

Menin Inhibitor Shows Promise for Acute Leukemia

About 1 in 4 adults and children treated with revumenib, new type of targeted therapy, achieved complete remission.

January 31, 2024 By [Liz Highleyman](#)

Revumenib, an oral menin inhibitor, led to partial or complete remission in nearly two thirds of previously treated acute leukemia patients with a specific genetic alteration, according to study results reported at the [American Society of Hematology \(ASH\) annual meeting](#). In many cases, treatment with revumenib alone enabled participants to receive a curative stem cell transplant.

“Any time you have relapsed or refractory acute leukemia, the only cure is transplant, but to do that, you have to have a response,” presenter Ibrahim Aldoss, MD, of City of Hope National Medical Center, said in an [ASH news release](#). “We observed encouraging durable and meaningful responses, and many of these patients were able to proceed successfully to transplant. We have not seen this level of activity with any other available treatment in this advanced disease setting.” Furthermore, he noted, response rates were similar for adult and pediatric patients.

Revumenib (SNDX-5613), from Syndax Pharmaceuticals, interferes with the interaction between [menin](#), a scaffold protein, and histone-lysine N-methyltransferase 2A, a protein encoded by the KMT2A gene. Together, they act as an epigenetic regulator to control gene expression. Two genetic alterations—KMT2A rearrangement and nucleophosmin 1 (NPM1) mutation—can trigger the production of leukemia cells. Menin inhibitors bind to menin and halt this process, returning blood cells to normal. Several other menin inhibitors are in development, including Kura Oncology’s ziftomenib and Johnson & Johnson’s JNJ-75276617.

The Phase I/II AUGMENT-101 trial ([NCT04065399](#)) is evaluating revumenib in people with relapsed or refractory (nonresponsive) acute leukemia with a KMT2A rearrangement or NPM1 mutation. The study includes both adults and children, most of whom have tried multiple prior therapies.

The KMT2A rearrangement is present in up to 15% of children and adults with acute leukemias and around 80% of infants with acute lymphocytic leukemia (ALL). The NPM1 mutation is more common, occurring in up to 30% of patients with acute myeloid leukemia (AML). People with these alterations [tend to have very aggressive cancer](#), according to senior study investigator Eytan Stein, MD, of Memorial Sloan Kettering Cancer Center.

Last year, Stein and colleagues [reported data](#) from 60 evaluable patients with a KMT2A rearrangement or NPM1 mutation in the Phase I part of the study; most of them had AML. Revumenib led to remission in a majority and a complete response in a third. Twelve people who experienced remission went on to receive a stem cell transplant, and seven were still in remission for more than six months at the end of this analysis. The median duration of response was about nine months before the [development of resistance](#). However, as described in a poster at this year's ASH meeting, some patients continued on revumenib maintenance therapy for more than a year after stem cell transplantation, and a few remain in remission.

Also at ASH 2023, Aldoss reported more recent results from the Phase II part of the trial. Cohort 2A includes adults and children with KMT2A-rearranged ALL or mixed phenotype acute leukemia, Cohort 2B includes people with KMT2A-rearranged AML and Cohort 2C includes people with NPM1-mutated AML. Based on dosing data from Phase I, participants receive the selected dose of revumenib as a twice-daily pill with no additional leukemia drugs. In this single-arm trial, there is no comparison group taking a placebo or other medications.

In the first two cohorts, 94 patients with KMT2A-rearranged AML (86%), ALL (12%) or mixed acute leukemia (2%) were treated with revumenib. A majority were female, nearly a quarter were children and three quarters were white. Most had previously relapsed after at least one prior salvage regimen, and nearly half had already undergone stem cell transplantation.

In an analysis of 57 evaluable patients, the overall response rate, meaning complete or partial remission, was 63%. Among those assessed for minimal residual disease (MRD) status, 68% were MRD negative. Thirteen people (23%) achieved complete remission (CR) or complete remission with partial hematologic recovery (CRh), meaning blood cell counts returned to adequate levels. Ten of the 13 complete responders were assessed for MRD status; seven of them were MRD negative.

The CR/CRh rate was the same for adults and children. Responses were seen in all major subgroups regardless of age, the number of prior treatments or previous stem cell transplantation. Fourteen responders (40%) underwent a stem cell transplant, and half of them received posttransplant revumenib maintenance therapy.

The median time to reach CR/CRh was about two months. The median duration of response at the time of the analysis was six months, and six of the 13 complete responders (46%) remained in remission; follow-up is ongoing. But looking at the entire group, the median overall survival time was just eight months, reflecting the dire prognosis for people with these types of acute leukemia.

Revumenib was generally safe and well tolerated, and side effects were "manageable," Aldoss reported. About a quarter of patients (26%) experienced QTc prolongation, a reversible heart rhythm abnormality. More than a quarter (28%) developed [differentiation syndrome](#), a rapid release of cytokines as cells return to normal that usually can be managed with anti-inflammatory medications. However, just 9% of adverse events led to revumenib dose reduction, and 6% led to treatment discontinuation; no one stopped due to QTc prolongation, differentiation syndrome or

low blood cells counts.

Based on these interim findings, the study's Independent Data Monitoring Committee recommended that enrollment of patients with KMT2A-rearranged acute leukemias should be halted, as efficacy has been demonstrated for this population.

In [last year's look-ahead](#) to trends in blood cancer for 2023, Leukemia and Lymphoma Society chief scientific officer Lee Greenberger, PhD, predicted that menin inhibitors "could be the next new class of drug approved to treat some forms of acute myeloid leukemia," potentially in two to five years. However, he cautioned that combination therapy will be needed because AML is marked by many mutations that can change over time, leading to drug resistance.

In other ASH 2023 presentations, researchers reported early data from clinical trials combining revumenib with various standard-of-care therapies for people with KMT2A-rearranged or NPM1-mutated acute leukemias.

In the SAVE AML trial, an analysis of nine people with relapsed or refractory AML or mixed phenotypic acute leukemia who received revumenib, venetoclax (Venclexta) and decitabine/cedazuridine (Invoqi) showed that 78% achieved complete remission, and 67% became MRD negative. An analysis of 13 newly diagnosed AML patients in the BEAT AML trial, which is evaluating revumenib plus venetoclax and azacitidine (Vidaza or Onureg) as first-line therapy, showed that 100% had complete remission by various measures, and 92% became MRD negative. The AUGMENT-102 trial is evaluating revumenib plus fludarabine/cytarabine chemotherapy for predominantly pediatric AML patients. In an analysis of 12 participants treated with the higher of two revumenib doses, 33% achieved complete remission. In all these studies, revumenib was well tolerated with no new safety signals beyond those observed with the standard-of-care regimens alone, according to a [Syndax press release](#).

"The potential to safely combine with standard of care positions revumenib to become a cornerstone of treatment across a range of acute leukemia populations," said Syndax CEO Michael Metzger.

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