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

by Meira Yisraeli Salman and Eytan M. Stein

Received: June 18, 2024.
Accepted: July 25, 2024.


Publisher’s Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors’ final approval; the final version of the manuscript will then appear in a regular issue of the journal.
All legal disclaimers that apply to the journal also pertain to this production process.
Title: Revumenib for patients with acute leukemia: a new tool for differentiation therapy

Authors and Affiliations:

Meira Yisraeli Salman1,2, Eytan M. Stein1

1. Leukemia Service, Division of Hematologic Malignancies, Memorial Sloan Kettering Cancer Center, New York, NY, USA
2. Department of Hematology, Shaare Zedek Medical Center, Jerusalem, Israel

Corresponding Author:
Name: Eytan M. Stein, MD
Address: 545 East 73rd Street, New York, NY 10021
Email: steine@mskcc.org
Phone/Fax: (646) 608-3749

M.Y.S. received consultancy fees from Intellisphere, LLC
E.M.S. has a consulting or advisory role or has received research funds from Syndax Therapeutics and Kura Oncology

Both authors contributed equally to the manuscript.
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 are the 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: 1) Acute Myeloid Leukemia (AML) with a mutation in Nucleophosmin 1 (NPM1), and 2) 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 AML, and 10% of patients with Acute Lymphoblastic Leukemia (ALL).
This review follows the journey of revumenib, as a representative of menin inhibitors, from bench to bedside. It will focus 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 will also be explored, as well as future directions in using 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 forty years pre-clinical studies have identified these alterations, illustrating how they can cause leukemia, alone and in concert. This enabled development of pharmaceuticals for inhibition of pathways induced by these aberrations. 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. One of the more recent additions to this category are the menin inhibitors. Initially developed to target leukemia with rearrangements in the 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 (NDA) has been submitted to the Food and Drug Administration (FDA) for revumenib, formerly known as SNDX-5613, to treat relapsed or refractory (R/R) patients with 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 AML and ALL

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 (MPAL). Associated with an unfavorable prognosis, 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, 7 of which constitute most of the cases. 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-r 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 promotores. HOX genes, particularly from the HOX-A cluster, are transcription factors which serve as tissue-specific master regulators of cell morphogenesis and differentiation. They have also been shown to cause differentiation arrest and cell proliferation when over-expressed in mouse models. Aberrant KMT2A, regardless of its fusion partner, is associated with upregulation of several HOX-A 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. 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 the 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 HOX-A/MEIS1 overexpression and subsequent differentiation arrest, cell proliferation and leukemic transformation (see Figure 1.A+1.B)

Menin is a scaffold protein which 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 HOX-A 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 leukemia phenotype in cells, with restoration of maturation processes 

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. Structural and biochemical characterization of the menin-KMT2A interface established the foundation for successful pharmaceutical targeting of their interaction. In 2012, Grembecka et al. reported on the first two molecules capable of binding menin and inhibit 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. The compound that is currently farthest along in clinical development is revumenib, an oral therapeutic formerly known as SNDX-5613, a close analog to VTP-50469. Patient-derived-xenograft (PDX) 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 (see Figure 1.D). Several other menin inhibitors demonstrated similar results, Early reports of in-vitro and in-vivo differences between the inhibitors are being acknowledged. For example, while all appear to down-regulate the MEIS1 co-factor, suppression of HOX-A 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 with some menin inhibitors but not with revumenib. It is yet unknown what the clinical implications of these differences are, and it is an active area of research.

As the investigation of menin inhibitors continued, a striking finding emerged from testing PDX leukemia models harboring NPM1 mutations, suggesting that this AML sub-type was also sensitive to menin-KMT2A disruption.

NPM1-mutated AML

NPM1 is a nuclear-based chaperone protein, important for cell growth regulation and DNA repair. Mutations in this gene are common in AML, occurring in close to a third of newly-diagnosed AML. Patients with NPM1 mutations (NPM1-m) can have a variable clinical course, dictated by co-occurring cytogenic and molecular abnormalities.
The underlying mechanism of NPM1 mutations in driving leukemogenesis is less understood than in KMT2A-r leukemias. The discovery of abnormally high expression of HOX-A 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 leukemia subset. It has recently been suggested that the mutated NPM1 protein directly interacts with the wild-type menin-KMT2A interaction, resulting in enhancement of HOX-A/MEIS1 transcription, similar to what occurs when the KMT2A is rearranged. Several studies have demonstrated elimination of preleukemic cells with menin inhibition in NPM1-m cells, suggesting that menin is crucial for leukemogenesis in this sub-type as well (see Figure 1.C).

Phase I clinical data

Based on the pre-clinical data, menin inhibitors entered clinical stage investigations. The first in-human study with revumenib was the phase I/II AUGMENT-101 trial. This was a multi-center, open label, dose escalation study that began enrollment in 2019, among patients with R/R acute leukemia. Because of FDA feedback, the trial originally enrolled all patients with R/R 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, expand the age of patients allowed to enroll on the study down to the age of one month, and split dose escalation into two arms - Arm A for patients not on a strong CYP3A4 inhibitor and Arm B for patients on a strong CYP3A4 inhibitor. This, because revumenib is metabolized through the CYP3A4 pathway and early pharmacokinetic studies indicated a significant difference in the drug metabolism among patients who were on the antifungal agents posaconazole or voriconazole, both strong CYP3A4 inhibitors.

A total of 68 patients were enrolled, the majority had R/R AML, 16% had ALL, and 1 patient had MPAL. There were 46 (68%) patients with KMT2A-r, 14 (21%) with NPM1-m, 8 with neither (patients who had been enrolled prior to protocol amendment). Median age was 42.5 years, with 60 adult patients and 8 below the age of 18. Patients had a median of four previous lines of therapy, 46% were patients who had relapsed post allogeneic stem cell transplant (allo-HSCT).

The Overall Response Rate (ORR) for the cohort was 53%, with a CR/CRh (Complete Remission + Complete Remission with partial hematologic recovery) 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%. Median Overall Survival (OS) for the entire cohort was 7 months, and 12 of the patients proceeded to allo-HSCT. Median duration of response was 9.1 months.

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 HOX-A/MEIS1, with upregulation of genes related to differentiation.

Safety assessment identified prolongation of the QTc interval on ECG as the only dose-limiting toxicity, occurring at any grade in 53% of the patients, and grade 3 or 4 in 16%. There were no
grade 5 events (ventricular arrhythmia), and the grade 3 prolongations were reversible. Management included electrolyte repletion, holding of revumenib if QTc ≥ 481 msec and reducing dose if not resolved within two weeks. 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. An important identification of differentiation syndrome was reported in 16% of the patients, all were considered grade 2. Management included prompt initiation of steroids, with addition of hydroxyurea in cases of WBC above 25x10^9/L. Onset of differentiation syndrome was variable, between day 5 to day 41 of treatment. There were no cases that necessitated holding of revumenib.

Interestingly, in many patients with KMT2A-r who achieved morphologic remission after one cycle, 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 (APL) with differentiation agents, but has also been reported to a lesser degree following treatment with some of the novel targeted therapies in AML\textsuperscript{25}.

**Pivotal phase II clinical data**

Phase II was initiated after the recommended phase II dose for revumenib was identified. This study was divided into three cohorts; patients with ALL or MPAL 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\textsuperscript{26} and included 94 patients who were evaluated for safety (receiving at least one dose of study drug), 57 were 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 were primarily with AML, 77% above the age of 18, median age 34. Median prior lines of therapy was 2, with 44% having received 3 or more, and 45% were post allo-HSCT. ORR was 63%, with a composite CR (CRc) reported in 44%, defined as CR+Crh+Cr+i+Crp (Cr+i= CR with incomplete count recovery, Crp= 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 allo-HSCT (see Table 1). Following this interim analysis, the endpoint for efficacy was met in the KMT2A-r group, both AML and 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 graded 3 or higher were found in 54% of patients, 16% with differentiation syndrome, 14% QTc prolongation and 14% febrile neutropenia. None of the 6.4% who discontinued revumenib because of adverse events, were due to differentiation syndrome or QTc prolongation (see Table 2).

Taken together, these results in such a heavily pretreated cohort, whose median OS has been estimated at 2.4 months with a CR rate of 5%\textsuperscript{8}, can be considered promising.
A total of 12 patients from the phase I trial continued to allo-HSCT after achieving remission with single agent revumenib, most were MRD negative prior to transplant. For more than half of them it was not their first transplant. As of data cut-off, 9/12 remained in remission, 4 for over a year. One patient, for whom this had been a third transplant, died from sepsis two months after allo-HSCT, and two patients relapsed post-transplant. From the phase II cohort, 14 patients underwent allo-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. The differences between the 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. 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 treated with more than 2 cycles. 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 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. Firstly, they validate the specificity of revumenib’s on-target activity. 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 HOX-A/MEIS1 upregulation that may be sensitive to menin inhibition, is underway.

One such example is a rare type of AML, found in approximately 5% of childhood AML, characterized by rearrangements in the Nuclear Pore Complexes 98 (NUP98), and associated with a dismal prognosis. Some of the NUP98 fusions involve HOX-A genes, and mouse models have demonstrated dependency of this leukemia on the menin-KMT2A interaction.
Recent in-vivo and in-vitro studies have showed suppression of leukemogenesis with menin inhibition 34, prompting the inclusion of patients with NUP98 rearrangements in some of the menin inhibitor clinical trials. Other leukemia subsets with HOX-A/MEIS1 over-expression are also being investigated 35.

It is possible that this genetic signature is not limited to molecularly pre-defined sub-groups, and may also evolve throughout treatment course. Thus, for example, a distinct genetic phenotype has been described among patients with AML who have acquired resistant to venetoclax-based therapy, with upregulation of HOX-A 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 pre-treated patients, generally as monotherapy. Revumenib and the other menin inhibitors are no exception. After establishing safety and efficacy as a single agent in R/R patients, focus is now expanding to the front-line setting and to investigation with different combinations- chemotherapy or targeted. Table 3 summarizes ongoing studies with revumenib. Interim results are being reported for some of these trials. For example, at EHA 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, 2 of the 13 patients relapsed, 2 proceeded to allogeneic stem cell transplant, 2 died, and 5 continue with treatment. Several other menin inhibitors are also being studied in newly diagnosed patients, as monotherapy and with various combinations 32. Investigation of 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. Once such example is an inhibitor 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 pre-clinical 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 R/R 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 (DS) is a
rarer side effect, but important to be aware of and dealt with promptly, as described above. In severe cases revumenib should be held until resolution of DS symptoms. Particularly encouraging are the relatively rapid responses, with high rates of MRD negativity among responders, and a substantial number of patients consolidated with allo-HSCT. As long-term durability with this treatment is yet unclear, allo-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 is much anticipated, perhaps with second generation menin inhibitors or therapeutic combinations. 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 HOX-A/MEIS1 expression could prove to be efficacious in guiding treatment choice 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.
References

27. Issa GC, Cuglievan B, Stein E, et al. Outcomes after Transplant in Relapsed/Refractory KMT2Ar (MLLr) and mNPM1 (NPM1c) leukemia Patients Achieving Remissions after Menin Inhibition: SNDX-5613 (revumenib) Ph1 Experience. Blood. 2022;140(Supplement 1):914-916.
Table 1: Summary of Outcomes, Phase I + II AUGMENT-101

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of Outcomes, Phase I + II AUGMENT-101</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (efficacy + safety)</strong></td>
<td><strong>Phase I (n=68)</strong></td>
</tr>
<tr>
<td>Median age</td>
<td>42.5 (range 0.8-79)</td>
</tr>
<tr>
<td>Number of arms/cohorts</td>
<td>2 arms: A: without strong CYP3A4 inhibitors B: with strong CYP3A4 inhibitors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results (efficacy population)</th>
<th>KMT2A-r, AML + ALL (n=46)</th>
<th>NPM1-m AML (n=14)</th>
<th>Total (n=60)</th>
<th>KMT2A-r AML (n=49)</th>
<th>Total (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>27 (59%)</td>
<td>5 (36%)</td>
<td>32 (53%)</td>
<td>32 (65%)</td>
<td>36 (63%)</td>
</tr>
<tr>
<td>CR</td>
<td>9 (20%)</td>
<td>3 (21%)</td>
<td>12 (20%)</td>
<td>9 (18%)</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>CR/CRh</td>
<td>15 (33%)</td>
<td>3 (21%)</td>
<td>18 (30%)</td>
<td>12 (24%)</td>
<td>13 (23%)</td>
</tr>
<tr>
<td>CR/CRh/CRi/CRp = CRc</td>
<td>--</td>
<td>--</td>
<td>22 (45%)</td>
<td>25 (44%)</td>
<td></td>
</tr>
<tr>
<td>CRp</td>
<td>5 (11%)</td>
<td>0</td>
<td>5 (8%)</td>
<td>9 (18%)</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>MLFS</td>
<td>7 (15%)</td>
<td>2 (14%)</td>
<td>9 (15%)</td>
<td>10 (20%)</td>
<td>10 (18%)</td>
</tr>
<tr>
<td>Negative MRD % from CR/CRh</td>
<td>11/15 (73%)</td>
<td>3/3 (100%)</td>
<td>14/18 (78%)</td>
<td>6/9 (67%)</td>
<td>7/10 (70%)</td>
</tr>
<tr>
<td>Negative MRD, % from CRc</td>
<td>13/19 (68%)</td>
<td></td>
<td></td>
<td>15/22 (68%)</td>
<td></td>
</tr>
<tr>
<td>Median duration of response</td>
<td>9.1 months (2.7 - not reached)</td>
<td>6.4 months (3.4 - not reached)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to first morphologic response in months (range)</td>
<td>0.95 (0.9-3.7)</td>
<td>0.99 (1-1.9)</td>
<td>0.95 (0.9-3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proceed to HSCT, % from ORR</td>
<td>12/32 (37%)</td>
<td></td>
<td>14/36 (39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow up</td>
<td>11.9 months</td>
<td></td>
<td>6.1 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>7 months (4.3-11.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR= Complete Remission, CRh= CR with incomplete hematologic recovery, CRp= CR with incomplete platelet recovery, CRi= CR with incomplete count recovery, MLFS= Morphologic Leukemia Free State
ORR: Overall Response Rate: CR+CRh+CRi+CRp+MLFS+partial remission
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
Table 2: Adverse Events of interest

<table>
<thead>
<tr>
<th>Event</th>
<th>Phase I (n=68)</th>
<th>Phase II – interim analysis (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc prolongation in more than 20% (any grade)</td>
<td>38 (56%)</td>
<td>22 (23%)</td>
</tr>
<tr>
<td>QTc prolongation (Grade 3 or above)</td>
<td>9 (13.2%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>Differentiation syndrome (any grade)</td>
<td>11 (16.2%)</td>
<td>25 (27%)</td>
</tr>
<tr>
<td>Differentiation syndrome (Grade 3 or above)</td>
<td>--</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>Nausea in more than 20%, any grade</td>
<td>34 (50%)</td>
<td>26 (28%)</td>
</tr>
<tr>
<td>Febrile neutropenia in more than 5% (Grade 3 or above)</td>
<td>21 (31%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>Thrombocytopenia in more than 5% (Grade 3 or above)</td>
<td>13 (19%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Anemia in more than 5% (Grade 3 or above)</td>
<td>9 (13%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>TRAE that led to discontinuation of treatment</td>
<td>--</td>
<td>6 (6%)</td>
</tr>
</tbody>
</table>

TRAE: Treatment Related Adverse Event
Table 3 – Ongoing Studies with Revumenib

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Phase</th>
<th>Setting</th>
<th>Disease</th>
<th>Mutation/Cytogenetics</th>
<th>Revumenib +</th>
<th>Ages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04065399</td>
<td>II</td>
<td>R/R</td>
<td>Any acute leukemia</td>
<td>KMT2A-r, NPM1-m, NUP98-r</td>
<td>Only revumenib</td>
<td>Above 1 month</td>
<td>AUGMENT-101, continuing enrollment only for NPM1-m</td>
</tr>
<tr>
<td>NCT05761171</td>
<td>II</td>
<td>R/R</td>
<td>ALL, ALAL, MPAL</td>
<td>KMT2A-r</td>
<td>Chemotherapy</td>
<td>1 month to 6 years</td>
<td>Not for AML</td>
</tr>
<tr>
<td>NCT05326516</td>
<td>I</td>
<td>R/R</td>
<td>Any acute leukemia</td>
<td>KMT2A-r, KMT2A-amplification, NPM1-m, NUP98-r</td>
<td>Chemotherapy</td>
<td>≥ 1 month</td>
<td>AUGMENT-102</td>
</tr>
<tr>
<td>NCT06222580</td>
<td>I</td>
<td>R/R</td>
<td>AML</td>
<td>FLT3-m + either KMT2A-r /NPM1-m / any other Hox-A/Meis1 overexpression</td>
<td>Gilteritinib</td>
<td>≥ 18</td>
<td></td>
</tr>
<tr>
<td>NCT06177067</td>
<td>I</td>
<td>R/R</td>
<td>AML, ALAL</td>
<td>KMT2A-r, NPM1-m, NUP98-r, others2</td>
<td>Azacitidine + Venetoclax + IT therapy</td>
<td>≥ 1 year and ≤ 30 years</td>
<td></td>
</tr>
<tr>
<td>NCT06229912</td>
<td>II</td>
<td>R/R</td>
<td>Any acute leukemia</td>
<td>Several sub-sets associated with upregulation of Hox-A³</td>
<td>Only revumenib</td>
<td>≥ 12 years</td>
<td>Not including KMT2A-r or NPM1-m</td>
</tr>
<tr>
<td>NCT06284486</td>
<td>I/II</td>
<td>MRD-positive</td>
<td>AML</td>
<td>KMT2A-r, NPM1-m, NUP98-r</td>
<td>Venetoclax</td>
<td>≥ 12 years</td>
<td>CR1 or CR2</td>
</tr>
<tr>
<td>NCT05360160</td>
<td>I/II</td>
<td>R/R, De-novo</td>
<td>AML, MPAL</td>
<td>KMT2A-r, NPM1-m, NUP98-r</td>
<td>Decitabine/cedazuridine (Inqovi) + Venetoclax</td>
<td>≥ 12 years</td>
<td>SAVE Trial</td>
</tr>
<tr>
<td>NCT05886049</td>
<td>Ib</td>
<td>De-novo</td>
<td>AML</td>
<td>KMT2A-r, NPM1-m</td>
<td>Chemotherapy (7+3)</td>
<td>18-75 years</td>
<td></td>
</tr>
<tr>
<td>NCT06226571</td>
<td>I</td>
<td>De-novo</td>
<td>AML</td>
<td>KMT2A-r, NPM1-m, NUP98-r</td>
<td>Chemotherapy (7+3)</td>
<td>18-75 years</td>
<td></td>
</tr>
<tr>
<td>NCT03013998</td>
<td>Ib</td>
<td>De-novo</td>
<td>AML</td>
<td>KMT2A-r, NPM1-m</td>
<td>Azacitidine + Venetoclax</td>
<td>≥ 60 years</td>
<td>BEAT-AML (BAML-16-001-S17)</td>
</tr>
</tbody>
</table>

R/R = relapsed or refractory; De-novo = newly diagnosed; MRD=Measurable Residual Disease; ALL= Acute Lymphoblastic Leukemia; MPAL=Mixed Phenotypic Leukemia; ALAL= Acute Leukemia of Ambiguous Lineage; AML = Acute Myeloid Leukemia; KMT2A-r= Lysine Methyltransferase 2A rearranged; NPM1-m= Nucleophosmin 1 mutated; NUP98-r= Nucleoporin 98 rearranged; FLT3=FMS-like tyrosine kinase 3; HOX-A=Homeobox genes; 7+3= Daunorubicin + Cytarabine ; IT=intrathecal; CR1= First Complete Response; CR2=Second Complete Response

1 Had to have been initially diagnosed before the age of 2.
2 Several other translocations: PICALM::MLLT10, DEK::NUP214, UBTF-TD, KAT6A::CREBBP, or SET::NUP214
3 Cytogenetics KMT2A-PTD = Normal karyotype; NPM1-MLF1 = t(3;5)(q25;q34); NUP98r = 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
**Figure 1:** Leukemogenesis driven by KMT2A-menin interaction and activity of menin inhibition

A. In normal cells:
   a. Normal KMT2A (Lysine Methyltransferase 2A) binds with menin via a highly conserved binding pocket at its N-terminal.
   b. This complex acts on chromatin as a transcriptional regulator of Homeobox (HOX-A) genes and their cofactor MEIS1, maintaining HOX-A/MEIS1 expression.
   c. Result is maintenance of normal hematopoiesis.

B. In KMT2A rearranged cells:
   a. Rearranged KMT2A binds with menin via the same binding pocket at the N-terminal.
   b. This complex acts on chromatin, but loss of an inhibitory domain, coupled with gain of function from fusion partner, causes upregulation of HOX-A/MEIS1 expression.
   c. Result is dysregulated hematopoiesis and differentiation arrest, leading to leukemogenesis.

C. In NPM1 mutant cells:
   a. Normal KMT2A binds with menin via the same binding pocket at the N-terminal.
   b. Mutant NPM1 (Nucleophosmin 1) enhances KMT2A-menin activity (mechanism not entirely understood, see text), causing upregulation of HOX-A/MEIS1 expression.
   c. Result is dysregulated hematopoiesis and differentiation arrest, leading to leukemogenesis.

D. Menin inhibition:
   a. Revumenib binds to menin, inhibiting its ability to bind to KMT2A – both rearranged and wild-type.
   b. KMT2A cannot act on chromatin.
   c. The result is downregulation of the HOX-A/MEIS1 gene expression and transcription activity.
   d. Normal hematopoiesis is restored, with reversal of differentiation arrest.
In normal cells

- Normal KMT2A
- Maintenance of HOXA gene expression
- Normal hematopoiesis

In KMT2A rearranged cells

- KMT2A-r
- DNA
- Enhanced HOXA gene expression
- Dysregulated hematopoiesis (leukemia)

In NPM1 mutant cells

- Mutated NPM1
- Normal KMT2A
- DNA
- Enhanced HOXA gene expression
- Dysregulated hematopoiesis (leukemia)

Menin inhibition with Revumenib

- KMT2A-r
- Menin
- Revumenib
- Downregulated HOXA gene expression
- Normal hematopoiesis is restored