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Menin inhibition with revumenib for NPM1-mutated (NPM1m) relapsed or refractory acute myeloid leukemia: AUGMENT-101

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Abstract:
The prognosis for relapsed or refractory (R/R) nucleophosmin 1–mutated (NPM1m) acute myeloid leukemia (AML) is poor and represents an urgent unmet medical need. Revumenib, a potent, selective menin inhibitor, was recently approved for the treatment of R/R acute leukemia with a KMT2A translocation in patients aged ≥1 year based on results from the phase 1/2 AUGMENT-101 study. Here we present results from patients with R/R NPM1m AML enrolled in the phase 2 portion of AUGMENT-101. Enrolled patients received revumenib with or without a strong CYP3A4 inhibitor every 12 hours in 28-day cycles. Primary endpoints were rate of complete remission (CR) or CR with partial hematologic recovery (CRh; CR+CRh), and safety and tolerability. Secondary endpoints included overall response rate (ORR) and duration of response. As of September 18, 2024, 84 patients received ≥1 dose of revumenib. Median age was 63 years; 1 patient was aged <18 years. The protocol-defined efficacy-evaluable population for the primary analysis included 64 adult patients (≥3 prior lines of therapy, 35.9%; prior venetoclax, 75.0%). The CR+CRh rate was 23.4% (1-sided P=.0014); the ORR was 46.9%. Median duration of CR+CRh was 4.7 months. Five of 30 responders (16.7%) proceeded to hematopoietic stem cell transplant (HSCT); 3 resumed revumenib after HSCT. Treatment-related adverse events led to treatment discontinuation in 4 patients (4.8%). Revumenib demonstrated clinically meaningful responses in this heavily pretreated, older population with NPM1m AML, including remissions that enabled HSCT. The safety profile of revumenib was consistent with previously reported results. This trial was registered at www.clinicaltrials.gov as NCT04065399.

Conflict of interest: COI declared - see note

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Clinical trial registration information (if any): NCT04065399; clinicaltrials.gov

TITLE (limit: 115/120 characters, including spaces)

Menin inhibition with revumenib for *NPM1*-mutated (*NPM1*m) relapsed or refractory acute myeloid leukemia: AUGMENT-101

RUNNING HEAD (limit: 46/50 characters, including spaces)

Revumenib for *NPM1*m relapsed or refractory AML

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Data sharing statement

Syndax Pharmaceuticals, Inc, is committed to data sharing that advances science and medicine while protecting patient privacy. The data supporting the findings of this study, including the study protocol and statistical analysis plan, are available within the article and its Data Supplement. Any additional data requests from qualified scientific researchers are available upon reasonable request. Deidentified participant data are available to request after all trial prespecified analyses have been completed and after the indication studied has been approved in the United States or European Union, whichever is later. Access is provided after a research proposal has been approved by an appropriate review committee and after receipt of a signed data sharing agreement. Additional details may be requested at https://syndax.com/contact-us/.

KEY POINTS (1 to 2 required; limit: 140 characters, including spaces)

- Revumenib exhibited a promising complete response rate and manageable safety profile in patients with *NPM1*-mutated relapsed/refractory AML (140/140 characters)
- Responses were seen across subgroups regardless of co-mutations, prior HSCT, or number of prior lines of therapy (115/140 characters)

ABSTRACT (current: 244 words; limit: 250 words)

The prognosis for relapsed or refractory (R/R) nucleophosmin 1–mutated (*NPM1*m) acute myeloid leukemia (AML) is poor and represents an urgent unmet medical need. Revumenib, a potent, selective menin inhibitor, was recently approved for the treatment of R/R acute leukemia with a *KMT2A* translocation in patients aged ≥1 year based on results from the phase 1/2 AUGMENT-101 study. Here we present results from patients with R/R *NPM1*m AML enrolled in the phase 2 portion of AUGMENT-101. Enrolled patients received revumenib with or without a strong CYP3A4 inhibitor every 12 hours in 28-day cycles. Primary endpoints were rate of complete remission (CR) or CR with partial hematologic recovery (CRh; CR+CRh), and safety and tolerability. Secondary endpoints included overall response rate (ORR) and duration of response. As of September 18, 2024, 84 patients received ≥1 dose of revumenib. Median age was 63 years; 1 patient was aged <18 years. The protocol-defined efficacy-evaluable population for the primary analysis included 64 adult patients (≥3 prior lines of therapy, 35.9%; prior venetoclax, 75.0%). The CR+CRh rate was 23.4% (1-sided *P*=.0014); the ORR was 46.9%. Median duration of CR+CRh was 4.7 months. Five of 30 responders (16.7%) proceeded to hematopoietic stem cell transplant (HSCT); 3 resumed revumenib after HSCT. Treatment-related adverse events led to treatment discontinuation in 4 patients (4.8%). Revumenib demonstrated clinically meaningful responses in this heavily pretreated, older population with *NPM1*m AML, including remissions that enabled HSCT. The safety profile of revumenib was consistent with previously reported results. This trial was registered at www.clinicaltrials.gov as NCT04065399.

INTRODUCTION

Acute myeloid leukemia (AML) is a clonal hematopoietic malignancy, characterized by the rapid growth of myeloid stem cells that fail to differentiate into functional cells.[1] Nucleophosmin 1 (*NPM1*) mutations, the most common genetic aberrations in adult AML, are found in about 28% of new cases.[2] NPM1 is an intracellular chaperone protein predominantly found in the nucleolus with roles vital for cellular processes, such as genetic stability.[3,4] Mutations in NPM1 lead to cytoplasmic translocation of the protein; however, a fraction of mutant NPM1 remaining in the nucleolus interacts with the lysine methyltransferase 2A (KMT2A)–menin complex and influences oncogenic gene transcription.[4-6] In *NPM1*-mutated (*NPM1*m) AML, as in *KMT2A*-rearranged (*KMT2A*r) acute leukemias, the KMT2A-menin interaction leads to aberrant homeobox (*HOX*)-mediated and Meis homeobox 1 (*MEIS1*) oncogenic expression that blocks stem cell differentiation.[4-8] Selectively blocking the interactions between KMT2A and menin reverses the aberrant expression of these critical leukemogenic targets (ie, *MEIS1* and *HOX*).[7,8]

Currently, no therapies are approved for patients with *NPM1*m AML. While *NPM1*m AML displays favorable response rates with intensive chemotherapy or venetoclax plus hypomethylating agents in frontline settings,[2,9,10] there is no standard of care or targeted therapies in case of relapse or refractory disease.[11] Upon recurrence, the disease becomes difficult to treat, especially if the disease-free interval is short.[12] After first-line therapy, patients with *NPM1*m AML often have improved outcomes compared with those without *NPM1*m[9,10]; however, approximately 50% of adult patients with *NPM1*m AML experience progressive disease or death.[13,14] Responses to salvage therapy can be achieved after first relapse,[15,16] but time to second relapse, response to subsequent salvage therapies, and overall survival (OS) shorten with each subsequent line of therapy—similar to patients with *NPM1* wild-type AML.[17] Outcomes after venetoclax failure are poor, with overall response rates (ORRs) ranging from 6% to 23%.[18-21] Co-mutations are also very common in *NPM1*m AML, including at relapse; fms-related receptor tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD), DNA methyltransferase 3 alpha (*DNMT3A*), and WT1 transcription factor (*WT1*) co-mutations are associated with poorer outcomes and an increased incidence of relapse after achieving measurable residual disease (MRD) negativity.[22] The poor outcomes associated with relapsed or refractory (R/R) *NPM1*m AML, combined with limited treatment options and high relapse rates, highlight the need for new therapies to improve patient outcomes.

Revumenib is a first-in-class, potent, oral menin inhibitor that selectively blocks the *KMT2A*-menin interaction,[8,23] resulting in downregulation of *MEIS1* and *HOX* expression and consequently enabling terminal differentiation of leukemic to normal hematopoietic cells.[8,23-25] Revumenib was recently approved for the treatment of R/R *KMT2A*-translocated acute leukemia in patients ≥1 year of age based on data from AUGMENT-

101 (NCT04065399), an ongoing phase 1/2 study in patients with R/R *KMT2A*r acute leukemia or R/R *NPM1*m AML.[26] Here we report the primary efficacy analysis of revumenib in patients with R/R *NPM1*m AML from the phase 2 portion of the AUGMENT-101 study.

METHODS

Study design and patients

AUGMENT-101 is a phase 1/2, open-label, dose-escalation and -expansion study of revumenib in adult and pediatric (>30 days old) patients with documented R/R *NPM1*m or *KMT2A*r acute leukemias. *NPM1* mutation status was determined by local testing for eligibility; all treated patients with *NPM1*m AML were in the safety analysis population. Patients with centrally confirmed *NPM1* mutation (using Focus Myeloid panel, Flagship Biosciences, Inc, or *NPM1* Mutation assay, Invivoscribe, Inc) and ≥5% blasts in bone marrow at baseline within 28 days prior to the start of study treatment were considered efficacy evaluable. As prespecified in the statistical analysis plan and protocol, the first 64 adult patients in the study who met these criteria were included in the adult efficacy-evaluable population. There was no restriction on the number or types of prior therapies. Co-mutation testing was performed locally but was not required. Patients with central nervous system (CNS) disease at the most recent relapse were eligible if no active CNS disease remained present at the start of study therapy. Ongoing intrathecal therapy or prophylaxis was allowed concurrent with revumenib. See the Protocol for full inclusion and exclusion criteria.

Treatment

Revumenib was administered orally in capsule, tablet, or liquid formulation every 12 hours (q12h) in 28-day continuous cycles. The recommended phase 2 dose of revumenib was 270 mg (160 mg/m^2 if body weight <40 kg) q12h or, given that revumenib is a cytochrome P450 3A4 (CYP3A4) substrate, 160 mg (95 mg/m^2 if body weight <40 kg) q12h if patients were also receiving a strong CYP3A4 inhibitor.[25] Revumenib treatment was continued until lack of response after up to 4 cycles, disease progression, unacceptable adverse events (AEs), withdrawal of consent, investigator decision, or loss to follow-up (see Protocol for further details).

Patients who achieved composite complete remission (CRc; complete remission [CR] + CR with partial hematologic recovery [CRh] + CR with incomplete hematologic recovery [CRi] + CR with incomplete platelet recovery [CRp]), morphological leukemia-free state (MLFS), or partial remission (PR) were allowed to undergo allogeneic hematopoietic stem cell transplant (HSCT) without leaving the study. Revumenib was stopped before the HSCT conditioning regimen but, per a protocol amendment (approved on September 24, 2021, prior to enrollment of all patients in this analysis), could be

resumed as maintenance therapy after allogeneic HSCT if the patient was between 30 and 180 days post HSCT, had successful engraftment, did not have acute or chronic graft-vs-host disease that required systemic immunosuppression, and remained in CRc.

Study endpoints and assessments

The primary endpoints were the rate of CR+CRh and the evaluation of safety and tolerability of revumenib. Secondary endpoints included rate of CRc, ORR (CRc+MLFS+PR), time to response (defined as the number of months from the date of first dose to the date of initial response [CR+CRh or CRc]), duration of response (DOR), event-free survival (EFS; defined as the number of months from the date of first dose to the date of first documented relapse/progression or death, whichever occurred first; **Table S1**), and OS. Responses were assessed by the investigators according to the European LeukemiaNet 2017 response criteria.[27] CRp was defined as all CR criteria except for platelet count <100x10^9/L).. Details on secondary endpoints and response definitions are available in the Protocol.

AEs were collected from the time of the first revumenib dose until 30 days after the last dose, including maintenance therapy, and were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. AEs of special interest included differentiation syndrome (an expected on-target effect of inducing differentiation of leukemia cells into normal hematopoietic cells), prolongation of the corrected QT interval by Fridericia (QTcF) interval of grade ≥2, and peripheral neuropathy. Study investigators received guidelines for managing AEs of special interest (see Supplemental Methods). Hydroxyurea for cytoreduction, intrathecal chemotherapy for CNS prophylaxis, and steroids for differentiation syndrome were allowed during the study.

Gene transcription analysis

Transcriptional changes following 1 cycle of revumenib were evaluated for target genes of interest. Samples from bone marrow aspirates (RNA) were isolated using the Maxwell RSC simplyRNA kit (Promega Corporation) and quantified using the NanoDrop 2000 (Thermo Fisher Scientific Inc). Total RNA quality and molecular weight distribution were evaluated using the Agilent 2100 Bioanalyzer (Agilent Technologies, Inc). Multiplex gene analysis was performed using a custom-designed QuantiGene assay (Thermo Fisher Scientific Inc). Seven genes of interest (*MEIS1*, *HOXA9*, *PBX3*, *FLT3*, *CD11b*, *CD14*, and *CD13*) and 5 housekeeping genes (*PGK1*, *B2M*, *RPL13A*, *POLR2A*, and *HPRT1*) were included in the custom assay. *PGK1* and *HPRT1* were selected as housekeeping genes for analysis because of variability seen in the other housekeeper genes. The raw data were analyzed using QuantiGene Plex Data Analysis software

(Thermo Fisher Scientific Inc) to generalize normalized expression data. All steps were performed by Flagship Biosciences.

Co-mutations by next-generation sequencing (NGS) and response

Baseline genetic alterations were evaluated to determine if a particular co-mutation was associated with response. Bone marrow–derived DNA from adult patients in the protocol-defined efficacy-evaluable population, collected before the start of revumenib treatment, was genomically profiled using the Focus Myeloid panel conducted by Flagship Biosciences. The gene coordinates used were part of the standard TruSight™ Myeloid Sequencing Panel (Illumina, Inc., San Diego, CA, USA) **(Table S2)** , which is commercially available.[28] The analytical sensitivity of this assay is 5% at >500× read depth, with 100% accuracy demonstrated during validation.[28] Somatic short variants were identified and analyzed according to the manufacturer's instructions.

Statistical analysis

The sample size was driven by the primary analysis in the adult efficacy-evaluable population. The number of adult efficacy-evaluable patients in the R/R *NPM1*m AML population evaluated in each stage, as well as the minimum number of responders needed to continue to the next stage, were determined based on the minimax version of Simon's 2-stage design,[29] with 90% power and a 1-sided significance level of 2.5%. Sixty-four adult efficacy-evaluable patients were included in the R/R *NPM1*m AML population for this primary analysis. The primary hypothesis test used a null hypothesis of a 10% CR+CRh rate. A CR+CRh rate >10% was considered the lower threshold for antileukemic activity.

Safety was summarized for all patients with R/R *NPM1*m AML who received ≥1 dose of revumenib (safety population). No formal statistical hypothesis testing for safety analyses was conducted. Time-to-event endpoints were estimated using the Kaplan-Meier method, and descriptive statistics were used for other clinical or laboratory variables, with subgroup analyses performed for efficacy.

Co-mutations by NGS and response

Statistical analysis of co-mutation data was performed by Fios Genomics Ltd. to identify associations between clinical outcomes and gene mutations. In all analyses, an applied threshold of unadjusted $P<.05$ defined an association as statistically significant.

Mutation data provided the input for statistical hypothesis testing, in which features that were significantly different between sample groups were identified. Statistical comparisons were performed using Fisher exact test. Significance values (*P* values)

were adjusted for multiple testing by controlling the false discovery rate. For each binary comparison (eg, responders vs nonresponders), a positive log2 odds ratio indicated a positive association between responders and the presence of a mutation relative to nonresponders, while a negative log2 odds ratio indicated a positive association between nonresponders and the presence of a mutation relative to responders.

Ethics statement

The study was conducted in accordance with principles outlined in the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The protocol and amendments were approved by the relevant authorities and institutional review board or ethics committee at participating centers, and all patients or their legal guardians provided written informed consent. Important changes to the methods to expand eligibility were to adjust the design to include children and to allow patients to resume revumenib treatment post transplant. Throughout the study, an independent data monitoring committee monitored safety and efficacy according to predefined parameters detailed in the protocol and provided recommendations for continuing or terminating the study. MLA, GCI, EMS, RMS, TK, ET, JSB, ARS, LY, YC, and RGB analyzed the data; all authors had access to the clinical trial data. The details of the study design are provided in the study protocol.

RESULTS

Patient baseline demographics and characteristics

From October 1, 2021, to September 18, 2024, 84 patients with R/R *NPM1*m AML in 9 countries received ≥1 dose of revumenib and comprised the safety population (**Figure 1**). At baseline, the median age was 63 years (range, 11-84); 83 patients (98.8%) were adults (**Table 1**). *FLT3*-ITD and -tyrosine kinase domain (TKD) co-mutations were identified in 31.0% and 7.1% of patients, respectively; other co-mutations included isocitrate dehydrogenase 1 (*IDH1*; 13.1%), isocitrate dehydrogenase 2 (*IDH2*; 11.9%), tumor protein 53 (*TP53*; 4.8%), and *RAS* (3.6%). Patients were heavily pretreated, with 34.5% having received ≥3 prior lines of therapy (median, 2 [range, 1-7]); 73.8% received prior venetoclax, 38.1% received prior FLT3 inhibitor therapy, 6.0% received prior IDH1 inhibitor therapy, and 6.0% received prior IDH2 inhibitor therapy. Almost one-fourth of patients (23.8%) had undergone a prior HSCT, 8.3% had extramedullary disease at enrollment, and 2.4% had active CNS disease at their most recent relapse. The primary efficacy analysis included 64 efficacy-evaluable adults with centrally confirmed *NPM1*m AML and ≥5% blasts in bone marrow at baseline (**Figure 1**)**.**

Safety

Treatment-emergent AEs (TEAEs) were experienced by 83 patients (98.8%; grade ≥3, 77 [91.7%]; **Table S3**). A total of 66 of 84 patients (78.6%) experienced ≥1 treatment-related AE (TRAE) with revumenib (**Table 2**); 50 patients (59.5%) experienced a grade ≥3 TRAE. Dose modifications occurred in 64 patients (76.2%), with 56 patients (66.7%) requiring dose interruptions (**Table S4**). TRAEs leading to dose reduction occurred in 10 patients (11.9%) (**Table 2**). Four patients (4.8%) discontinued revumenib due to a TRAE (cardiac arrest, differentiation syndrome, osteomyelitis [n=1 patient each], and 1 patient experienced QTcF prolongation and syncope). One patient (1.2%) died because of a treatment-related event (cardiac arrest); the investigator reported 2 possible causes (intracranial hemorrhage or arrythmia), and an autopsy was not performed (**Table 2**).

Treatment-emergent differentiation syndrome (any grade) occurred in 16 patients (19.0%), of whom 9 (10.7%) had a grade 3 event, 2 (2.4%) had a grade 4 event, and none had a grade 5 event. All 16 patients were treated with corticosteroids, with the addition of hydroxyurea for associated leukocytosis in 5 patients. Differentiation syndrome led to interruption of revumenib in 7 patients and discontinuation in 1 patient with a grade 3 event. The median time to initial onset was 10 days (range, 4-34), and median duration of the initial event of differentiation syndrome was 14.5 days (range, 3-57).

Treatment-emergent QTcF prolongation (any grade) occurred in 36 patients (42.9%), of whom 17 (20.2%) had a grade 3 event, 2 (2.4%) had a grade 4 event, and none had a grade 5 event. QTcF prolongation was managed per treatment guidelines as described in the Supplement; the median times to initial onset and median duration of the initial event were 8 days (range, 1-84) and 4 days (range, 1-14), respectively. QTcF prolongation resulted in dose interruption in 18 patients, dose reduction in 8, and discontinuation in 1.

Grade ≥3 treatment-related cytopenias and electrolyte imbalances, which occurred in ≥5% of patients, included anemia (12 [14.3%]) and thrombocytopenia (8 [9.5%]). Revumenib dose reductions due to cytopenias were infrequent (thrombocytopenia, 1 [1.2%]; neutropenia, 1 [1.2%]; white blood cell count decreased, 1 [1.2%]), and no patient discontinued due to grade ≥3 cytopenias or electrolyte imbalances.

Efficacy

Primary efficacy: adults

The study met the primary efficacy endpoint for patients with R/R *NPM1*m AML, with 15 of 64 adult patients achieving CR or CRh (CR+CRh, 23.4%; 95% CI, 13.8-35.7; 1-sided *P*=.0014; **Table 3**). The rate of CRc was 29.7% (95% CI, 18.9-42.4).The ORR was 46.9% (95% CI, 34.3-59.8).

The median time to first response was 1.84 months (range, 0.9-4.6), and the median time to first CR or CRh was 2.76 months (range, 1.8-8.8; **Figure 2**). The median time to MRD negativity for those achieving CR+CRh was 2.79 months (range, 1.8-4.7; **Table 3**). Changes in neutrophil and platelet counts in patients achieving CR or CRh are shown in **Figure S1**.

While the study was not powered to evaluate differences among subgroups, responses were observed across the various subgroups assessed. Notably, responses were seen regardless of prior HSCT (CR+CRh rate [yes vs no], 21.4% [3/14; 95% CI, 4.7-50.8] vs 24.0% [12/50; 95% CI, 13.1-38.2]) and number of prior lines of therapy (CR+CRh rate [1 vs 2 vs ≥3 prior lines of therapy], 25.0% [4/16; 95% CI, 7.3-52.4] vs 20.0% [5/25; 95% CI, 6.8-40.7] vs 26.1% [6/23; 95% CI, 10.2-48.4]; **Figure 3**). CR+CRh rates were numerically similar in adults <65 years of age (7/31; 22.6%; 95% CI, 9.6-41.1) and ≥65 years of age (8/33; 24.2%; 95% CI, 11.1-42.3). The CR+CRh rate was 16.7% (8/48; 95% CI, 7.5-30.2) and 43.8% (7/16; 95% CI, 19.8-70.1) in patients with and without prior venetoclax exposure, respectively (**Figure 3**). In patients with prior *FLT3* inhibitor use, the CR+CRh rate was 13.3% (4/30; 95% CI, 3.8-30.7), the CRc rate was 20.0% (95% CI, 7.7-38.6; CR, n=4; CRp, n=1; and CRi, n=1), and the ORR was 40.0% (95% CI, 22.7-59.4%). Patients with *IDH1* or *IDH2* co-mutations with *NPM1* mutation at baseline achieved CR+CRh at higher rates than the overall population (75.0% [6/8] and 50.0% [4/8], respectively).

Across all responders, the median duration of CR+CRh was 4.7 months (95% CI, 1.2-8.2; **Figure 4A**), and the median duration of CRc was 4.7 months (95% CI, 1.9-8.2). Across all 64 adult efficacy-evaluable patients, the median EFS was 3.0 months (95% CI, 2.0-3.8; **Figure 4B**) and the median OS was 4.0 months (95% CI, 2.5-7.2; **Figure 4C**); the median OS in the 15 CR+CRh responders was 23.3 months (95% CI, 7.2-NR).

Pediatric efficacy

One pediatric patient (female, 11 years old) was not included in the protocol-defined primary efficacy analysis consisting of the adult efficacy-evaluable population but did otherwise meet the efficacy-evaluable criteria. This patient was diagnosed 98.2 months (8.2 years) before enrolling in the study, had an *IDH2* mutation at baseline, had received 4 prior treatments (including venetoclax), and had undergone a prior HSCT. This patient was treated for 17.6 weeks and achieved a CRh response. Treatment continued for 2 cycles after CRh was achieved, at which point the patient relapsed and withdrew consent from the study.

Efficacy and safety in patients undergoing HSCT

Among 64 adult efficacy-evaluable patients who achieved an overall response (n=30), 5 (16.7%) underwent an allogeneic HSCT while in remission. Three of the 5 HSCT

recipients resumed revumenib after HSCT. The duration of maintenance therapy with post-transplant revumenib ranged from 2 to 60 weeks, with no patients remaining on revumenib post HSCT at the time of the data cutoff (discontinued due to AE [fatigue], progressive disease, or other reason [relapsed disease]; n=1 each; **Figure 2**). No instances of differentiation syndrome, grade ≥2 QTcF prolongation, or grade 5 TEAEs were observed among the patients who resumed revumenib post HSCT.

Translational analysis: co-mutations and prior therapies

Gene transcription analysis: transcriptional changes in responders and nonresponders and co-mutations by NGS and response

Transcriptional changes were evaluated in 18 adult efficacy-evaluable patients with available RNA at baseline and after 1 cycle of revumenib treatment. Following 1 cycle of revumenib, downregulation of most leukemogenic target genes (*MEIS1*, *PBX3*, and *FLT3*) was observed. *HOXA9* expression was upregulated in all 5 nonresponders and downregulated in 10 of 13 responders. Expression of genes associated with differentiation (*CD11b*, *CD14*, and *CD13*) was markedly increased regardless of response (**Figure S2**).

Co-mutations were evaluated in the 54 adult efficacy-evaluable patients whose *NPM1* mutation status was centrally confirmed by Flagship Biosciences on the Focus Myeloid NGS panel. In the NGS co-mutation vs response analysis, when responders were compared with nonresponders, no mutations were significantly associated with response or lack of response. However, *IDH1* mutation was significantly associated with CR+CRh (*P*=.0084) or CRc (*P*=.0013) response vs nonresponse, and *STAG2* mutation was significantly associated with nonresponse when compared with patients who achieved a CRc response (*P*=.049; **Figure S3**).

DISCUSSION

No currently approved therapies specifically target the *NPM1* mutation in AML, in either the frontline or relapsed setting. Patients with *NPM1*m AML that relapses or is refractory to initial therapies have a poor prognosis.[12,17,30] Historical data suggest that only 48% and 10% of patients achieve CR when receiving high- or low-intensity treatments, respectively, as first salvage therapy, with CR rates decreasing with each subsequent line (second salvage CR, 30% and 8%; subsequent salvage CR, 11% and 2%, respectively).[17] These dismal outcomes highlight the urgent need for improved therapies, especially for patients unable to tolerate intensive chemotherapy and/or patients whose disease relapses after treatment with venetoclax. Novel therapies, such as those directed at menin, including revumenib—the first US Food and Drug Administration–approved menin inhibitor—ziftomenib[31,32] and bleximenib[33], provide a promising approach to targeting leukemogenesis driven by the KMT2A-menin interaction.[26,32,34,35]

Patients with R/R *NPM1*m AML who enrolled in the phase 2 part of AUGMENT-101 had high-risk baseline characteristics. In the safety population, the median age was 63 years (range, 11-84), and the median number of prior lines of therapy was 2 (range, 1-7), with 34.5% of patients having received ≥3 prior lines of therapy and 19.0% having received ≥4. Importantly, 73.8% of treated patients had previously received a venetoclax-containing treatment regimen, 38.1% had received a prior FLT3 inhibitor, and 23.8% had undergone a prior HSCT, with 9.5% having received >1 prior HSCT. At study entry, approximately 57.1% of patients had disease refractory to the most recent line of therapy. This clinical trial patient population is representative of the real-world population of patients with R/R *NPM1*m AML for whom standard-of-care therapies failed and/or who relapsed after HSCT, both of which are characteristics that confer poor outcomes independent of the presence of an *NPM1* mutation.

The phase 2 portion of AUGMENT-101 met the primary endpoints in patients with R/R *NPM1*m AML. The CR+CRh rate achieved with revumenib in the adult efficacy-evaluable population was 23.4% (95% CI, 13.8-35.7; 1-sided *P*=.0014). Almost half of patients achieved a response (ORR, 46.9%), which allowed a subset of patients to proceed to HSCT. The 1 pediatric patient treated achieved CRh. Efficacy of revumenib monotherapy was observed across various subgroups, including by age, prior lines of therapy, prior venetoclax, and prior FLT3 inhibitor exposure. Notably, the CR+CRh rates in patients receiving prior venetoclax or a FLT3 inhibitor were 16.7% and 13.3%, respectively. While these CR+CRh rates are lower than the 23.4% observed in the overall population with R/R *NPM1*m AML in this study, they were numerically greater than historical CR rates with salvage therapies after failure of venetoclax or a FLT3 inhibitor (4.2% and 6%, respectively).[18,19] The median time to first CR+CRh was 2.8 months (range, 1.8-8.8), and the median DOR was an additional 4.7 months (95% CI, 1.2-8.2) thereafter. These clinical data confirm the oncogenic role between menin and KMT2A in *NPM1*m AML and demonstrate that disruption of this interaction with revumenib, an orally administered targeted inhibitor, provides meaningful antileukemic activity.

The safety profile of revumenib in R/R *NPM1*m AML was consistent with that seen in other acute leukemias and was predictable, with AEs primarily related to the underlying disease, mechanism of action based on preclinical characterization of revumenib, and characteristics of this population (older aged and heavily pretreated). QTc prolongation and differentiation syndrome were known possible AEs with revumenib, and both were manageable. Differentiation syndrome was managed using steroids and hydroxyurea when necessary and appears to be a class effect of menin inhibition.[36]

Gene expression analysis showed that *HOXA9* expression increased in all nonresponders but decreased in most responders over the first cycle of revumenib treatment. This observation suggests that changes in *HOXA9* expression may be an early biomarker of revumenib response in *NPM1*m AML.[37] The co-mutation analysis showed that several genes were mutated exclusively or predominantly in responders or

nonresponders; however, none reached statistical significance when responders were compared with nonresponders. Notably, *IDH1* was significantly associated with both CR+CRh and CRc responses vs nonresponse; *STAG2* expression was significantly associated with nonresponse vs CRc response. These results should be interpreted with caution as bulk gene expression analysis is not able to distinguish between changes in cell composition and changes in gene expression in equivalent cells. Further studies are warranted to assess these possible relationships.

This single-agent study of revumenib has limitations that should be noted. Co-mutations were assessed locally at the discretion of the investigator, which may have resulted in inconsistencies due to variability in reporting. In addition, assessments of genetic markers of revumenib resistance have not yet been performed. Lastly, the nature of single-arm clinical trials has inherent limitations compared with studies with control arms.

These results build upon the first evidence from AUGMENT-101 that demonstrated that a targeted treatment could benefit patients with R/R *NPM1*m AML.[25] Treatment with revumenib, a selective, first-in-class menin inhibitor, continued to provide a meaningful clinical benefit and manageable safety profile for patients with R/R *NPM1*m AML. Additional studies assessing revumenib in combination for R/R *NPM1*m AML (SAVE [NCT05360160]) and in the frontline newly diagnosed AML setting for fit (SNDX-5613-0708 [NCT06226571]) and unfit (Beat AML [NCT03013998]; EVOLVE-2 [NCT06652438]) patients are ongoing.[38-41] In conclusion, these results suggest that revumenib has the potential to provide substantial improvement over currently available treatments in patients with R/R *NPM1*m AML.

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AUTHORSHIP CONTRIBUTION

G.C.I., M.J.T., J.F.D., R.M.S., E.M.S., J.S.B., A.R.S., L.Y., and R.G.B. contributed to the conception, design, or planning of the study; M.L.A., G.C.I., E.M.S., R.M.S., T.K., E.T., J.S.B., A.R.S., L.Y., Y.C., and R.G.B. contributed to data analysis and interpretation; M.L.A., A.C.S., A.Z., C.S.G., C.P., A.E.P., G.C.I., A.B., D.S.D., M.W.M.K., I.M., H.D., Y.C., L.Y., R.G.B., and A.R.S. contributed to drafting the manuscript; all authors contributed to the critical review of the manuscript, contributed to the provision of study materials or data acquisition, approved the final manuscript for submission, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST DISCLOSURE

M.L.A. reports advisory board participation for Syndax Pharmaceuticals, Inc; **M.J.T.** reports institutional funding from Syndax Pharmaceuticals, Inc, AbbVie, Merck, and Nurix; and honoraria from AbbVie; **J.F.D.** reports funding from MacroGenics, Wugen, BioLineRx, and Incyte; royalties/licenses from Magenta Therapeutics and Wugen; and consulting fees from RiverVest, Vertex Pharmaceuticals, and BioLineRx; **E.M.S.** reports consulting fees from AbbVie, Agios, Astellas, AstraZeneca, Celgene, Daiichi Sankyo, Genentech, Gilead, Jazz, and Servier; **A.C.S.** reports research funding from AbbVie, Amgen, Astellas, Bristol Myers Squibb, GlycoMimetics, Kite/Gilead, Loxo, Novartis, Pfizer, Servier, and Syndax Pharmaceuticals, Inc; and advisory board participation for AbbVie, Amgen, Astellas, Bristol Myers Squibb, Jazz, Kite/Gilead, Novartis, Paladin, Pfizer, Servier, and Teva; **A.Z.** reports consultancy fees from AbbVie, Astellas, Pfizer, Novartis, and Johnson & Johnson; honoraria from AbbVie, Astellas, Novartis, and Johnson & Johnson; and travel expenses from AbbVie, Novartis, Johnson & Johnson, and Takeda; **S.d.B.** reports research funding from Auron; consultancy for Servier, BMS, GSK, Syndax Pharmaceuticals, Inc., Remix, Auron, and Rigel; honoraria from Bristol Myers Squibb, AbbVie, Servier, Jazz Pharmaceuticals, Astellas, and Loxo; and travel fees from AbbVie, Servier, Johnson & Johnson, Daiichi Sankyo, and Rigel; **C.B.** reports honoraria from AbbVie, Astellas Pharma, Bristol Myers Squibb, Jazz Pharmaceuticals,

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TABLES

Table 1. Baseline demographics and clinical characteristics

Parameter	Adult efficacy-evaluable population (n=64)	Safety population (N=84)
Age, median (range), years	65 (19-84)	63 (11-84)
<18, n (%)	0	1 (1.2)
≥18 to <65, n (%)	31 (48.4)	42 (50.0)
≥65, n (%)	33 (51.6)	41 (48.8)
Sex, n (%)		
Female	38 (59.4)	50 (59.5)
Male	26 (40.6)	34 (40.5)
Race, n (%)		
Black or African American	6 (9.4)	7 (8.3)
Asian	4 (6.3)	5 (6.0)
White	38 (59.4)	48 (57.1)
Multiple	1 (1.6)	1 (1.2)
Other	3 (4.7)	3 (3.6)
Unknown	9 (14.1)	17 (20.2)
Missing	3 (4.7)	3 (3.6)
Disease status at baseline, n (%)		
Primary refractory	5 (7.8)	7 (8.3)
Relapsed refractory	35 (54.7)	41 (48.8)
Early untreated relapse*	17 (26.2)	23 (27.4)
Late untreated relapse†	7 (10.8)	13 (15.5)
Extramedullary disease, n (%)	4 (6.3)	7 (8.3)
Co-occurring mutations, n (%)		
FLT3-ITD	22 (34.4)	26 (31.0)
FLT3-TKD	4 (6.3)	6 (7.1)
RAS	2 (3.1)	3 (3.6)
TP53	4 (6.3)	4 (4.8)
Previous therapies		
Median (range)	2 (1-7)	2 (1-7)
≥3, n (%)	23 (35.9)	29 (34.5)
≥4, n (%)	14 (21.9)	16 (19.0)
Venetoclax, n (%)	48 (75.0)	62 (73.8)
HSCT, n (%)	14 (21.9)	20 (23.8)
>1 prior HSCT, n (%)	4 (6.3)	8 (9.5)
FLT3 inhibitor, n (%)	30 (46.9)	32 (38.1)
IDH1 inhibitor, n (%)	3 (4.7)	5 (6.0)
IDH2 inhibitor, n (%)	4 (6.3)	5 (6.0)

FLT3, fms-related receptor tyrosine kinase 3; HSCT, hematopoietic stem cell transplant; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; ITD, internal tandem duplication; TKD, tyrosine kinase domain; TP53, tumor protein p53.

*Early untreated relapse was defined as <1 year from initial complete remission to relapse.

†Late untreated relapse was defined as ≥1 year from initial complete remission to relapse.

Table 2. Summary of AEs based on treatment-emergent AE incidence ≥15% and treatment-emergent SAE incidence ≥5%

	Safety population (N=84)			
	Treatment-emergent AE		Treatment-related AE	
All terms, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
AE	83 (98.8)	77 (91.7)	66 (78.6)	50 (59.5)
AE (treatment emergent), incidence ≥15%				
QTcF prolongation	36 (42.9)	19 (22.6)	34 (40.5)	18 (21.4)
Vomiting	31 (36.9)	3 (3.6)	17 (20.2)	1 (1.2)
Febrile neutropenia	29 (34.5)	28 (33.3)	12 (14.3)	11 (13.1)
Hypokalemia	27 (32.1)	8 (9.5)	7 (8.3)	2 (2.4)
Nausea	24 (28.6)	5 (6.0)	14 (16.7)	2 (2.4)
Anemia	23 (27.4)	21 (25.0)	13 (15.5)	12 (14.3)
Diarrhea	23 (27.4)	5 (6.0)	6 (7.1)	1 (1.2)
Fatigue	20 (23.8)	4 (4.8)	8 (9.5)	1 (1.2)
Pyrexia	20 (23.8)	1 (1.2)	3 (3.6)	0
Epistaxis	18 (21.4)	4 (4.8)	3 (3.6)	2 (2.4)
Peripheral edema	18 (21.4)	0	4 (4.8)	0
Differentiation syndrome	16 (19.0)	11 (13.1)	15 (17.9)	11 (13.1)
Dyspnea	16 (19.0)	3 (3.6)	4 (4.8)	1 (1.2)
Pneumonia	16 (19.0)	12 (14.3)	3 (3.6)	1 (1.2)
Dysgeusia	14 (16.7)	0	10 (11.9)	0
Platelet count decreased	14 (16.7)	14 (16.7)	9 (10.7)	9 (10.7)
Thrombocytopenia	14 (16.7)	12 (14.3)	8 (9.5)	8 (9.5)
Abdominal pain	13 (15.5)	2 (2.4)	3 (3.6)	0
Arthralgia	13 (15.5)	1 (1.2)	1 (1.2)	0
Constipation	13 (15.5)	0	1 (1.2)	0
Decreased appetite	13 (15.5)	1 (1.2)	5 (6.0)	1 (1.2)
Sepsis	13 (15.5)	13 (15.5)	0	0
Serious AE	64 (76.2)	—	31 (36.9)	—
Serious AE (treatment emergent), incidence ≥5%				
Febrile neutropenia	18 (21.4)	—	7 (8.3)	—
Differentiation syndrome	11 (13.1)	—	11 (13.1)	—
Sepsis	11 (13.1)	—	0	—
Pneumonia	7 (8.3)	—	1 (1.2)	—
Anemia	6 (7.1)	—	3 (3.6)	—

QTcF prolongation	6 (7.1)	—	6 (7.1)	—
AE leading to dose reduction	10 (11.9)	—	10 (11.9)	—
AE leading to dose interruption*	56 (66.7)	—	42 (50.0)	—
AE leading to treatment discontinuation	25 (29.8)†	—	4 (4.8)	—
AE leading to death	21 (25.0)	—	1 (1.2)‡	—

AE, adverse event; QTcF, corrected QT interval by Fridericia; TRAE, treatment-related adverse event.

*This includes patients who had interruptions and restarted treatment on the same day as directed by protocol for electrolyte management and/or QTcF prolongation.

†Patients may have experienced >1 treatment-emergent AE leading to discontinuation. Of these 25 patients in the safety population who discontinued treatment due to an AE, 21 were in the efficacy-evaluable population (**Figure 1**).

‡The treatment-related AE leading to death was classified as cardiac arrest; however, the investigator reported 2 possible causes of death: intracranial hemorrhage (patient had profound thrombocytopenia since baseline [platelet counts, 6-13 G/L]) or arrhythmia; an autopsy was not performed.

Table 3. Efficacy response

Parameter	Adult efficacy-evaluable population (n=64)
ORR, n (%)	30 (46.9)
95% CI	34.3-59.8
Time to first response, median (range), months	1.84 (0.9-4.6)
Duration of first response, median (95% CI), months	4.4 (1.2-5.6)
CR+CRh rate, n (%)	15 (23.4)
95% CI	13.8-35.7
P value, 1-sided	.0014
Time to first CR+CRh, median (range), months	2.76 (1.8-8.8)
Duration of CR+CRh, median (95% CI), months	4.7 (1.2-8.2)
CRc, n (%)	19 (29.7)
95% CI	18.9-42.4
Best response, n (%)	
CR	12 (18.8)
CRh	3 (4.7)
CRi*	2 (3.1)
CRp*	2 (3.1)
MLFS	9 (14.1)
PR	2 (3.1)
No response	19 (29.7)
Disease progression	5 (7.8)
Other†	10 (15.6)
	)
No. of responders who proceeded to HSCT, n/N (%)	5/30 (16.7)
Resumed treatment after HSCT, n/N (%)	3/5 (60.0)

CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; MRD, measurable residual disease; ORR, overall response rate; PCR, polymerase chain reaction; PR, partial remission.

*CRi per European LeukemiaNet 2017 was defined as all CR criteria except for residual neutropenia (<1x10^9/L) or thrombocytopenia (<100x10^9/L). CRp was defined as all CR criteria except for platelet count <100x10^9/L.[27]

†Includes patients not evaluable due to death (n=9, none were treatment-related) or withdrew consent (n=1) before a postbaseline disease assessment could be obtained.

FIGURE LEGENDS

Figure 1. Patient flow diagram.

AE, adverse event; HSCT, hematopoietic stem cell transplant; NPM1m, nucleophosmin 1 mutation; PD, progressive disease; PR, partial remission; QTcF, corrected QT interval by Fridericia.

*These patients started treatment after the 64th adult efficacy-evaluable patient and thus did not have the opportunity for ≥6 months of follow-up.

†Mutational status was reviewed locally for eligibility in phase 2 and centrally confirmed for inclusion in the efficacy-evaluable population.

‡Twenty-one patients in the adult efficacy-evaluable population experienced treatment-emergent AEs that led to study drug discontinuation (patients may have experienced >1 treatment-emergent AE leading to discontinuation): sepsis (n=5); septic shock (n=2); acute respiratory failure, agitation, cardiac arrest, cardiorespiratory arrest, cerebral hemorrhage, death, febrile neutropenia, intracranial hemorrhage, osteomyelitis, posterior reversible encephalopathy syndrome, QTcF prolongation, stress cardiomyopathy, sudden death, syncope, and upper gastrointestinal hemorrhage (each n=1).

§Other reasons for discontinuation included patient moved to hospice (n=2) and patient wished to discontinue due to worry over AEs (n=1).

‖Five patients proceeded to HSCT while in remission during the study, including 1 patient who was taken off study due to AE but subsequently proceeded to HSCT 6 weeks later while still in remission without any intervening antileukemia therapy.

Figure 2. Swimmer plot of duration of treatment (adult efficacy-evaluable population).

CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; PR, partial remission.

Figure 3. Forest plot of CR+CRh rate by subgroup (adult efficacy-evaluable population).

AML, acute myeloid leukemia; CNS, central nervous system; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DNMT3A, DNA methyltransferase 3 alpha;

ECOG, Eastern Cooperative Oncology Group; FLT3, fms-related receptor tyrosine kinase 3; HSCT, hematopoietic stem cell transplant; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; ITD, internal tandem duplication; PS, performance status; TKD, tyrosine kinase domain; TP53, tumor protein p53.

*One patient with an ECOG PS of 3 was included. This patient had an ECOG PS of 0-2 at screening per protocol but an ECOG PS of 3 on cycle 1 day 1. The most recent status prior to the first dose of study treatment was used for baseline characteristics.

†Primary refractory disease was defined as no CR or CRi after 2 courses of intensive induction treatment, excluding patients with death during aplasia or death due to indeterminate cause.[27] Refractory relapse was defined as disease remission (CR or CRi) in response to prior therapy followed by relapse but without attaining a remission with reinduction therapy. Early untreated relapse was defined as occurring <1 year after prior remission. Late untreated relapse was defined as occurring ≥1 year after remission.

Figure 4. Kaplan-Meier curves for (A) duration of CR+CRh response (n=15), (B) event-free survival in the adult efficacy-evaluable population (n=64), and (C) overall survival in the adult efficacy-evaluable population (n=64).

CR, complete remission; CRh, complete remission with partial hematologic recovery; EFS, event-free survival; OS, overall survival.

*EFS was defined as the number of months from the date of first dose to the date of first documented relapse/progression or death, whichever occurred first.

†OS was defined as the percentage of at-risk patients who did not experience an event of death up to that time point.

Figure 1

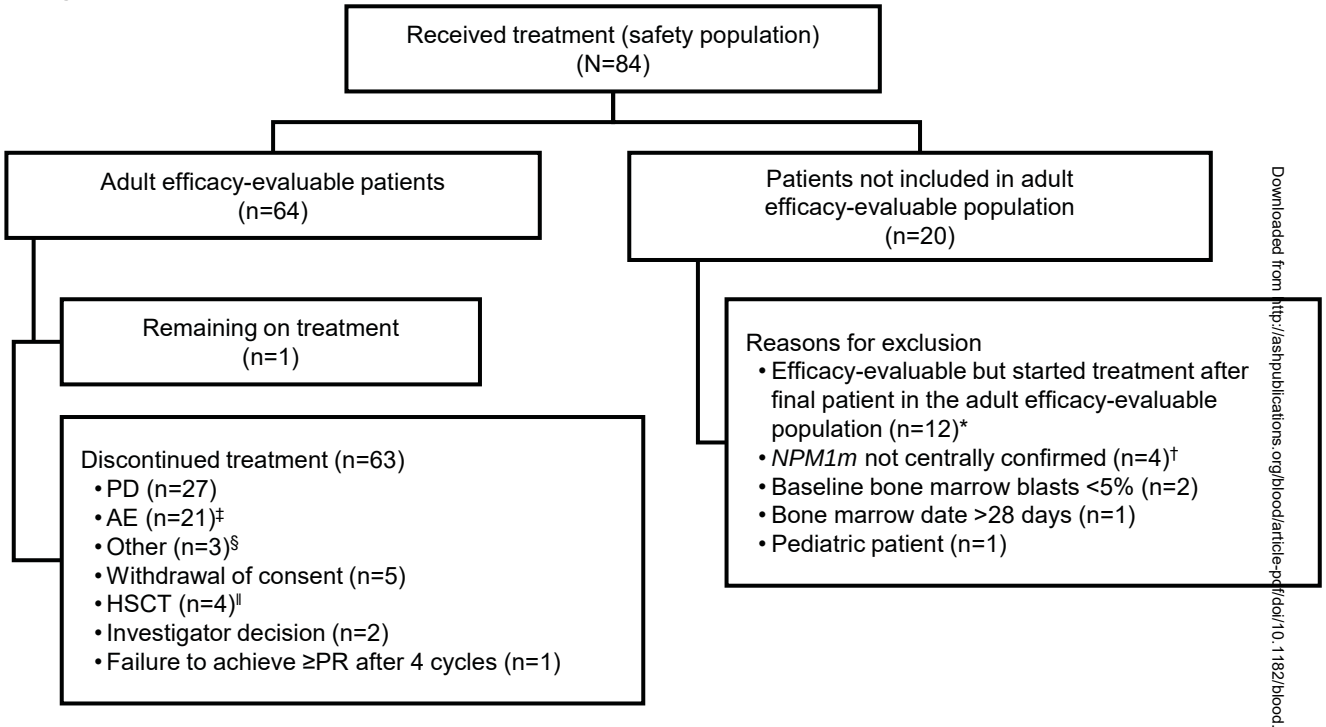


Figure 2

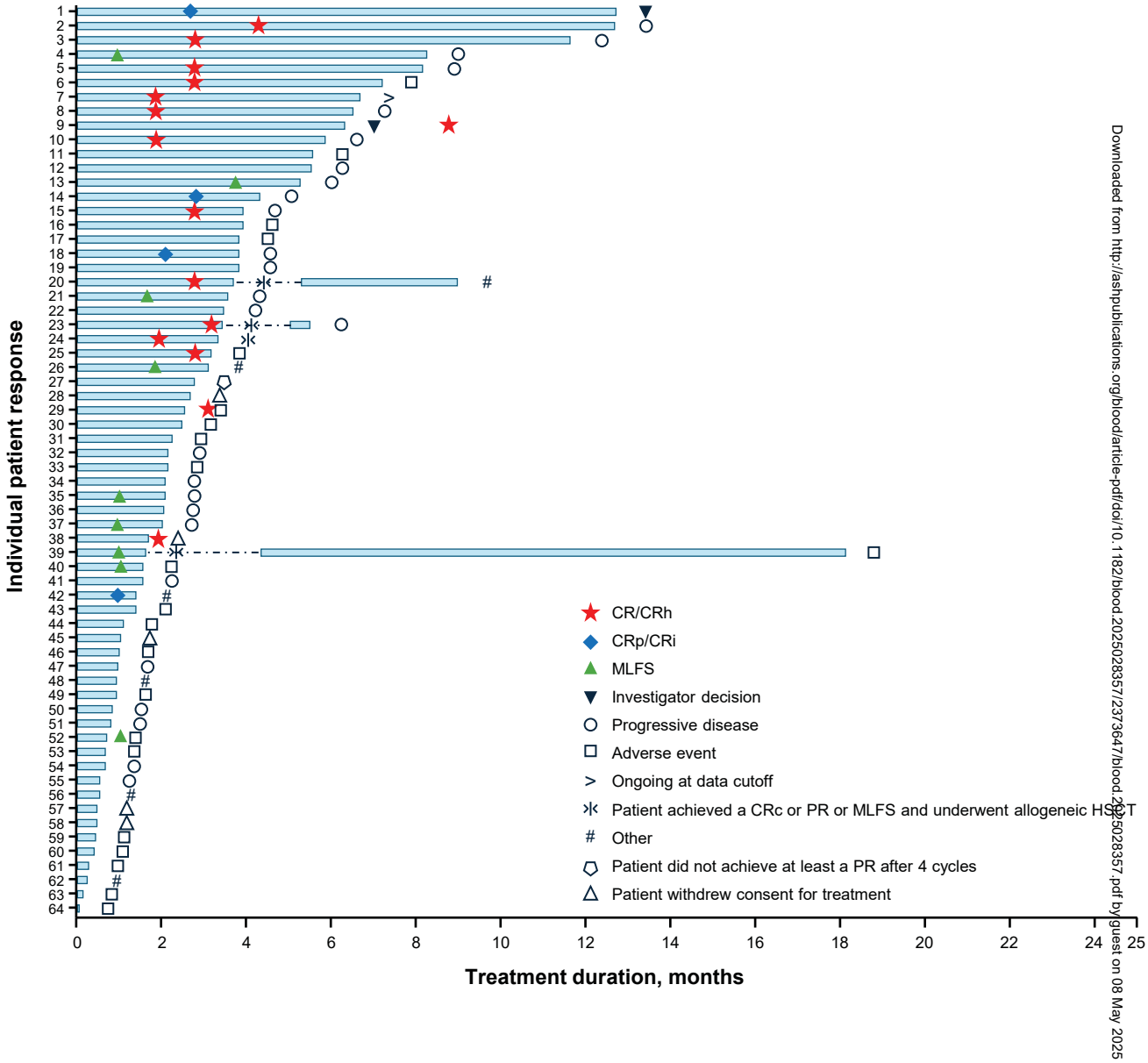
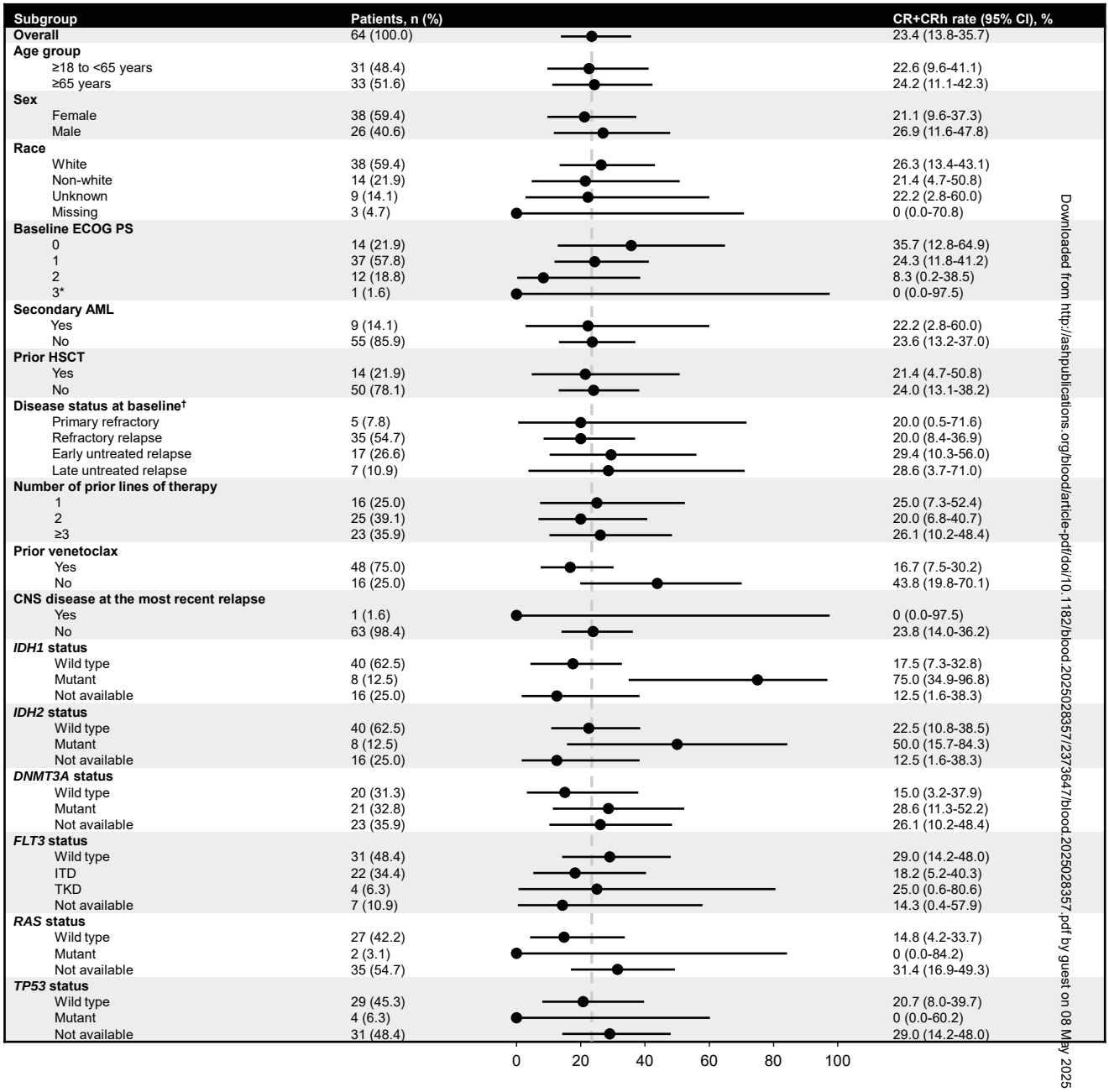


Figure 3



Subgroup	Patients, n (%)	CR+CRh rate (95% CI), %
Overall	64 (100.0)	23.4 (13.8-35.7)
Age group		
≥18 to <65 years	31 (48.4)	22.6 (9.6-41.1)
≥65 years	33 (51.6)	24.2 (11.1-42.3)
Sex		
Female	38 (59.4)	21.1 (9.6-37.3)
Male	26 (40.6)	26.9 (11.6-47.8)
Race		
White	38 (59.4)	26.3 (13.4-43.1)
Non-white	14 (21.9)	21.4 (4.7-50.8)
Unknown	9 (14.1)	22.2 (2.8-60.0)
Missing	3 (4.7)	0 (0.0-70.8)
Baseline ECOG PS		
0	14 (21.9)	35.7 (12.8-64.9)
1	37 (57.8)	24.3 (11.8-41.2)
2	12 (18.8)	8.3 (0.2-38.5)
3*	1 (1.6)	0 (0.0-97.5)
Secondary AML		
Yes	9 (14.1)	22.2 (2.8-60.0)
No	55 (85.9)	23.6 (13.2-37.0)
Prior HSCT		
Yes	14 (21.9)	21.4 (4.7-50.8)
No	50 (78.1)	24.0 (13.1-38.2)
Disease status at baseline†		
Primary refractory	5 (7.8)	20.0 (0.5-71.6)
Refractory relapse	35 (54.7)	20.0 (8.4-36.9)
Early untreated relapse	17 (26.6)	29.4 (10.3-56.0)
Late untreated relapse	7 (10.9)	28.6 (3.7-71.0)
Number of prior lines of therapy		
1	16 (25.0)	25.0 (7.3-52.4)
2	25 (39.1)	20.0 (6.8-40.7)
≥3	23 (35.9)	26.1 (10.2-48.4)
Prior venetoclax		
Yes	48 (75.0)	16.7 (7.5-30.2)
No	16 (25.0)	43.8 (19.8-70.1)
CNS disease at the most recent relapse		
Yes	1 (1.6)	0 (0.0-97.5)
No	63 (98.4)	23.8 (14.0-36.2)
***IDH1* status**		
Wild type	40 (62.5)	17.5 (7.3-32.8)
Mutant	8 (12.5)	75.0 (34.9-96.8)
Not available	16 (25.0)	12.5 (1.6-38.3)
***IDH2* status**		
Wild type	40 (62.5)	22.5 (10.8-38.5)
Mutant	8 (12.5)	50.0 (15.7-84.3)
Not available	16 (25.0)	12.5 (1.6-38.3)
***DNMT3A* status**		
Wild type	20 (31.3)	15.0 (3.2-37.9)
Mutant	21 (32.8)	28.6 (11.3-52.2)
Not available	23 (35.9)	26.1 (10.2-48.4)
***FLT3* status**		
Wild type	31 (48.4)	29.0 (14.2-48.0)
ITD	22 (34.4)	18.2 (5.2-40.3)
TKD	4 (6.3)	25.0 (0.6-80.6)
Not available	7 (10.9)	14.3 (0.4-57.9)
***RAS* status**		
Wild type	27 (42.2)	14.8 (4.2-33.7)
Mutant	2 (3.1)	0 (0.0-84.2)
Not available	35 (54.7)	31.4 (16.9-49.3)
***TP53* status**		
Wild type	29 (45.3)	20.7 (8.0-39.7)
Mutant	4 (6.3)	0 (0.0-60.2)
Not available	31 (48.4)	29.0 (14.2-48.0)

Figure 4

Figure 4A

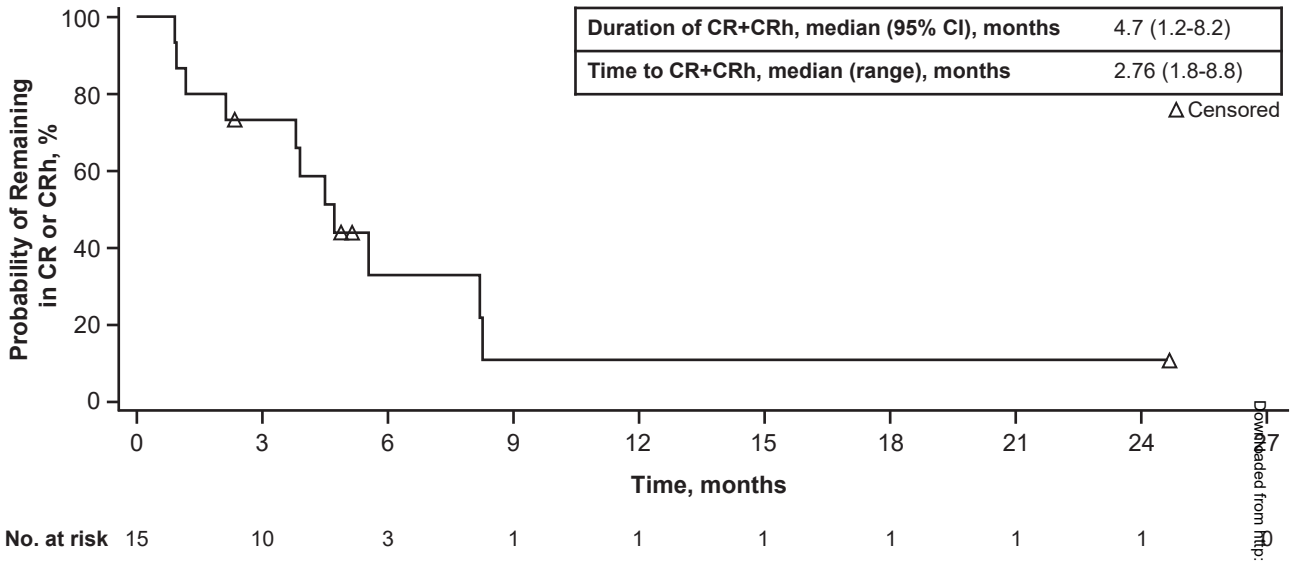


Figure 4B

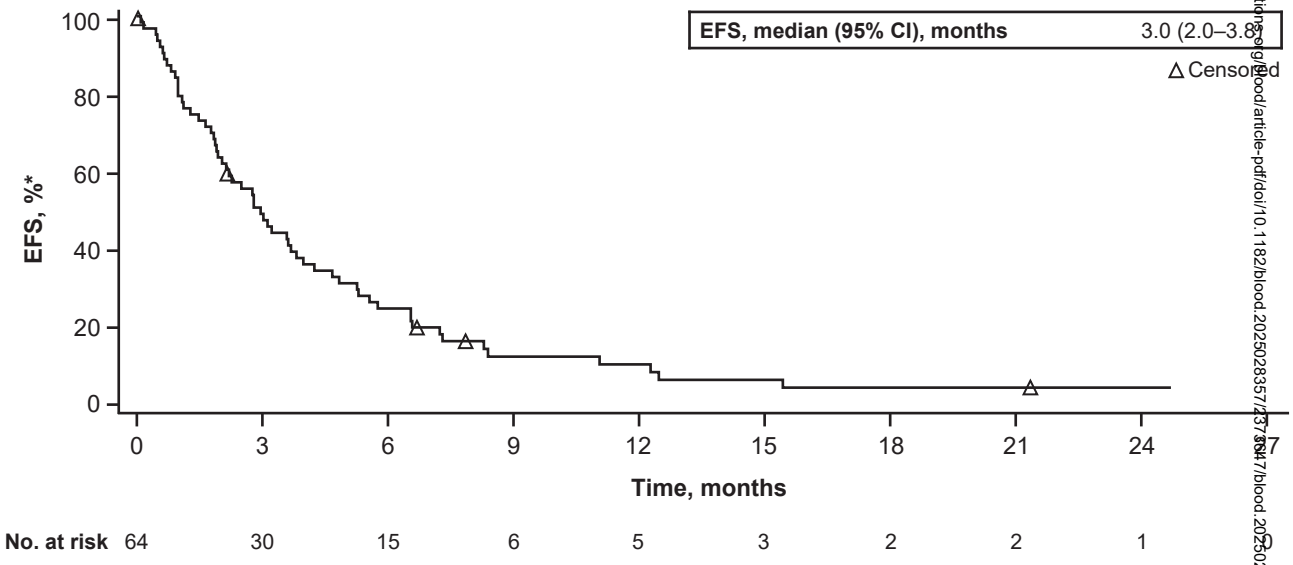
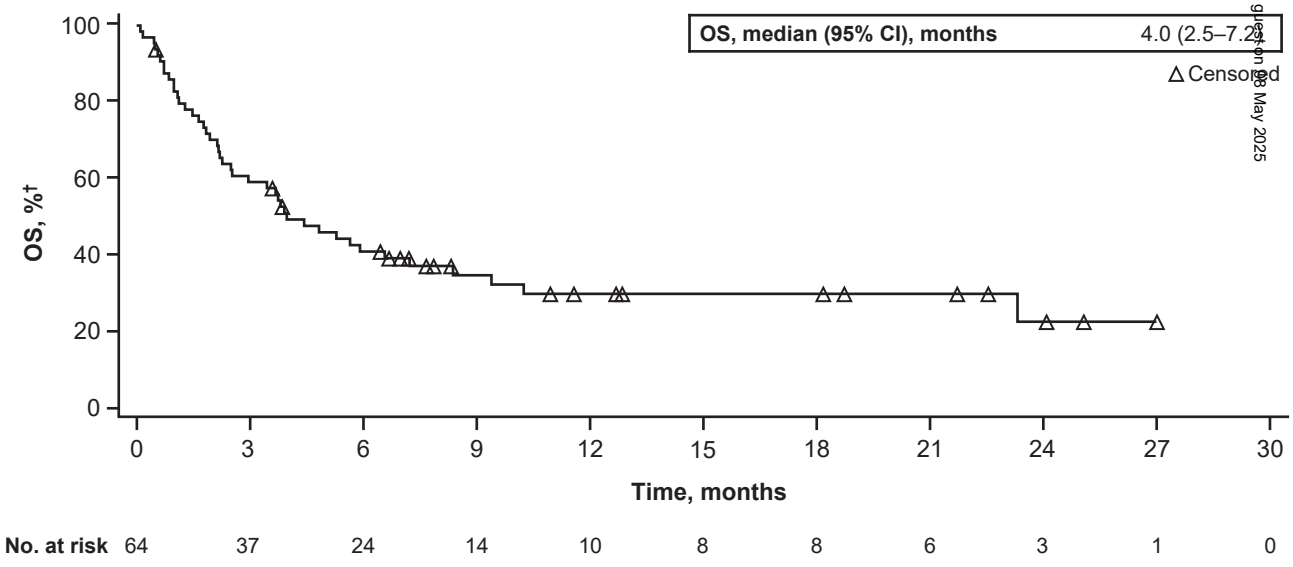


Figure 4C



Menin Inhibition With Revumenib for *NPM1*-Mutated Relapsed or Refractory Acute Myeloid Leukemia (AML)

Context of Research

- The prognosis for patients with ***NPM1*–mutated (*NPM1*m)** relapsed/refractory (R/R) AML is poor, representing an urgent unmet medical need
- **Revumenib** is a potent, selective menin inhibitor that targets leukemogenesis in *NPM1*m AML

Patients and Methods

ClinicalTrials.gov ID NCT04065399

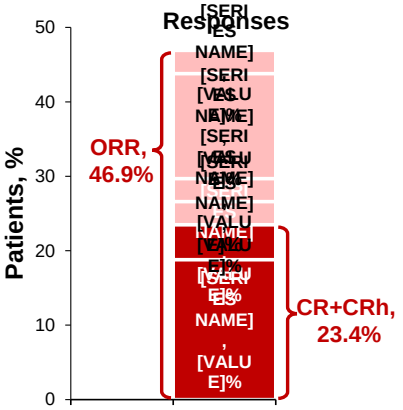
84 patients:
- Aged ≥30 days diagnosed with R/R *NPM1*m AML
- Treated with revumenib in 28-day cycles

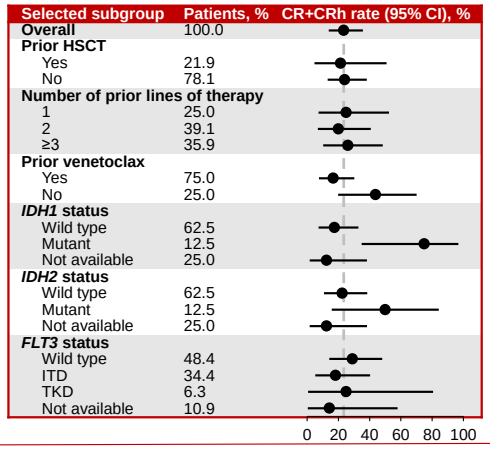
Endpoints
- Primary: CR+CRh rate, safety
- Key secondary: ORR

Main Findings

Adult Efficacy Results (n=64)

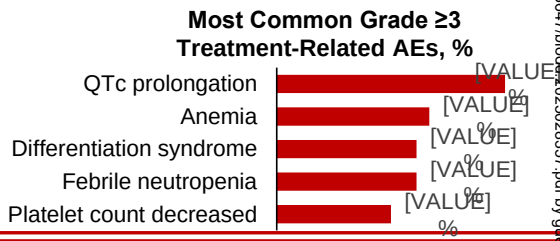
- **Almost half of all patients experienced a clinically meaningful response** (ORR 47%), with 23% achieving a complete response (CR or CRh) across various subgroups.





Safety Results (N=84)

- Fewer than 5% of treated patients discontinued due to a treatment-related adverse event



Conclusions: In patients with *NPM1*m R/R AML, revumenib demonstrated a favorable complete response rate and a manageable safety profile.

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