identified these alterations, illustrating how they can cause leukemia, alone and in concert. This enabled development of pharmaceuticals to inhibit pathways induced by these aberrations.[1] The examples of effective targeted therapies have fortunately become myriad and include tyrosine kinase inhibitors for *BCR-ABL*-positive acute lymphoblastic leukemia (ALL), FMS-like tyrosine kinase 3 (*FLT3*) inhibitors for *FLT3*-mutant acute myeloid leukemia (AML), and isocitrate dehydrogenase (IDH) inhibitors for *IDH*-mutant AML.[2-4] One of the more recent additions to this category is the group of menin inhibitors. Initially developed to target leukemia with rearrangements in lysine methyltransferase 2A (*KMT2A*), menin inhibition was also found to be effective in patients with AML and mutations in nucleophosmin 1 (*NPM1*) and possibly others. A New Drug Application has been submitted to the Food and Drug Administration for revumenib, formerly known as SNDX-5613, to treat patients with relapsed or refractory leukemia characterized by *KMT2A* rearrangements. This novel targeted therapy, relevant to a significant proportion of patients with acute leukemia, is the topic of this review.

KMT2A rearrangements in acute leukemias

Abnormal rearrangements leading to fusions at chromosome locus 11q23 occur in approximately 5%-10% of patients with newly diagnosed AML, 10% of patients with ALL, and 8% of patients with mixed phenotypic acute leukemia.[5] Associated with an unfavorable prognosis,[6-8] these rearrangements were previously known as mixed-lineage leukemia (*MLL*) fusions because of the propensity of patients to develop lineage switches between lymphoblastic and myeloid leukemia (and *vice versa*) during the course of their disease. Now known as *KMT2A* rearrangements (*KMT2A*-r), over 100

different fusion partners have been identified, seven of which constitute most of the cases.[7] In ALL, *KMT2A*-r are the sole genetic aberration found in the majority of infant ALL cases. In AML, these rearrangements frequently occur in patients with therapy-related acute leukemia, following exposure to cytotoxic chemotherapy.

Pathophysiology of *KMT2A*-rearranged leukemias

KMT2A is a large, multi-protein chromatin modifier. In healthy hematopoietic cells, it plays a role in maintaining adequate expression of several homeobox (*HOX*) genes by association with their promotors.[9,10] *HOX* genes, particularly from the *HOXA* cluster, are transcription factors that serve as tissue-specific master regulators of cell morphogenesis and differentiation. They have also been shown to cause differentiation arrest and cell proliferation when overexpressed in mouse models.[11] Aberrant *KMT2A*, regardless of its fusion partner, is associated with upregulation of several *HOXA* genes, and their co-factor *MEIS1*. Hence, the mere presence of any chromosomal breakage and fusion at the 11q23 locus leads to similar genetic expression, resulting in leukemogenesis.[12,13] Fortunately, this can potentially simplify the therapeutics of *KMT2A*-r leukemias with the theoretical need to target only one, rather than multiple pathways.

While the mechanism is not entirely understood, it has been shown that fusion of the N-terminus of *KMT2A*-r to a C-terminus of any of the partners results in the loss of a regulatory domain, which possibly contributes to the hyperactivity of the resulting complex. The fusion partners are also thought to play a role in *KMT2A*-r dysregulation, with a net effect of *HOXA/MEIS1* overexpression and subsequent differentiation arrest, cell proliferation and leukemic transformation (Figure 1A, B).[14]

Menin is a scaffold protein that interacts with both the wild-type and rearranged *KMT2A*, regardless of its fusion partner, via a highly preserved binding pocket in the N-terminus. In preclinical studies, menin was found to be crucial for KMT2A activity and the maintenance of *HOXA* expression, but not essential for hematopoiesis in healthy cells. In addition, it was shown to be necessary for ongoing leukemogenesis in *KMT2A*-r models, whereas its elimination resulted in immediate reversal of the leukemia phenotype in cells, with restoration of processes of maturation.[9] In the burgeoning world of molecular therapies in leukemia, it became clear that the menin-KMT2A interaction was an exciting potential therapeutic target, being both necessary and sufficient for leukemogenesis but not crucial for normal hematopoiesis.[12]

Development of menin inhibitors

Protein-protein interactions tend to be challenging targets due to their flat structure, and it is often difficult for medicinal chemistry to successfully inhibit these associations.[15] Structural and biochemical characterization of the menin-KMT2A interface established the foundation for successful pharmaceutical targeting of their interaction. In 2012, Grembecka *et al.*[12] reported on the first two molecules capable of binding menin and inhibiting its association with KMT2A, after high-throughput screening of 49,000 compounds. Since then, several orally available, small molecule menin inhibitors have been developed and rigorously studied.[15] The compound that is currently farthest along in clinical development is revumenib, an oral therapeutic formerly known as SNDX-5613, a close analog of VTP-50469. Patient-derived xenograft models treated with VTP-50469 showed rapid elimination of leukemia cells in *KMT2A*-r samples, with differentiation to mature forms and without disruption of normal hematopoiesis (Figure 1D).[16,17] Several other menin inhibitors demonstrated similar results. Early reports of *in-vitro* and *in-vivo* differences between the inhibitors are being acknowledged.[15] For example, while all appear to downregulate the *MEIS1* co-factor, suppression of *HOXA* genes is more variable. In addition, it has been suggested that the ability to degrade the menin protein, as opposed to merely displacing it, is a distinguishing factor, reported in studies with some menin inhibitors[15,18,19] but not with revumenib.[20] The clinical implications of these differences are unknown, as yet, and are an active area of research.

As the investigation of menin inhibitors continued, a striking finding emerged from testing patient-derived xenograft leukemia models harboring *NPM1* mutations, suggesting that this subtype of AML was also sensitive to menin-KMT2A disruption.

NPM1-mutated acute myeloid leukemia

NPM1 is a nuclear-based chaperone protein, important for cell growth regulation and DNA repair. Mutations in its gene are common in AML, occurring in almost a third of newly diagnosed cases of AML.[21] Patients with *NPM1* mutations (*NPM1*-m) can have a variable clinical course, dictated by co-occurring cytogenic and molecular abnormalities.[22]

The underlying mechanism of *NPM1*-m in driving leukemogenesis is less understood than that in *KMT2A*-r leukemias. The discovery of abnormally high expression of *HOXA* and *MEIS1* in *NPM1*-m AML, very similar to the genetic profile seen in *KMT2A*-r leukemias, sparked interest in the importance of the KMT2A-menin complex in this subset of leukemia.[16] It has recently been suggested that the mutated NPM1 protein interacts directly with the wild-type menin-KMT2A interaction, resulting in enhancement of *HOXA/MEIS1* transcription, similar to what occurs when *KMT2A* is rearranged.[23] Several studies have demonstrated elimination of preleukemic cells with menin inhibition in *NPM1*-m cells, suggesting that menin is crucial for leukemogenesis in this subtype as well (Figure 1C).

Phase I clinical data

Based on preclinical data, menin inhibitors entered clinical-stage investigations.

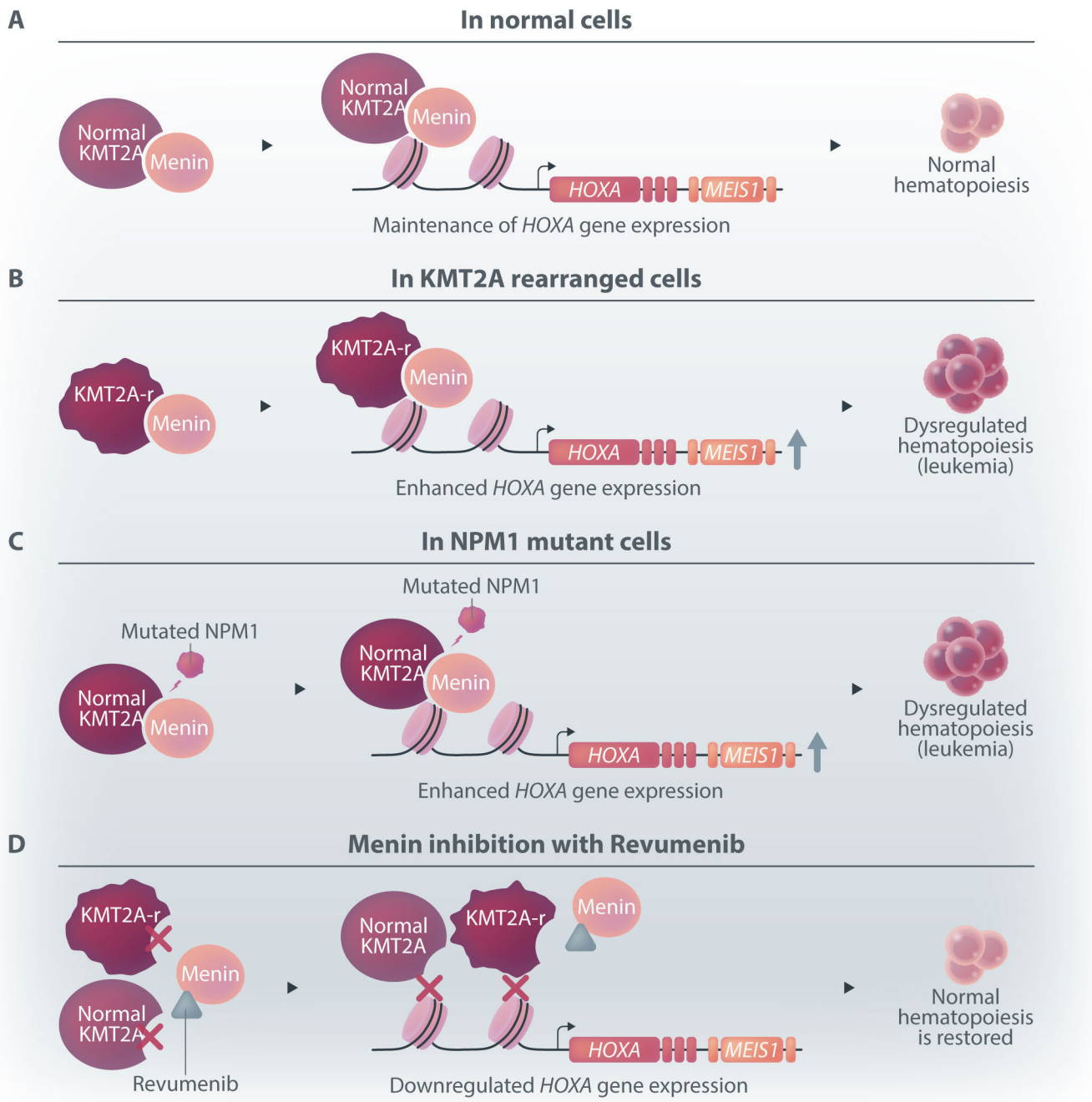

Figure 1. Leukemogenesis driven by the KMT2A-menin interaction and activity of menin inhibition. (A) In normal cells, normal KMT2A (lysine methyltransferase 2A) binds with menin via a highly conserved binding pocket at its N-terminal. This complex acts on chromatin as a transcriptional regulator of homeobox (*HOXA*) genes and their cofactor *MEIS1*, maintaining *HOXA/MEIS1* expression. The result is maintenance of normal hematopoiesis. (B) In *KMT2A* rearranged cells, rearranged KMT2A binds with menin via the same binding pocket at the N-terminal. This complex acts on chromatin, but loss of an inhibitory domain, coupled with gain of function from the fusion partner, causes upregulation of *HOXA/MEIS1* expression. The result is dysregulated hematopoiesis and differentiation arrest, leading to leukemogenesis. (C) In *NPM1* mutant cells, normal KMT2A binds with menin via the same binding pocket at the N-terminal. Mutant NPM1 (nucleophosmin 1) enhances KMT2A-menin activity (through a not entirely understood mechanism, see text), causing upregulation of *HOXA/MEIS1* expression. The result is dysregulated hematopoiesis and differentiation arrest, leading to leukemogenesis. (D) Menin inhibition. Revumenib binds to menin, inhibiting its ability to bind to KMT2A – both rearranged and wild-type – so KMT2A cannot act on chromatin. The result is downregulation of *HOXA/MEIS1* gene expression and transcription activity. Normal hematopoiesis is restored, with reversal of differentiation arrest.

The first-in-human study with revumenib was the phase I/II AUGMENT-101 trial. This was a multicenter, open-label, dose escalation study that began enrollment in 2019 among patients with relapsed or refractory acute leukemia.[24] Because of Food and Drug Administration feedback, the trial originally enrolled all patients with relapsed or refractory acute leukemia. After initially seeing no clinical activity among patients without a *KMT2A*-r or *NPM1*-m, the protocol was amended to restrict enrollment only to patients with either *KMT2A*-r or *NPM1*-m, expanding the age of patients allowed to enroll on the study down to the age of 1 month, and incorporating split dose escalation into two arms – one for patients not on a strong CYP3A4 inhibitor and the other for patients on a strong CYP3A4 inhibitor. This was because revumenib is metabolized through the CYP3A4 pathway and early pharmacokinetic studies indicated a significant difference in drug metabolism among patients who were receiving treatment with the antifungal agents posaconazole or voriconazole, which are both strong CYP3A4 inhibitors.

A total of 68 patients were enrolled: the majority had relapsed or refractory AML, 16% had ALL, and one patient

had mixed phenotypic acute leukemia. There were 46 (68%) patients with *KMT2A*-r, 14 (21%) with *NPM1*-m, and eight with neither (patients who had been enrolled prior to the protocol amendment). The median age was 42.5 years, with 60 adults and eight patients below the age of 18 years. Patients had received a median of four previous lines of therapy and 46% had relapsed after allogeneic hematopoietic stem cell transplantation (HSCT).

The overall response rate for the cohort was 53%, with a complete remission (CR) + complete remission with partial hematologic recovery (CRh) rate of 30%, and a median time to CR/CRh of 1.9 months (range, 0.9-4.9). Among patients with CR/CRh, measurable residual disease (MRD) was negative in 78%. The median overall survival for the entire cohort was 7 months, and 12 of the patients proceeded to allogeneic HSCT. The median duration of response was 9.1 months (Table 1).

In concordance with preclinical understanding of the pathophysiology of *KMT2A*-r and *NPM1*-m leukemia, transcriptional studies with RNA sequencing demonstrated downregulation of several leukemogenic genes including *HOXA/MEIS1*, with upregulation of genes related to differentiation.

Safety assessments identified prolongation of the QTc interval on electrocardiography as the only dose-limiting toxicity, occurring at any grade in 53% of the patients, and being grade 3 or 4 in 13%. Management included electrolyte repletion, withholding revumenib if the QTc was ≥481 msec and reducing the dose if the prolongation was not improved within 2 weeks. All prolongations were reversible and there were no events of ventricular arrhythmia. Other adverse events above grade 3 included febrile neutropenia (31%), thrombocytopenia (19%), sepsis (18%), and anemia (13.2%). There were no treatment discontinuations or deaths that were attributed to adverse events. Importantly, differentiation syndrome was reported in 16% of the patients, with all cases being considered grade 2. Management included prompt initiation of steroids, with addition of hydroxyurea in cases of white blood cell counts above $25x10^9$/L. The onset of differentiation syndrome was variable, between day 5 to day 41 of treatment. There were no cases that necessitated withholding revumenib (Table 2).

Interestingly, in many patients with *KMT2A*-r who achieved morphological remission after one cycle of treatment, there was continued evidence of *KMT2A* fusions, many with eventual cytogenetic clearing of *KMT2A*. In some cases, multiparameter flow cytometry demonstrated negative MRD prior to cytogenic normalization. This pattern of response may represent a differentiation process, by which blast cells gradually mature, still retaining their cytogenetic abnormality, but are no longer immunophenotypically recognized as blasts. A classic example of such a response dynamic is well described in the treatment of acute promyelocytic leukemia with differentiation agents, but has also been reported to a lesser degree following treatment with some of the novel targeted therapies for AML.[25]

Pivotal phase II clinical data

Phase II was initiated after the recommended phase II dose for revumenib had been identified. In the pivotal phase II study, patients were divided into three cohorts; patients with ALL or mixed phenotypic acute leukemia and *KMT2A*-r, patients with AML and *KMT2A*-r, and patients with AML and *NPM1*-m. The interim analysis has recently been presented as an abstract[26] and included 94 patients who were evaluated for safety (having received at least one dose of the study drug), with 57 evaluated for efficacy, 49 of whom were patients with AML. It did not include patients with *NPM1*-m, as this cohort is still enrolling. Patients in the efficacy analysis primarily had AML; 77% were above the age of 18 years and the median age was 34. The median number of prior lines of therapy was two, with 44% of the patients having received three or more lines, and 45% had already undergone allogeneic HSCT. The overall response rate was 63%, with a composite CR rate of 44% (the composite CR was defined as CR + CRh + CR with incomplete count recovery + CR with incomplete platelet recovery). Similar to phase I results, MRD negativity was found in approximately 70% of responders. Of those who responded, 39% proceeded to allogeneic HSCT (Table 1).

Following this interim analysis, the endpoint for efficacy was met in the *KMT2A*-r group, both in patients with AML and in those with ALL, and their enrollment was stopped. No new safety signals emerged in this preliminary report, with the most common adverse events being nausea (28%), differentiation syndrome (27%) and QTc prolongation (23%). Adverse events of grade 3 or higher were found in 54% of patients, 16% with differentiation syndrome, 14% with QTc prolongation and 14% with febrile neutropenia. None of the 6.4% of patients who discontinued revumenib because of adverse events did so because of differentiation syndrome or QTc prolongation (Table 2).

Taken together, these results in such a heavily pretreated cohort, whose median overall survival has been estimated at 2.4 months with a CR rate of 5%,[8] can be considered promising.

A total of 12 patients from the phase I trial continued to allogeneic HSCT after achieving remission with single-agent revumenib; most were MRD-negative prior to transplantation. For more than half of these patients, the post-revumenib HSCT was not their first transplant. As of data cutoff, nine of these 12 patients remained in remission, four for over a year. One patient, for whom this had been a third transplant, died from sepsis 2 months after the allogeneic HSCT, and two patients relapsed after their transplants.[27] From the phase II cohort, 14 patients underwent allogeneic HSCT, half of whom have continued with post-transplant maintenance with revumenib.

Several other menin inhibitors are also being investigated. Phase I clinical trials with ziftomenib (KO-539) and JNJ-75276617 are reporting what appear to be similar safety and efficacy results.[28-30] The differences between the

Table 1. Summary of the phase I and II AUGMENT-101 study.

	Phase I N=68			**Phase II – interim analysis N=94**	
Total efficacy and safety population					
Age in years, median (range)	42.5 (0.8-79)			37 (1.3-75)	
Number of arms/ cohorts	2 arms: A: without strong CYP3A4 inhibitors B: with strong CYP3A4 inhibitors			3 cohorts (interim includes only A+B): A: *KMT2A*-r AML B: ALL C: *NPM1*-m AML	
Efficacy population (results)					
	KMT2A-r, AML + ALL N=46	*NPM1*-m AML N=14	Total N=60	*KMT2A*-r AML N=49	Total N=57
Overall response*, N (%)	27 (59)	5 (36)	32 (53)	32 (65)	36 (63)
CR, N (%)	9 (20)	3 (21)	12 (20)	9 (18)	10 (17)
CR/CRh, N (%)	15 (33)	3 (21)	18 (30)	12 (24)	13 (23)
CRc**, N (%)	-	22 (45)	25 (44)		
CRp, N (%)	5 (11)	0	5 (8)	9 (18)	11 (19)
MLFS, N (%)	7 (15)	2 (14)	9 (15)	10 (20)	10 (18)
Negative MRD in patients with CR/CRh, N (%)	11/15 (73)	3/3 (100)	14/18 (78)	6/9 (67)	7/10 (70)
Negative MRD in patients with CRc, N (%)	-	-	-	13/19 (68)	15/22 (68)
Duration of response in months, median (range)	9.1 (2.7 - not reached)			6.4 (3.4 - not reached)	
Time to first morphological response in months, median (range)	0.95 (0.9-3.7)	0.99 (1-1.9)	0.95 (0.9-3.7)	-	-
Patients with any response who proceeded to HSCT, N (%)	12/32 (37)			14/36 (39)	
Follow-up in months	11.9			6.1	
OS in months, median (range)	7 (4.3-11.6)			-	

*Overall (any) response is defined as complete remission (CR) + CR with incomplete hematologic recovery (CRh) + CR with incomplete platelet recovery (CRp) + CR with incomplete count recovery (CRi) + morphological leukemia-free state + partial remission. **Composite complete response (CRc) is defined as CR + CRh + CRi + CRp. MLFS: morphological leukemia-free state; MRD: measurable residual disease; HSCT: hematopoietic stem cell transplant; OS: overall survival; *KMT2A*-r: lysine methyltransferase 2A-rearranged; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; *NPM1*-m: nucleophosmin 1-mutated.

menin inhibitors have yet to be elucidated, but should be comprehensively reviewed and compared when the much-anticipated results from phase I/II clinical trials are reported.

Resistance mechanisms

As with any new therapy, it is important to identify mechanisms of resistance as early as possible in drug development. Perner *et al.*[31] examined bone marrow specimens of patients who were treated in phase I of the AUGMENT-101 study, focusing on those who had initially responded to revumenib and subsequently relapsed. They identified several distinct somatic mutations within the multiple endocrine neoplasia type 1 (*MEN1*) gene, which codes for menin, that were not present at diagnosis and developed on revumenib treatment. Evidence of clonal expansion of these menin mutations was shown in 38.7% of evaluable patients given more than two cycles of treatment. The mutations do not appear to affect the KMT2A-menin interaction or its oncogenic properties, only its sensitivity to small molecule inhibition. When compared to cells with wild-type menin, cells with mutated menin exhibited significant resistance to different types of menin inhibitors, with varying affinities.

These findings have several important implications. First, they validate the specificity of revumenib's on-target activity.[32] Moreover, as resistance mechanisms are elucidated, efforts can be focused on developing menin inhibitors less sensitive to the selective pressure of treatment. In addition, investigational and then clinical monitoring of clonal expansion of these mutations should be considered during menin inhibitor treatment. These findings also highlight the importance of exploring combination therapy for synergism with other therapeutics that may overcome resistance. This is an active area of investigation.

Other menin-dependent leukemias

With the discovery of two different leukemias sharing a genetic profile that results in menin-dependence, the quest for additional subsets with *HOXA/MEIS1* upregulation, which may be sensitive to menin inhibition, is underway.

One such example is a rare type of AML, accounting for approximately 5% of childhood AML, characterized by rearrangements in the nuclear pore complexes 98 (*NUP98*), and associated with a dismal prognosis.[33] Some of the *NUP98* fusions involve *HOXA* genes, and mouse models have demonstrated dependency of this leukemia on the menin-KMT2A interaction. Recent *in-vivo* and *in-vitro* studies have shown suppression of leukemogenesis with menin inhibition,[34] prompting the inclusion of patients with *NUP98* rearrangements in some of the menin inhibitor

Table 2. Adverse events of interest.

Adverse event, N (%)	Phase I N=68	Phase II – interim analysis, N=94
QTc prolongation, any grade	38 (56)	22 (23)
QTc prolongation, grade ≥3	9 (13.2)	13 (14)
Differentiation syndrome, any grade	11 (16.2)	25 (27)
Differentiation syndrome, grade ≥3	-	15 (16)
Nausea, any grade	34 (50)	26 (28)
Febrile neutropenia, grade ≥3	21 (31)	13 (14)
Thrombocytopenia, grade ≥3	13 (19)	10 (10)
Anemia, grade ≥3	9 (13)	11 (12)
TRAE that led to discontinuation of treatment	-	6 (6)

TRAE: treatment-related adverse event.

Table 3. Ongoing studies with revumenib.

Trial ID	Phase	Setting	Disease	Mutation/Cytogenetics	Revumenib +	Age	Comments
NCT04065399	II	R/R	Any acute leukemia	*KMT2A*-r, *NPM1*-m, *NUP98*-r	Only revumenib	>1 month	AUGMENT-101, continuing enrollment only for *NPM1*-m
NCT05761171	II	R/R	ALL, ALAL, MPAL	*KMT2A*-r	Chemotherapy	1 month to 6 years*	Not for AML
NCT05326516	I	R/R	Any acute leukemia	*KMT2A*-r, *KMT2A*-amplification, *NPM1*-m, *NUP98*-r,	Chemotherapy	≥1 month	AUGMENT-102
NCT06222580	I	R/R	AML	*FLT3*-m + either *KMT2A*-r /*NPM1*-m / any other *HOXA/MEIS1* overexpression	Gilteritinib	≥18 years	-
NCT06177067	I	R/R	AML, ALAL	*KMT2A*-r, *NPM1*-m, *NUP98*-r, others[§]	Azacitidine + venetoclax + IT therapy	≥1 year and ≤30 years	-
NCT06229912	II	R/R	Any acute leukemia	Several subsets associated with upregulation of *HOXA*[#]	Only revumenib	≥12 years	Not including *KMT2A*-r or *NPM1*-m
NCT06284486	I/II	MRD-positive	AML	*KMT2A*-r, *NPM1*-m, *NUP98*-r	Venetoclax	≥12 years	CR1 or CR2
NCT05360160	I/II	R/R or *de novo*	AML, MPAL	*KMT2A*-r, *NPM1*-m, *NUP98*-r	Decitabine/ cedazuridine (Inqovi®) + venetoclax	≥12 years	SAVE trial
NCT05886049	Ib	*De novo*	AML	*KMT2A*-r, *NPM1*-m	Chemotherapy ("7+3")	18-75 years	-
NCT06226571	I	*De novo*	AML	*KMT2A*-r, *NPM1*-m, *NUP98*-r	Chemotherapy ("7+3")	18-75 years	-
NCT03013998	Ib	*De novo*	AML	*KMT2A*-r, *NPM1*-m	Azacitidine + venetoclax	≥60 years	BEAT-AML (*BAML-16-001-S17*)

*Had to have been initially diagnosed before the age of 2 years. [§]Several other translocations: *PICALM::MLLT10, DEK::NUP214, UBTF*-TD, *KAT6A::CREBBP*, or *SET::NUP214*. [#]Cytogenetics *KMT2A*-PTD = normal karyotype; *NPM1-MLF1* = t(3;5)(q25;q34); *NUP98*-r = 11p15 rearrangements; *SET-NUP214* = t(9;9)(q34;q34); *RUNX1-EVI1* = t(3;21)(q26;q22); *MYST3-CREBBP* = t(8;16)(p11;p13); *CDX2-ETV6* = t(12;13)(p13;q12); *CALM-AF10* = t(10;11)(p13;q14-21); *MN1-ETV6* = t(12;22)(p13;q12); *UBTF*-TD = normal karyotype. ID: identity; R/R: relapsed or refractory; *KMT2A*-r: lysine methyltransferase 2A rearranged; *NPM1*-m: nucleophosmin 1 mutated; *NUP98*-r: nucleoporin 98 rearranged; ALL: acute lymphoblastic leukemia; ALAL: acute leukemia of ambiguous lineage; MPAL: mixed phenotypic acute leukemia; AML: acute myeloid leukemia; *FLT3*-m: FMS-like tyrosine kinase 3 mutated; *HOXA*: homeobox genes; IT: intrathecal; MRD: measurable residual disease; CR1: first complete remission; CR2: second complete remission; *de novo*: newly diagnosed; "7+3": daunorubicin + cytarabine.

clinical trials. Other leukemia subsets with *HOXA/MEIS1* overexpression are also being investigated.[35]

It is possible that this genetic signature is not limited to molecularly predefined subgroups, and may also evolve throughout the course of treatment. Thus, for example, a distinct genetic phenotype has been described among patients with AML who have acquired resistance to venetoclax-based therapy, with upregulation of *HOXA* transcription evidenced at relapse but not at diagnosis.[36] This possibility significantly expands the potential population that may be susceptible to menin inhibition.

Future directions

Many cancer therapeutics are first introduced in a population of heavily pretreated patients, generally as monotherapy. Revumenib and the other menin inhibitors are no exception. After establishing safety and efficacy as a single agent in relapsed or refractory patients, the focus is now expanding to the front-line setting and to investigation with different combinations, with chemotherapy or other targeted treatments. Table 3 summarizes ongoing studies with revumenib.

Interim results are being reported for some of these trials. For example, at the European Hematology Association meeting in 2024, results were reported from a phase Ib study of induction with azacitidine and venetoclax combined with revumenib for newly diagnosed older patients with AML and either *KMT2A*-r or *NPM1*-m. According to the abstract, the first 13 patients demonstrated CR/CRh/CRi rates of 100% with undetectable MRD in the 12 who had been evaluable.[37] Differentiation syndrome and QTc prolongation occurred in over 30% of patients. Reportedly, two of the 13 patients relapsed, two proceeded to allogeneic HSCT, two died, and five continue with treatment. Several other menin inhibitors are also being studied in newly diagnosed patients, as monotherapy and in various combinations.[32] Revumenib and other menin inhibitors are being explored in maintenance therapy as well.

Combinations that have not yet reached the stage of clinical testing include targeting other components of the KMT2A complex. One such example is inhibition of a methyltransferase called known as DOT1L (disrupter of telomeric silencing 1-like). DOT1L was shown to be essential for *KMT2A*-r activity;[38] however, DOT1L inhibitors showed limited efficacy as monotherapy in a phase I clinical trial.[39] In preclinical studies, DOT1L inhibitors in combination with menin inhibitors are showing some promise.[15,40]

Conclusions

Revumenib provides an exemplary illustration of targeted therapy development, stemming from basic science and culminating with clinical trials, based on collaborative efforts, and fueled by a dire need for more effective therapies in acute leukemia.

Efficacy and safety analyses from phase I/II clinical trials with revumenib in patients with relapsed or refractory *KMT2A*-r and *NPM1*-m leukemias are promising. QTc prolongation has emerged as the primary dose-limiting adverse event and appears to be manageable. Differentiation syndrome is a rarer side effect, but important to be aware of and dealt with promptly, as described above. In severe cases revumenib should be withheld until symptom resolution.

The relatively rapid responses are particularly encouraging, together with the high rates of MRD negativity among responders, and a substantial number of patients consolidated with allogeneic HSCT. As the long-term durability of response is still unclear, allogeneic HSCT should be offered to any patient who achieves CR and is deemed fit.

Further research into mechanisms of resistance and ways to overcome them, perhaps with second-generation menin inhibitors or therapeutic combinations, is much needed. The applicability of menin inhibition to additional leukemia subsets with overexpression of *HOXA/MEIS1* is an active and fascinating area of investigation. It is possible that a clinically validated assay for *HOXA/MEIS1* expression could prove to be efficacious in guiding treatment choices or response assessment in the future. Results of clinical trials with other menin inhibitors are eagerly awaited, as are investigations into the use of menin inhibition in front-line settings and in maintenance, as monotherapy or in combination with other therapeutics.

Menin inhibitors represent both a remarkable scientific triumph, with successful inhibition of a protein-protein interaction in an epigenetic chromatin modifier, as well as a clinical accomplishment – as the first targeted therapy for *KMT2A*-r and *NPM1*-m leukemias.

Disclosures

MYS has received consultancy fees from Intellisphere, LLC. EMS has a consulting or advisory role or has received research funds from Syndax Therapeutics and Kura Oncology.

Contributions

Both authors contributed equally to the manuscript.

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