Article

# The menin inhibitor revumenib in *KMT2A*-rearranged or *NPM1*-mutant leukaemia

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Targeting critical epigenetic regulators reverses aberrant transcription in cancer, thereby restoring normal tissue function[1–3]. The interaction of menin with lysine methyltransferase 2A (KMT2A), an epigenetic regulator, is a dependence in acute leukaemia caused by either rearrangement of *KMT2A* or mutation of the nucleophosmin 1 gene (*NPM1*)[4–6]. *KMT2A* rearrangements occur in up to 10% of acute leukaemias and have an adverse prognosis, whereas *NPM1* mutations occur in up to 30%, forming the most common genetic alteration in acute myeloid leukaemia[7,8]. Here, we describe the results of the first-in-human phase 1 clinical trial investigating revumenib (SNDX-5613), a potent and selective oral inhibitor of the menin–KMT2A interaction, in patients with relapsed or refractory acute leukaemia (ClinicalTrials.gov, NCT04065399). We show that therapy with revumenib was associated with a low frequency of grade 3 or higher treatment-related adverse events and a 30% rate of complete remission or complete remission with partial haematologic recovery (CR/CRh) in the efficacy analysis population. Asymptomatic prolongation of the QT interval on electrocardiography was identified as the only dose-limiting toxicity. Remissions occurred in leukaemias refractory to multiple previous lines of therapy. We demonstrate clearance of residual disease using sensitive clinical assays and identify hallmarks of differentiation into normal haematopoietic cells, including differentiation syndrome. These data establish menin inhibition as a therapeutic strategy for susceptible acute leukaemia subtypes.

The prognosis of acute leukaemias harbouring rearrangements of the gene lysine methyltransferase 2A (*KMT2A*), previously known as mixed-lineage leukaemia (*MLL*), is poor, with a 5-year overall survival of less than 25% (ref. [7]). *KMT2A* rearrangements (*KMT2A*r) occur in 80% of infant acute lymphoblastic leukaemia (ALL) and in 5–15% of children and adults with acute leukaemia, whether myeloid, lymphoid or mixed phenotype[9]. Mutated nucleophosmin 1 gene (*NPM1*) is the most common genetic alteration in adult acute myeloid leukaemia (AML), occurring in up to 30% of patients[8]. Currently there are no targeted therapies specifically approved for acute leukaemia with *KMT2A*r or mutated *NPM1*.

Genetic rearrangements of *KMT2A* lead to aberrant expression of homeobox (*HOX*) genes and their DNA-binding cofactor *MEIS1* (ref. [10]). This gene expression programme, normally expressed in stem cells, causes a haematopoietic differentiation block and leukaemic transformation[11]. For leukaemias driven by *KMT2A*r, menin is a critical oncogenic cofactor[4]. The menin-binding motif is preserved throughout all KMT2A fusion proteins, and menin is an essential cofactor for binding to *HOX* gene promoters[7]. Similarly, in AML with mutated *NPM1*, the interaction between wild-type *KMT2A* and menin leads to *HOX*- and *MEIS1*-mediated leukaemogenic transcription[6,12]. Blockade of the menin–KMT2A interaction disrupts the assembly of oncogenic KMT2A wild-type or fusion complexes on chromatin[12]. Preclinical studies showed that menin inhibition downregulates *HOX* and *MEIS1* transcription and reverses leukaemogenesis in *KMT2Ar*- or *NPM1*-mutated leukaemia models[5,12,13]. Revumenib, previously known as SNDX-5613, is a potent, oral, selective inhibitor of the menin–KMT2A interaction. Treatment with revumenib led to abrogation of aberrant *HOX* gene expression and dramatic antileukaemic activity in those models (Extended Data Fig. 1; GEO accession no. for RNA sequencing (RNA-seq) data, GSE216730). In this first-in-human clinical trial we assessed the safety, maximum tolerated dose (MTD), recommended phase 2 dose (RP2D) and pharmacokinetic and pharmacodynamic profiles in patients with relapsed or refractory acute leukaemia, and present the clinical activity of revumenib in patients with *KMT2A*r or mutated *NPM1*.

This phase 1 dose-escalation study was conducted across nine sites in the United States. Because revumenib is a substrate of cytochrome P450 3A4 (CYP3A4), two parallel dose-escalation cohorts, one without

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(Arm A) and one with (Arm B) strong CYP3A4 inhibitors, were conducted. Revumenib was administered orally every 12 h (q12h) in continuous 28-day cycles. Although all patients could enrol at study initiation regardless of cytogenetic and mutational profile, given the strong preclinical rationale demonstrating that the menin–KMT2A interaction is a targetable vulnerability in acute leukaemia with *KMT2A*r or mutated *NPM1*, an early amendment to the protocol restricted enrolment to patients with relapsed or refractory acute leukaemia with *KMT2A*r or mutated *NPM1* (88% of the total study population). Between 5 November 2019 and 31 March 2022, a total of 68 patients (37 in Arm A and 31 in Arm B) were enroled and treated. The data cutoff date for this analysis was 31 March 2022. Patient disposition is presented in Extended Data Fig. 2.

Baseline characteristics of patients are provided in Extended Data Table 1. There were 56 patients (82%) with relapsed or refractory AML, 11 (16%) with ALL and one with mixed-phenotype acute leukaemia (2%). Forty-six patients (68%) had *KMT2A*r, 14 (21%) had mutated *NPM1* and eight (12%) had neither *KMT2A*r nor *NPM1* mutations. Sixty patients were adults (at least 18 years old) and eight were children or adolescents (under 18 years of age). The median age was 42.5 years (range, 0.8–79). The median age of adult patients was 50.5 years (range, 19–79) and the median age among paediatric patients was 2.5 years (range, 0.8–16). The study population was heavily pretreated with a median of four previous lines of therapy (range, 1–12), and 31 patients (46%) had relapsed after an allogenic stem cell transplant. All patients who received at least one dose of revumenib were included in the safety analysis whereas only patients with *KMT2A*r or mutated *NPM1* were included in the efficacy analysis.

The dose-escalation schema is shown in Extended Data Fig. 3. The only dose-limiting toxicity observed in both Arm A and Arm B was grade 3 prolongation of the QT interval (over 500 ms) on electrocardiography (ECG), a toxicity predicted in preclinical animal studies. These events occurred without any clinical correlate or symptoms. This dose-limiting toxicity was observed in Arm A at dose levels of 226 mg q12h ($n = 1$) and 339 mg q12h ($n = 2$), and in Arm B at 113 mg q12h ($n = 1$) and 226 mg q12h ($n = 2$). The incidence of grade 3 QT prolongation was 10% at dose levels either at or below MTD.

A total of 67 treated patients (99%) had an adverse event during treatment with revumenib whereas 53 patients (78%) had a treatment-related adverse event (TRAE) of any grade (Table 1). The most frequent treatment-emergent adverse events (TEAEs) of any grade, irrespective of a relationship to revumenib, were prolongation of the QT interval (56%), nausea (50%), vomiting (40%) and febrile neutropenia (31%); a full listing of these adverse events in at least 20% of the patients is given in Table 1. The most frequent TEAEs of grade 3 or higher were febrile neutropenia (31%), thrombocytopenia (19%) and sepsis (18%) (Extended Data Table 2). The most frequent TRAE was prolongation of the QT interval, in 36 patients (53%). Eleven patients (16%) had grade 3 or 4 TRAEs (Extended Data Table 2). The most frequent grade 3 TRAE was prolongation of the QT interval, in nine patients (13%). There were no ventricular arrythmias, and all episodes of grade 3 QT prolongation resolved either before the next dose or with protocol-directed dose hold. All patients with grade 3 QT prolongation were able to resume dosing at the next-lower dose level. Other grade 3 TRAEs included diarrhoea (3%), hypercalcaemia (2%), tumour lysis syndrome (2%), anaemia (3%), asthenia (2%), fatigue (2%), neutropenia (2%), thrombocytopenia (2%), and hypokalaemia (2%). Grade 4 TRAEs included neutropenia (2%) and thrombocytopenia (2%), with one event each. No patients permanently discontinued revumenib due to TRAEs, and no TRAEs led to death.

A common occurrence in antileukaemia therapies that induce myeloid differentiation is the development of a clinically apparent differentiation syndrome. Differentiation syndrome is caused by cytokine alterations associated with haematopoietic differentiation, with common manifestations including fever, arthralgias, leukocytosis, pleural or pericardial effusions and respiratory or renal failure in severe cases[14,15]. This had been mostly reported in patients with myeloid leukaemias treated with all-trans retinoic acid, arsenic trioxide and isocitrate dehydrogenase inhibitors[14–16]. In this study, differentiation syndrome was reported in 11 patients (16%), all grade 2. All cases of differentiation syndrome resolved following treatment with corticosteroids, with the addition of hydroxyurea for associated leukocytosis seen in five of the 11 patients (Extended Data Figs. 4 and 5). One patient missed one day of dosing, but otherwise treatment with revumenib was uninterrupted because of differentiation syndrome. The median time of onset of differentiation syndrome was 18 days (range, 5–41) with manifestations including bone pain or arthralgia, pericardial effusion, pleural effusion, pulmonary infiltrates, increase in creatinine, rash, oedema and pyrexia.

Pharmacokinetic studies showed that dose-proportional exposure was achieved in both Arm A (no strong CYP3A4 inhibitor) and Arm B (with a strong CYP3A4 inhibitor). Steady-state levels were achieved in approximately 48 h, with no evidence of drug accumulation (Extended Data Fig. 6).

Following a review of prespecified protocol criteria on safety, tolerability and pharmacokinetic data, the revumenib doses of 226 mg q12h and 276 mg q12h in Arm A and 113 mg q12h and 163 mg q12h in Arm B met the prespecified criteria for RP2D.

The pharmacodynamic effects of revumenib were assessed through transcriptional changes following treatment using RNA-seq of bone marrow cells (Fig. 1). Consistent with the established mechanism of action, menin inhibition using revumenib resulted in downregulation of the critical leukaemogenic target genes *MEIS1,* homeobox A9 (*HOXA9*), pre-B-cell leukaemia transcription factor 3 (*PBX3*) and cyclin-dependent kinase 6 (*CDK6*), and an increase in expression of genes associated with differentiation, such as integrin alpha M (*CD11b*)

**Table 1 | Any-grade treatment-related and TEAEs, regardless of causality**

| Event | Overall population ($n$=68) |
|---|---|
| **Any-grade TRAE (5% or over)** | 53 (77.9%) |
| ECG QT prolonged | 36 (52.9%) |
| Nausea | 18 (26.5%) |
| Differentiation syndrome | 11 (16.2%) |
| Vomiting | 11 (16.2%) |
| Diarrhoea | 7 (10.3%) |
| Decreased appetite | 5 (7.4%) |
| Dysgeusia | 5 (7.4%) |
| **Any-grade TEAE (20% or over)** | 67 (98.5%) |
| ECG QT prolonged | 38 (55.9%) |
| Nausea | 34 (50.0%) |
| Vomiting | 27 (39.7%) |
| Febrile neutropenia | 21 (30.9%) |
| Diarrhoea | 20 (29.4%) |
| Fatigue | 18 (26.5%) |
| ALT increased | 17 (25.0%) |
| Headache | 16 (23.5%) |
| Hyperphosphataemia | 16 (23.5%) |
| Hypokalaemia | 15 (22.1%) |
| Hyponatraemia | 15 (22.1%) |
| Thrombocytopenia | 15 (22.1%) |
| Epistaxis | 14 (20.6%) |
| Peripheral oedema | 14 (20.6%) |

All AEs shown as $n$ (%).
ALT, alanine aminotransferase.

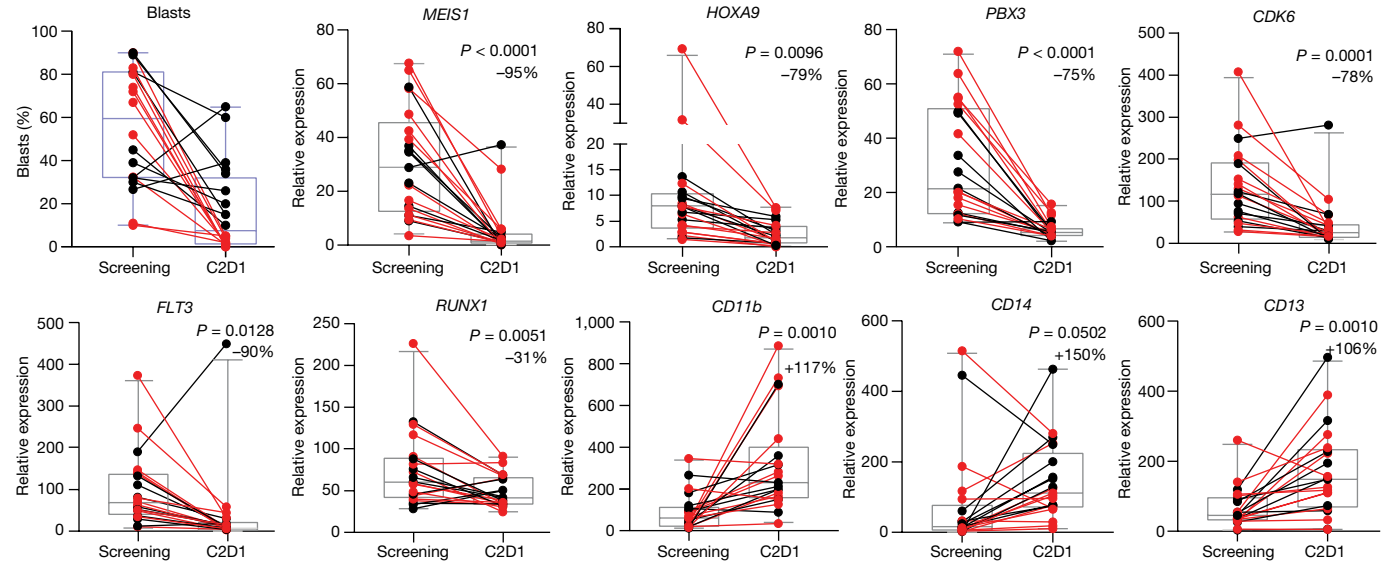


**Fig. 1 | Transcriptional changes following treatment with the menin inhibitor revumenib in patients with relapsed or refractory acute leukaemia with *KMT2A*r or mutated *NPM1*.** RNA-seq before and after treatment with revumenib, showing downregulation of critical leukaemogenic target genes *MEIS1*, *HOXA9* and *PBX3* and increase in expression of genes associated with differentiation (*CD11b*, *CD14*), with transcriptional suppression of *FLT3*, a putative transcriptional target of MEIS1. The change in bone marrow blast percentage following treatment is shown. Box plots represent median gene expression or median bone marrow blast percentage, and the 95% CI along with percentage change in gene expression following treatment. Responders are shown in red, nonresponders in black. Results were obtained using a paired *t*-test with a two-sided *P* value. Adjustments were not made for multiple comparisons. This analysis included a cohort of 21 evaluable patients. Revumenib was administered in continious 28-day cycles. C2D1, day 1 of treatment cycle 2.

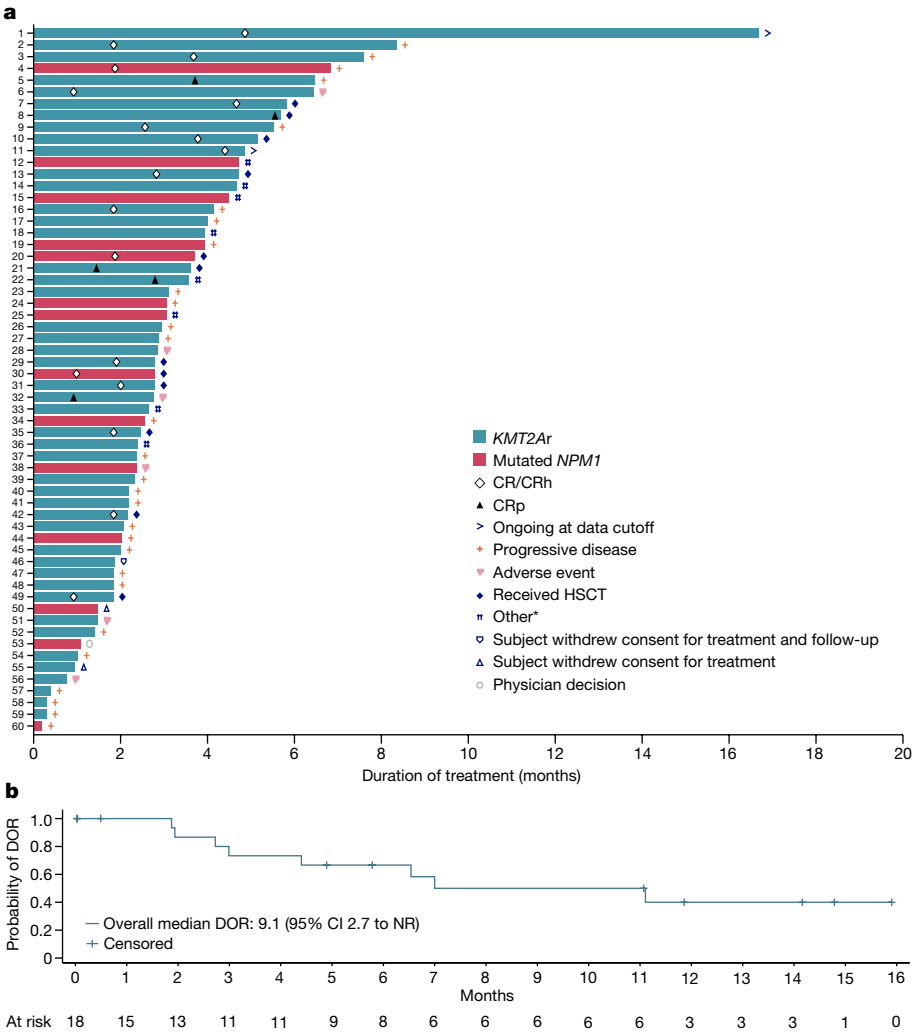


**Fig. 2 | Characterization of remissions with the menin inhibitor revumenib in susceptible relapsed or refractory acute leukaemia subtypes. a**, Time to response, duration of treatment (censored at time of HSCT) and patient status by the cutoff date. *Other reasons for treatment discontinuation included no response, relapse, death and donor lymphocyte infusion. **b**, Kaplan–Meier curve of duration of response (DOR) in patients with CR or CR/CRh without censoring at the time of an allogeneic stem cell transplant performed in 12 of 18 evaluable patients.

and *CD14*. We also observed transcriptional suppression of fms-like tyrosine kinase 3 (*FLT3*) following treatment, a putative transcriptional target of MEIS1; *FLT3* is frequently mutated in multiple subtypes of AML, including *KMT2A*r AML (10%), and is particularly common in AML with mutated *NPM1* (60%)[8,17–19].

The rate of complete remission or complete remission with partial haematologic recovery (CR/CRh) was 30% (95% confidence interval (CI) 18.8–43.2) in 18 of 60 evaluable patients with undetectable measurable residual disease (MRD), as assessed by multiparameter flow cytometry, in 14 of 18 patients (78%) who achieved CR/CRh (Fig. 2a and Table 2). The overall response rate (CR/CRh/complete remission with incomplete platelet recovery (CRp)/complete remission with incomplete haematologic recovery (CRi)/morphologic leukaemia-free state) was 53% (32 of 60 evaluable patients). The median time to CR/CRh was 1.9 months (range, 0.9–4.9). Although imaging assessment was not mandated on study, responses were notably seen in both bone marrow and extramedullary sites in two of six evaluable patients with extramedullary leukaemia at enrolment, with representative imaging shown in Extended Data Fig. 7. In an exploratory descriptive analysis, we evaluated responses by both leukaemia lineage and the adult and paediatric (under 18 years of age) populations. Morphologic remissions were identified in 27 of 49 patients (55%) with AML (95% CI 40.2–69.3), in four of ten patients (40%) with ALL (95% CI 12.2–73.8) and in the one patient with a mixed-phenotype acute leukaemia. Morphologic remission was noted in four of eight paediatric patients (50%; 95% CI 15.7–84.3) and in 28 of 52 adults (54%; 95% CI 39.5–67.8).

In patients with *KMT2A*r who achieved morphologic remission following the first cycle of therapy with revumenib, 21 of 25 (84%) retained the detectable fusions causing *KMT2A*r during concomitant cytogenetic analyses. However, most patients later had clearance of these *KMT2A* rearrangements with subsequent cycles of therapy. The rate of complete cytogenetic response in patients with *KMT2A*r who achieved morphologic clearance of their myeloblasts was 16 of 25 (64%) (Extended Data Table 3); these typically occurred after morphologic remission and, in some cases, after MRD negativity as assessed by immunophenotyping via flow cytometry. The median time to achieving complete cytogenetic response was 1.9 months (range, 0.9–2.8). These findings are consistent with the mechanism of action of differentiation agents, for which response leads first to a phenotypic differentiation of cells such that they retain the genetic fusion but are without aberrant morphology or leukaemia surface marker expression (as detected by flow cytometry)[20,21]. Subsequently with additional cycles following phenotypic remission, fusions are no longer detected by fluorescence in situ hybridization, probably because of apoptosis of differentiated cells or replacement by normal haematopoiesis.

With a median follow-up of 11.9 months (95% CI 4.9–14.8) in patients who achieved CR/CRh, the median duration of response was 9.1 months (95% CI 2.7 to not reached (NR)) (Fig. 2b). Median overall survival in the efficacy population, regardless of remission status, was 7 months (95% CI 4.3–11.6) (Extended Data Fig. 8) and median follow-up of overall survival in the efficacy population was 14.3 months (95% CI 10.6–16.7). Twelve patients received an allogeneic stem cell transplant as consolidation following response to revumenib, with nine in remission at the time of the data cutoff, seven of whom have been in remission for over 6 months. The median duration of response in those who achieved CR/CRh with censoring at the time of allogeneic stem cell transplant was 4.4 months (95% CI 1.9–NR) (Extended Data Fig. 9).

Consistent with the preclinical hypothesis regarding the efficacy of menin inhibition in patients with *NPM1* mutations or *KMT2A*r, there were no responses in the eight patients enroled on study who lacked either a *KMT2A*r or *NPM1* mutation. In evaluable patients for whom a targeted sequencing panel was performed at baseline, no specific *KMT2A* translocation or comutation was clearly associated with response in a limited analysis (Extended Data Fig. 10). Notably among evaluable patients with *KMT2A*r or mutated *NPM1*, 14 had a comutation in *FLT3*, of whom 13 had been treated with a FLT3 inhibitor before enrolment. Among the 11 patients with comutated *NPM1* and *FLT3*, three responded whereas two of the three patients with *KMT2A*r and concomitant *FLT3* mutations achieved a response. All responders had previously received a FLT3 inhibitor.

**Table 2 | Responses to treatment**

| Response | Efficacy population (*n*=60) | *KMT2A*r (*n*=46) | Mutated *NPM1* (*n*=14) |
|---|---|---|---|
| Overall response* | 32 (53%) | 27 (59%) | 5 (36%) |
| Median time to first morphologic response (range), months | 0.95 (0.9–3.7) | 0.95 (0.9–3.7) | 0.99 (1.0–1.9) |
| Best response* | | | |
| CR/CRh | 18 (30%) | 15 (33%) | 3 (21%) |
| CR | 12 (20%) | 9 (20%) | 3 (21%) |
| CRh | 6 (10%) | 6 (13%) | 0 |
| Median time to CR or CRh (range), months | 1.9 (0.9–4.9) | 2.0 (0.9–4.9) | 1.9 (1.0–1.9) |
| CRi | 0 | 0 | 0 |
| CRp | 5 (8%) | 5 (11%) | 0 |
| MLFS | 9 (15%) | 7 (15%) | 2 (14%) |
| Partial remission | 0 | 0 | 0 |
| No response | 19 (32%) | 12 (26%) | 7 (50) |
| Progressive disease | 7 (12%) | 6 (13%) | 1 (7%) |
| Missing | 2 (3%) | 1 (2%) | 1 (7%) |
| MRD† neg. rate within CR/CRh | 14/18 (78%) | 11/15 (73%) | 3/3 (100%) |
| Median time to MRD† neg. among patients with CR/CRh (range), months | 1.9 (0.9–4.9) | 1.9 (0.9–4.9) | 1.9 (1.0–2.8) |

*Responses were assessed by the investigators; responses and MRD-negative rates are shown as *n* (%).
†MRD, minimal or measurable residual disease assessed at participating sites by either multicolour flow cytometry or PCR; MRD status percentage based on patients with non-missing MRD status out of all responders.
MLFS, morphologic leukaemia-free state.

## Discussion

The treatment of patients who have relapsed or refractory acute leukaemia with *KMT2A*r is challenging. The rate of CR or complete remission with incomplete count recovery in relapsed *KMT2A*r AML following two previous lines of therapy is 9% (ref. [18]). Despite notable progress in the treatment of childhood acute leukaemia, infant *KMT2A*r acute leukaemias have remained a therapeutic challenge with high rates of resistance to multi-agent chemotherapy[22,23]. Mutations in *NPM1* are the most common alterations in AML, and targeting of vulnerabilities associated with this subset expand the reach of targeted therapy to the largest portion of patients with this disease. The menin inhibitor revumenib has the potential to address these unmet needs. In this first-in-human clinical trial, we provide clinical evidence of the effectiveness of menin inhibition with an oral targeted therapy, which is the first epigenetic therapy that evicts protein complexes from chromatin, leading to remissions in patients with acute leukaemia. We found an encouraging clinical benefit, with deep molecular remissions and minimal toxicities, in a heavily pretreated population of both children and adults with advanced acute leukaemia. However, recent data suggest that clinical resistance to targeted menin inhibition is mediated through the acquisition of mutations in menin that prevent inhibitor binding and can lead to clinical relapse[24]. The emergence of resistance

mutations highlights the critical role of the menin–KMT2A interaction in the pathogenesis of *KMT2A*r and *NPM1*-mutant acute leukaemia.

Because revumenib disrupts the effect of epigenetic regulators in leukaemia that are dependent on the menin–KMT2A interaction, this leads to abrogation of aberrant gene expression and removal of the haematopoietic differentiation block[12,13]. In this study, we show evidence of this mechanism of action with differentiation of leukaemia cells, persistence of cytogenetic abnormalities at the time of morphologic response and differentiation syndrome associated with menin inhibition in some patients, which resolved following appropriate therapy.

Other leukaemia genotypes have recently been identified as susceptible to menin inhibition, such as AML with rearrangement of the nucleoporin 98 gene (*NUP98*), a common and adverse genotype among children with relapsed and refractory disease[25]. Another example is the rare occurrence of AML with translocations involving the meningioma-1 gene (MN1)[26]. Therefore, menin inhibitors have the potential to reach a larger subset of acute leukaemia with similar dependency on the menin–KMT2A interaction, which could be identified using precision approaches testing characteristic gene expression.

In conclusion, in children and adults with highly refractory acute leukaemia with *KMT2A*r or *NPM1* mutation, menin inhibition with revumenib monotherapy was associated with promising antileukaemic activity leading to deep and sustained remission.

## Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-023-05812-3.


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# Methods

### Study design and oversights

We conducted a phase 1, multicentre, open-label, dose-escalation study (ClinicalTrials.gov, NCT04065399). Revumenib was administered orally in either capsule or liquid formulation, q12h, in 28-day continuous cycles with dose adjustment by body surface area for patients weighing under 40 kg (Extended Data Fig. 3). We employed a rolling-6 design, an algorithm-based extension of the 3+3 design that allows for concurrent accrual of two to six patients onto a dose level, thereby shortening the duration of phase 1 without increasing the risk of toxicity[27]. Therefore, the number of patients enrolled followed this dose-escalation design without an absolute prior estimation of sample size. The study included two parallel dose-escalation cohorts, for patients either not taking (Arm A) or taking (Arm B) strong CYP3A4 inhibitors. Dose expansion occurred at safe and efficacious doses. Dose-limiting toxic effects were defined as nonhaematologic toxic effects of grade 3 or higher during cycle 1, or as haematologic toxicities directly attributed to the study drug rather than to the underlying disease.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice. The protocol and amendments were approved by the institutional review board or ethics committee at The University of Texas MD Anderson Cancer Center, City of Hope, Washington University School of Medicine in St. Louis, Dana-Farber Cancer Institute, Winship Cancer Institute, Emory University School of Medicine, University of Chicago, Florida Cancer Specialists/Sarah Cannon Research Institute, University of Iowa and Memorial Sloan Kettering Cancer Center. All patients provided written informed consent. This study was designed by the sponsor (Syndax Pharmaceuticals) in collaboration with the investigators. The data were collected by the investigators and their research staff and were analysed by the sponsor and authors. Drafts of the manuscript were written by the first and last authors and revised in collaboration with all authors and the sponsor, all of whom vouch for the completeness and accuracy of the data and analyses, and for the adherence of the study to the protocol. Assistance in manuscript preparation for submission was provided by a professional service and paid for by the sponsor.

### Patients

An early amendment to the protocol allowed patients aged 30 days and older to be enroled on this study; additionally, it restricted the eligibility criteria from any relapsed or refractory acute leukaemia to only those with *KMT2A*r or mutated *NPM1* in Arms A and B of the study. Mutational status was assessed at each site.

### Study assessments

The primary objectives of the phase 1 portion of this study were to assess safety, the MTD or, if different, RP2D and to characterize the pharmacokinetic parameters of revumenib in arms based on concomitant CYP3A inhibitors. Exploratory objectives included assessment of antileukaemic activity in the efficacy population, which consisted of patients with *KMT2A*r or mutated *NPM1*. All study assessments and analyses included both paediatric and adult patients.

Adverse events were graded with use of the Common Terminology Criteria for Adverse Events, v.5.0. Clinical efficacy was assessed by the investigators with use of a modified version of the 2017 European LeukemiaNet response criteria, to additionally include CRh[28]. Guidelines for managing prolongation of the QT interval included electrolyte repletion and adjustment of revumenib dose. Investigators were encouraged to administer corticosteroids following suspicion of differentiation syndrome based on guidelines included in the protocol. Measurable residual disease assessment was performed in participating institutions using multicolour flow cytometry or PCR[29–31]. In an exploratory mutational analysis we used the ArcherDx VariantPlex Myeloid Panel, a 75-gene, next-generation targeted sequencing product examining genes frequently mutated in myeloid and lymphoid malignancies. Powered by Anchored Multiple PCR chemistry, the panel enables deep strand-specific amplification of unique molecular barcoded DNA fragments for sequencing. Archer Analysis software was used for the analysis and interpretation of sequencing data in the detection of single-nucleotide variants and indels. Variant calling was performed using Invitae's Comprehensive Targeted Mutation File (v.1.6), and the Vision variant caller to report well-classified variants.

### Statistical analysis

All patients who received at least one dose of revumenib were included in the safety analysis, whereas only those with *KMT2A*r or mutated *NPM1* were included in the efficacy analysis. Time-to-event end points were estimated using the Kaplan–Meier method. Descriptive statistics were used for other clinical, laboratory and pharmacokinetic variables. Clinical data were captured in Medidata Classic Rave 2021.2.0, and data analyses were performed using SAS v.9.4 and GraphPad Prism v.8.0. Changes in gene expression were analysed using a paired *t*-test.

RP2D was determined by the safety review committee based on review of pharmacokinetics, safety and tolerability data among evaluable patients.

### Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

## Data availability

Syndax Pharmaceuticals (Syndax) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. Syndax is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. Following submission of a request (to datarequest@syndax.com), Syndax will provide an outline of the process and requirements for submitting a data request. Feasible requests will be reviewed by a committee of Syndax subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with Syndax before Syndax may grant data access. Data will be made available for request after product approval in the United States and European Union, or after product development is discontinued. There are circumstances that may prevent Syndax from sharing requested data, including country- or region-specific regulations. If Syndax declines the request, it will communicate the decision to the investigator. Access to genetic or exploratory biomarker data requires a detailed statistical analysis plan that is collaboratively developed by the requester and Syndax subject matter experts.


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**Author contributions** G.C.I., E.M.S., G.R., M.L. M. and Y.G. conceptualized and designed the study. G.C.I. and E.M.S. prepared the first draft of the manuscript, provided critical review and revisions of the drafts and approved the decision to submit for publication. F.P., S.A.A. and J.A.P. designed, performed and analysed preclinical experiments using patient-derived xenografts. G.C.I., I.A., J.D.P., B.C., R.S., M.A., M.J.T., M.R.P., D.S.D., S.Shenoy, N.S., H.K. and E.M.S. enroled and treated patients. G.C.I., I.A., J.D.P., B.C., R.S., M.A., M.J.T., M.R.P., D.S.D., S. Shenoy, N.S., S.A.A., F.P., J.A.P., G.R., R.G.B., M.L.M., P.O., Y.G., V.K., S.Smith, G.M.M. and E.M.S. collected data, analysed and interpreted the results and reviewed and edited manuscript drafts. S.Smith participated in conception and design analysis and interpretation of results. M.R.P. and S.A.A. participated in trial conduct and clinical trial discussions. G.M.M. conceptualized and designed the study, analysed data and interpreted results for preclinical studies. V.K. collected data and analysed and interpreted results for pharmacodynamic studies. All authors have read and agreed on the content of the manuscript.

**Competing interests** G.C.I. received consultancy or advisory role fees from Novartis, Kura Oncology and NuProbe and received research funding from Celgene, Novartis, Kura Oncology, Syndax Pharmaceuticals, Merck, Cullinan Oncology and NuProbe. I.A. received consultancy or advisory role fees from Amgen, Pfizer, Jazz, AbbVie and Agios, research funding from AbbVie and Macrogenics and honoraria from Amgen, Pfizer, Jazz, AbbVie and Agios. J.D.P. has a consultancy role with Incyte and RiverVest Venture Partners, has served as a board member or advisory committee member for RiverVest Venture Partners, Magenta, hC Bioscience, Inc. and WUGEN, has received research funding from NeoImmune Tech, Macrogenics, Incyte, Bioline Rx and WUGEN and holds patents or pending patents for UCART7 for treatment of T-ALL, VLA-4 inhibitors for stem cell mobilization and NT-I7 for CART expansion. R.S. has served on the steering committee of AbbVie and advisory boards of AbbVie, AvenCell, CTI Pharma, Kura One, Genentech, Actinium, Arog, BMS, Boston Pharmaceuticals, GSK, Janssen, Jazz, Novartis, Syros, Takeda, Elevate Bio, Syndax Pharmaceuticals, Gemoab, BerGenBio, Foghorn Tera, Aprea, Innate, Actinium and OncoNova; served as DSMB for Aptevo, Epizyme, Takeda and Syntrix/ACI Clinical; on the focus group of BerGenBio; and on AML Expert Council of GSK and Grand Rounds of Jazz Pharmaceuticals. M.A. has served on the advisory boards of Kite Pharma and Syndax Pharmaceuticals. M.J.T. has a consulting or advisory role with AbbVie and CVS, has an expert testimony role with Apotex and received research funding from AbbVie, Gilead Sciences, Janssen, Merck, Pharmacyclics, Syndax Pharmaceuticals, TG Therapeutics and Tolero. M.R.P. served in a leadership role with ION Pharma; received honoraria from Pfizer, Pharmacyclics, Bayer, Janssen Oncology, Genentech and Adaptive Biotechnologies; has a consulting or advisory role with Pharmacyclics/Janssen and Pfizer/EMD Serono; served on the Speakers' Bureau of Exelixis, Genentech/Roche, Taiho Pharmaceutical and Celgene; and received research funding from Acerta Pharma, ADC Therapeutics, Agenus, Aileron Therapeutics, AstraZeneca, BioNTech AG, Boehringer Ingelheim, Celgene, Checkpoint Therapeutics, CicloMed, Clovis Oncology, Cyteir Therapeutics, Daiichi Sankyo, Lilly, EMD Serono, Evelo Therapeutics, FORMA Therapeutics, Genentech/Roche, Gilead Sciences, GlaxoSmithKline, H3 Biomedicine, Hengrui Therapeutics, Hutchison MediPharma, Ignyta, Incyte, Jacobio, Janssen, Klus Pharma, Kymab, Loxo, LSK Biopartners, Lycera, Macrogenics, Merck, Millennium, Mirati Therapeutics, Moderna Therapeutics, Pfizer, Placon, Portola Pharmaceuticals, Prelude Therapeutics, Ribon Therapeutics, Seven and Eight Biopharmaceuticals, Syndax Pharmaceuticals, Taiho Pharmaceutical, Takeda, Tesaro, TopAlliance BioSciences, Inc., Vigeo, ORIC, Artios, IgM Biosciences, Puretech, BioTheryX, Black Diamond Therapeutics, IgM Biosciences, NGM Biopharmaceuticals, Nurix, PureTech, Relay Therapeutics, Samumed, Silicon Therapeutics, TeneoBio, Treadwell Therapeutics, Zymeworks, Olema, Adagene, Astellas, NGM, Accutar Biotech, TeneoBio, Novartis, Compugen, Black Diamond Therapeutics, MabSpace Biosciences, Immunogen and Blueprint Pharmaceuticals. 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G.R. is a former employee of Syndax Pharmaceuticals and a current employee of Boston Pharmaceuticals. R.G.B. is an employee of Syndax Pharmaceuticals and has stock or other ownership at Syndax Pharmaceuticals. M.L.M., P.O. and G.M.M. are employees of Syndax Pharmaceuticals. M.L.M. has a consulting or advisory role at Nuvalent, holds patents, royalties and other intellectual property at Syndax Pharmaceuticals and Nuvalent and has stock or other ownership at Syndax Pharmaceuticals and Johnson & Johnson. P.O. has a consulting or advisory role at Patrys and Twentyeight-Seven Therapeutics, holds patents, royalties and other intellectual property at Syndax Pharmaceuticals and has stock or other ownership at Syndax Pharmaceuticals. G.M.M. has a consulting or advisory role at Syndax Pharmaceuticals, holds patents, royalties and other intellectual property at Syndax Pharmaceuticals and has stock or other ownership at Syndax Pharmaceuticals. Y.G. is an employee of Syndax Pharmaceuticals and has stock or other ownership at Syndax Pharmaceuticals and AstraZeneca. S. Smith has a consultancy or advisory role with Syndax Pharmaceuticals. E.M.S. has a consulting or advisory role with Gilead, CTI Biopharma, Epizyme, AbbVie, Pinotbio, Neoleukin Genesis, Genentech, Jazz, Novartis, Celgene, Calithera, Takeda, Janssen, BMS, Kronos, Kura, Auron, Syndax Pharmaceuticals, Servier, Agios and Remix and received research funding from Biotheryx, Agios, Servier, Eisai, BMS, Bayer, Syndax, Syros and Loxo. B.C., F.P., J.A.P., N.S. and V.K. declare no competing interests.

**Additional information**

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41586-023-05812-3.

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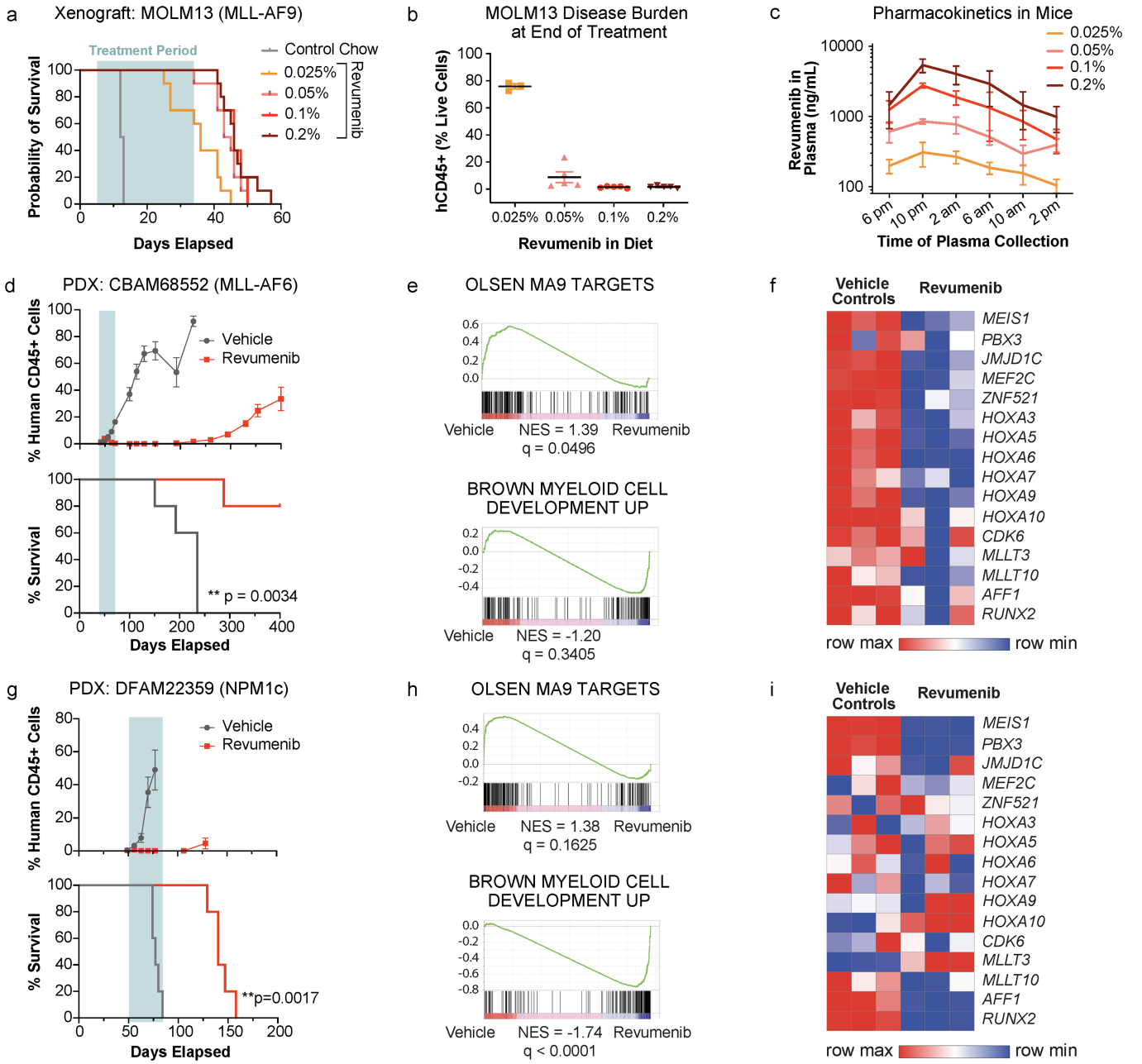
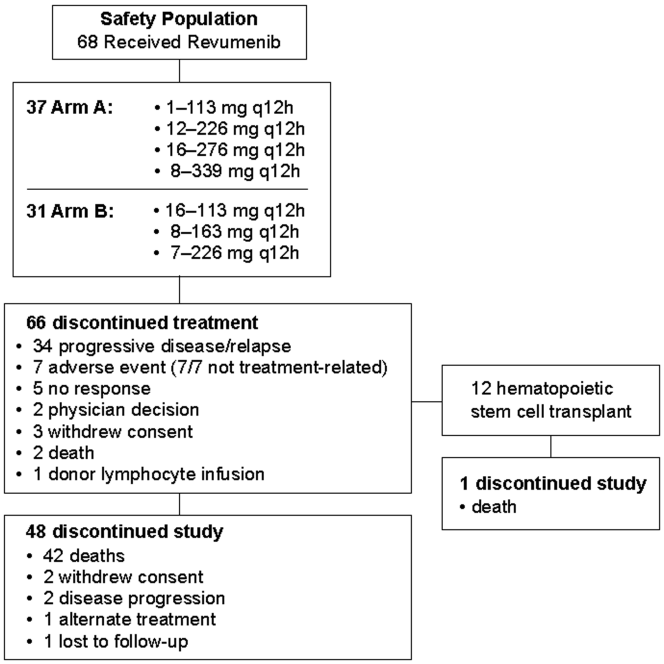
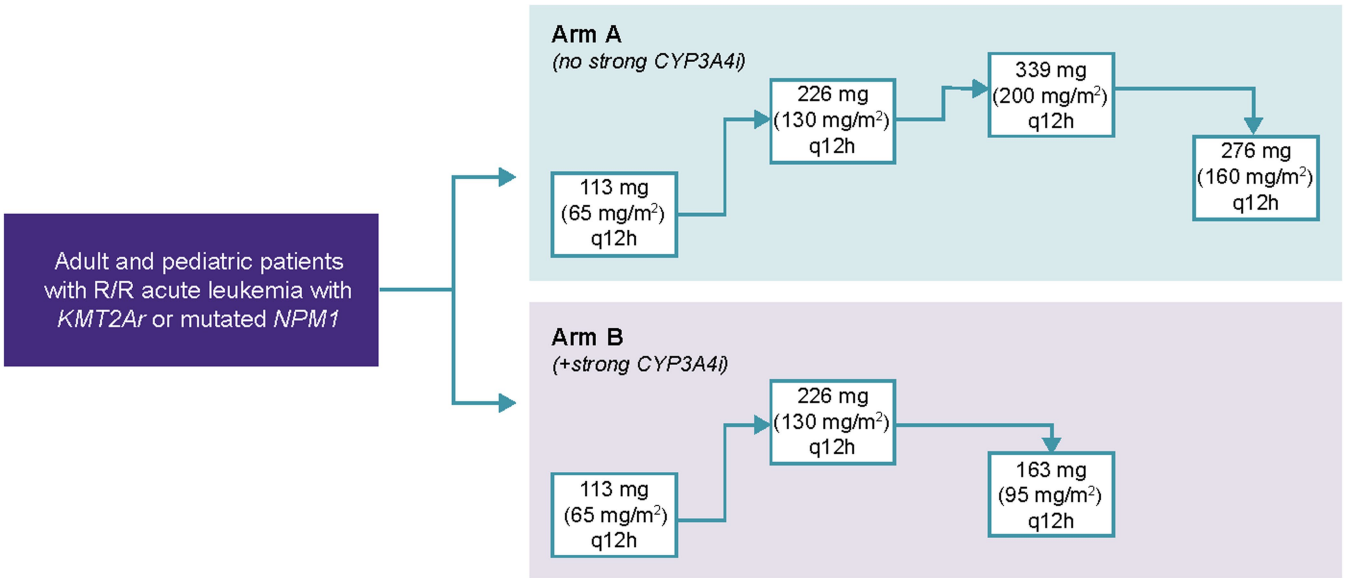
**Peer review information** *Nature* thanks Jorge Cortes, Eunice Wang and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.



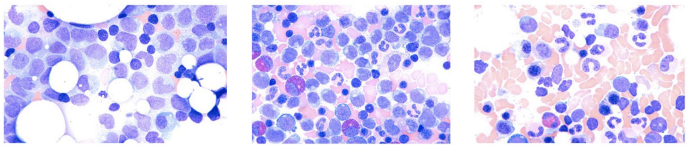

**Extended Data Fig. 1 | Revumenib suppresses both *KMT2A*r and *NPM1*-mutant AML in preclinical models of leukaemia.** NSG mice were engrafted with the *KMT2A*r cell line MOLM-13 (**a**; n = 10) or patient derived xenografts (PDX) harbouring either a *KMT2A*r (**d**; n = 5) or *NPM1* mutation (**g**; n = 5). Mice were treated for 28 days with revumenib, which was formulated in chow, across a dose range of 0.025% to 0.2% (**a**) or at 0.1% fixed dose (**d**, **g**). Leukaemic burden (CD45+) was assessed at end of treatment (**b**; 0.025%: n = 3; 0.05-0.2%: n = 5, data represent mean ± SEM) or throughout the study (**d**, **g**; data represent mean ± SEM). For MOLM-13 engrafted mice, revumenib showed clear dose-dependent exposure (**c**; n = 3 with 3 individual measurements per timepoint and dose, data represent mean ± SD), which translated into dose-responsive effect on survival benefit (**a**) and leukaemic burden at end of treatment (**b**). Similarly, revumenib treatment of the PDX models led to significant suppression of leukaemic burden and significant survival benefit in each (**d**, **g**). *P*-values were determined by log-rank (Mantel–Cox) tests. Adjustments were not made for multiple comparisons. Revumenib treatment also led to broad changes in the transcriptional program (**f**, **i**; n = 3 per treatment group; GEO accession number for RNAseq data, GSE216730) with GSEA results consistent with previously reported signatures (**e**, **h**; n = 3 per treatment group). GSEA, gene set enrichment analysis; NES, normalized enrichment score; NSG, NOD scid gamma; PDX, patient-derived xenograft; SD, standard deviation; SEM, standard error of the mean.



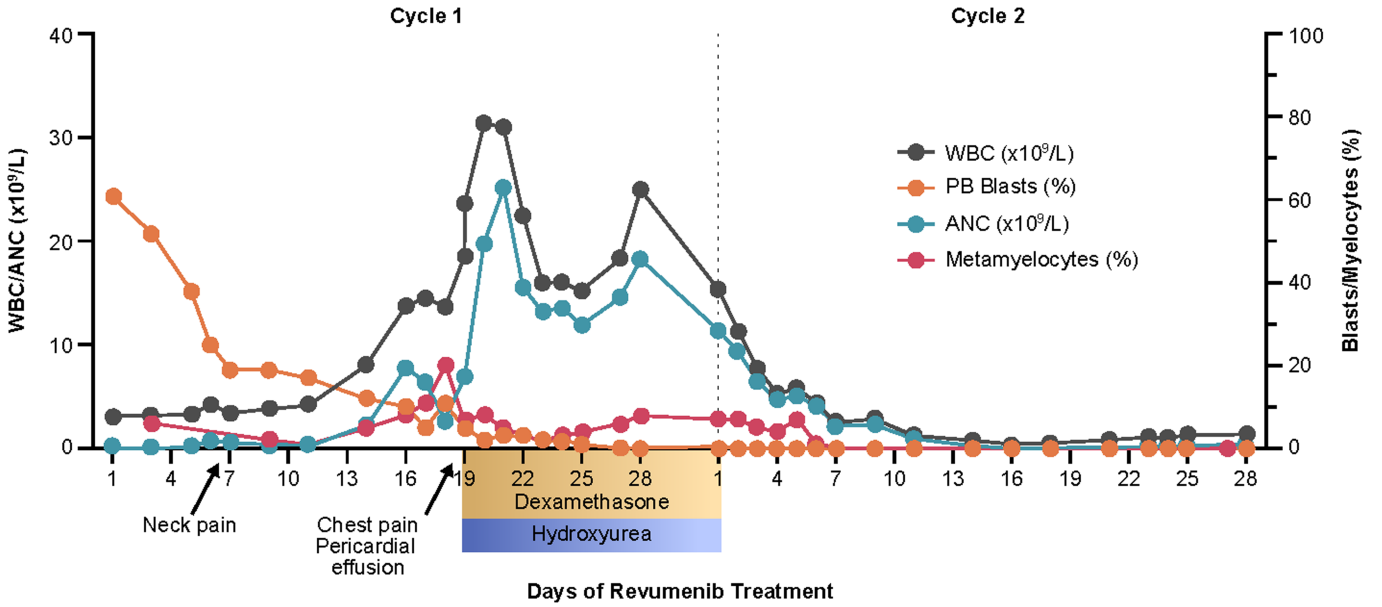

**Extended Data Fig. 2 | CONSORT diagram and patient disposition on trial.** The CONSORT diagram shows the number of patients from Arms A and B who discontinued treatment and lists the reasons for treatment and study discontinuation.



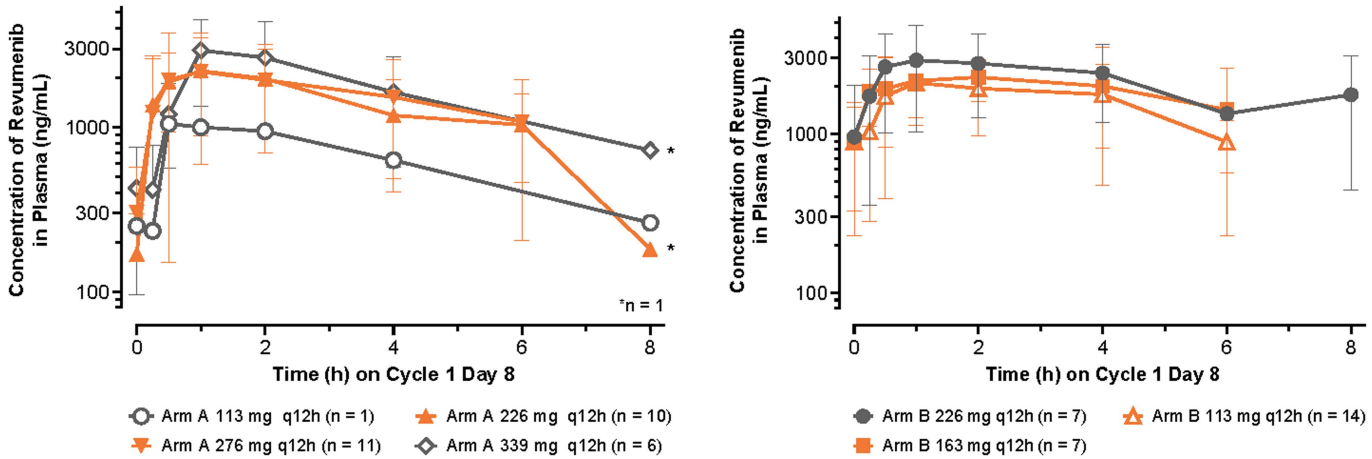

**Extended Data Fig. 3 | Dose escalation schema.** The revumenib dose was adjusted based on the body surface area (BSA) for patients weighing less than 40 kg as indicated for each corresponding dose level shown in parentheses. CYP3A4i, cytochrome P450 3A4 inhibitor; q12h, every 12 h; R/R, relapsed or refractory.



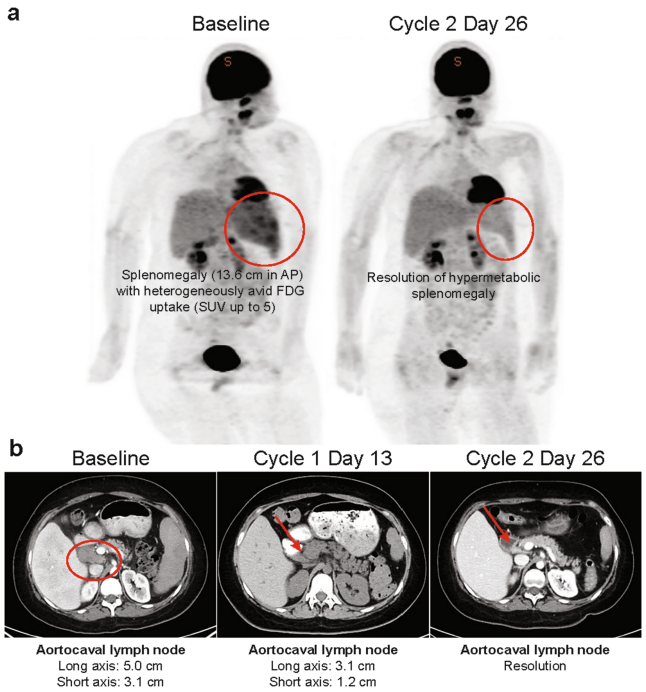

**Extended Data Fig. 4 | Morphologic evidence of myeloid differentiation.** Photomicrographs of bone marrow biopsies demonstrating morphologic evidence of myeloid differentiation in a patient who achieved complete remission; magnification is 40x.



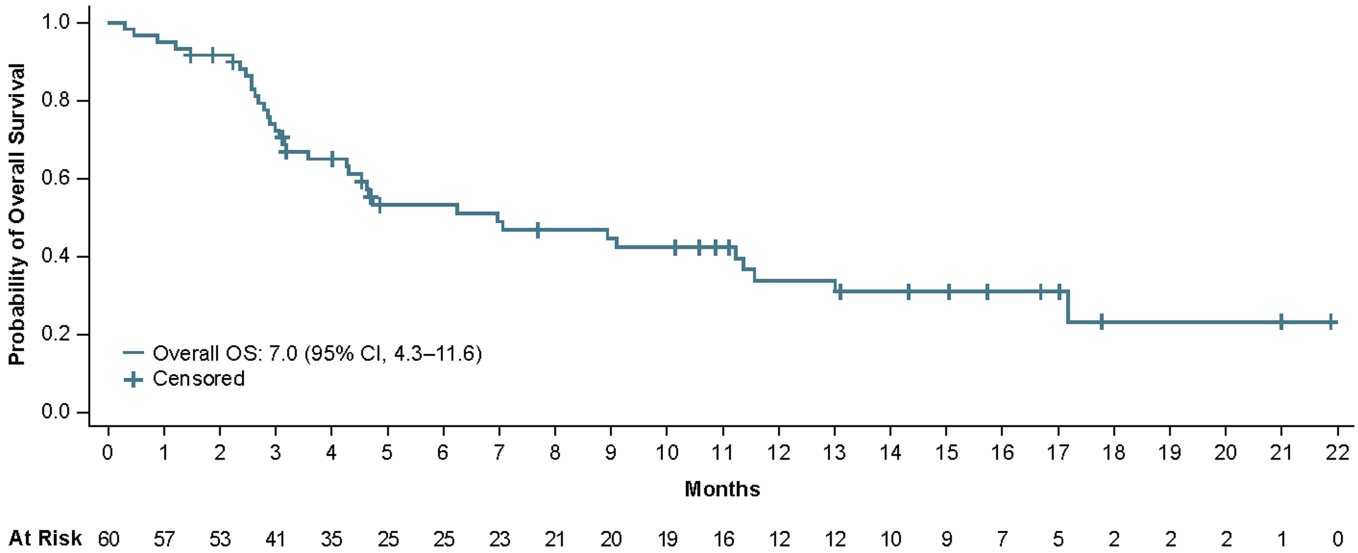

**Extended Data Fig. 5 | Changes in peripheral blood during differentiation syndrome are associated with the menin inhibitor revumenib.** Example from a 71-year-old patient with *KMT2A*r AML relapsed after an allogeneic stem cell transplant, who received revumenib at 339 mg PO q12h (Arm A), and achieved CRh, MRD negative remission. Differentiation syndrome manifested as chest pain with a small pericardial effusion, and a possible prodrome of neck pain likely related to expansion of cervical nodes, all resolved promptly with initiation of steroids followed by tapering doses. Hydroxyurea was used to control leukocytosis. AML, acute myeloid leukaemia; ANC, absolute neutrophil count; CRh, complete remission with partial haematologic recovery; MRD, minimal or measurable residual disease; PB, peripheral blood; PO, by mouth; q12h, every 12 h; WBC, white blood cell.



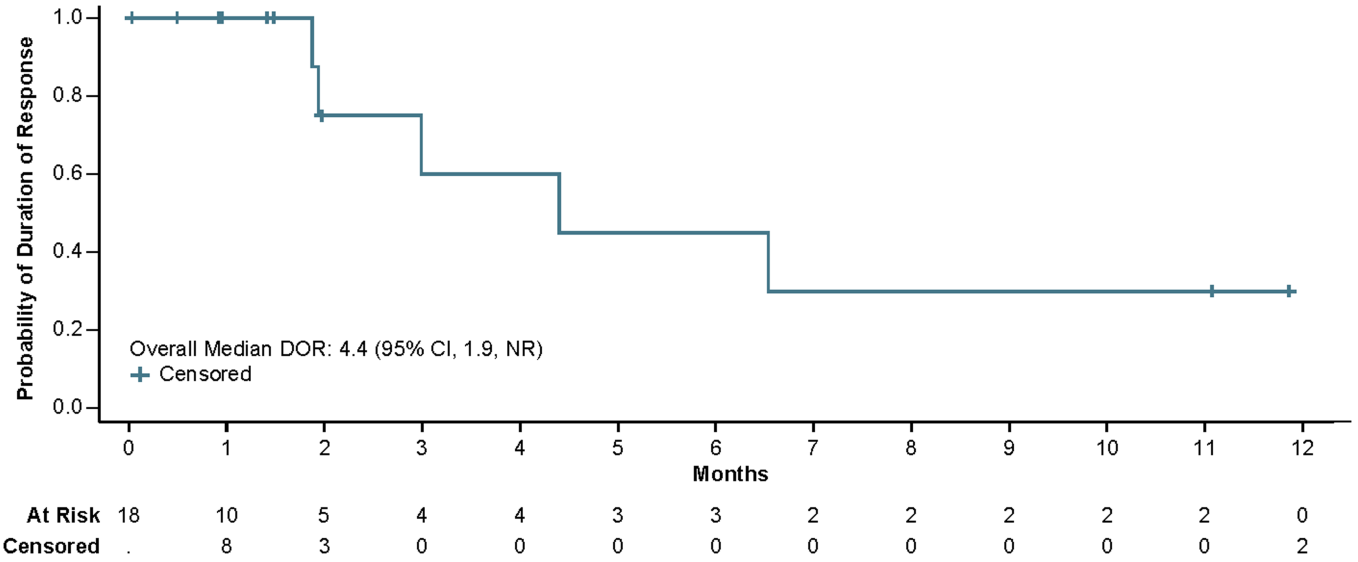

**Extended Data Fig. 6 | Dose proportional exposure was achieved across both arms.** The half-life of revumenib in Arm A (without strong CYP3A4 inhibitors) was approximately 3 h at the cycle 1 day 8 assessment of the 276-mg q12h dose level and was approximately 8 h at the same assessment in Arm B (with a strong CYP3A4 inhibitor) at the 163-mg q12h dose level. Data represent mean ± SD. Data cutoff date for pharmacokinetic analysis was July 11, 2022. CYP3A4, cytochrome P450 3A4; q12h, every 12 h; SD, standard deviation.




**Extended Data Fig. 7 | Response in extra-medullary disease. A.** PET scan at baseline and after 2 cycles of treatment. **B.** Computed tomographic scans of target lesions and spleen from a 19-year-old with relapsed *KMT2A*r AML, previously treated with three prior lines of therapy including 2 allogeneic stem cell transplants and local radiation to the spleen and abdominal nodes, received revumenib at 276 mg PO q12h (Arm A), achieved CRh, MRD negative remission with resolution of extramedullary disease in abdominal nodes and spleen. AML, acute myeloid leukaemia; AP, anterior-posterior; CRh, complete remission with partial haematologic recovery; D, day; FDG, fluorodeoxyglucose; MRD, minimal or measurable residual disease; PET, positron emission tomography; PO, by mouth; q12h, every 12 h; SUV, standardized uptake value.

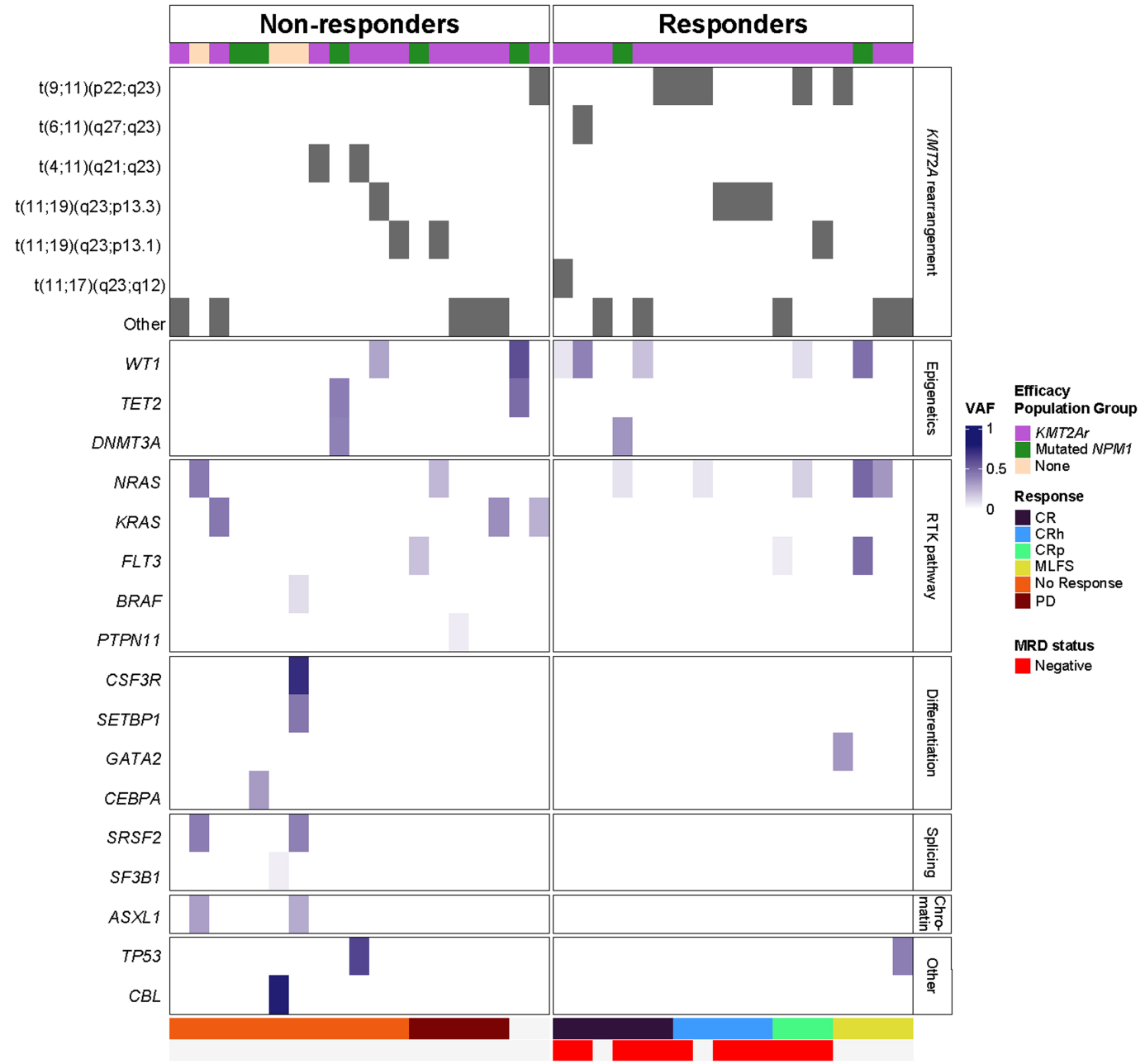



**Extended Data Fig. 8 | Overall survival in patients with *KMT2A*r or mutated *NPM1*.** OS, overall survival.




| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **At Risk** | 18 | 10 | 5 | 4 | 4 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 0 |
| **Censored** | . | 8 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |

**Extended Data Fig. 9 | Kaplan-Meier curve of duration of response in patients with complete remission or complete remission with partial haematologic recovery with censoring at time of the allogeneic stem cell transplant.** DOR, duration of response; NR, not reached.




**Extended Data Fig. 10 | Mutation analysis and response.** This cohort included 37 patients evaluable for this analysis. CR, complete remission; CRh, complete remission with partial haematologic recovery; CRp, complete remission with incomplete platelet recovery; MLFS, morphologic leukaemia-free state; NR, not reached; PD, progressive dVAF, variant allele frequency.

**Extended Data Table 1 | Baseline characteristics**

| Characteristic | Overall population (N = 68) |
|---|---|
| Median age, years (range) | 42.5 (1–79) |
| Sex, no. (%) | |
| Male | 26 (38%) |
| Female | 42 (62%) |
| Median % of bone marrow blasts (range) | 59.5% (1–95) |
| Acute leukemia type, no. (%) | |
| AML | 56 (82%) |
| Therapy-related AML | 7 (10%) |
| ALL | 11 (16%) |
| MPAL | 1 (2%) |
| Genotype, no. (%) | |
| *KMT2Ar* | 46 (68%) |
| t(9;11) (p21;q23) | 10 (15%) |
| t(4;11) (q21;q23) | 6 (9%) |
| t(11;19) (q23;p13.1) | 5 (7%) |
| t(11;19) (q23;p13.3) | 4 (6%) |
| t(6;11) (q27;q23) | 3 (4%) |
| t(11;17) (q23;q12) | 2 (3%) |
| Other 11q23 translocations | 16 (24%) |
| Mutated *NPM1* | 14 (21%) |
| *KMT2A* and *NPM1* wild type | 8 (12%) |
| Co-occurring mutations* | |
| *FLT3* | 14 (25%) |
| *RAS* | 12 (29%) |
| *TP53* | 4 (10%) |
| Previous therapies | |
| Median no. of previous therapies (range) | 4 (1–12) |
| Venetoclax | 41 (60%) |
| Allogeneic HSCT | 31 (46%) |

*In patients for whom co-occurring mutation data were available and assessed at each site.

AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; *FLT3*, fms-related tyrosine kinase; HSCT, haematopoietic stem cell transplant; MPAL, mixed phenotype acute leukaemia; *RAS*, rat sarcoma virus.

All values are shown as n (%) except otherwise indicated.

**Extended Data Table 2 | Grade 3 or higher treatment-related and treatment-emergent adverse events**

| Event | Overall population (N = 68) |
|---|---|
| ≥ Grade 3 treatment-related AE (>1 patient) | 11 (16.2%) |
| ECG QT prolonged | 9 (13.2%) |
| Anemia | 2 (2.9%) |
| Diarrhea | 2 (2.9%) |
| ≥ Grade 3 treatment-emergent AE (>5%) | 53 (77.9%) |
| Febrile neutropenia | 21 (30.9%) |
| Thrombocytopenia | 13 (19.1%) |
| Sepsis | 12 (17.6%) |
| ECG QT prolonged | 10 (14.7%) |
| Anemia | 9 (13.2%) |
| Neutropenia | 6 (8.8%) |
| Leukopenia | 5 (7.4%) |
| Respiratory failure | 5 (7.4%) |
| Back pain | 4 (5.9%) |
| Bacteremia | 4 (5.9%) |
| Cellulitis | 4 (5.9%) |
| Fatigue | 4 (5.9%) |
| Hypotension | 4 (5.9%) |
| Pneumonia | 4 (5.9%) |

AE, adverse event; ECG, electrocardiogram.
Adverse events are shown as n (%).

**Extended Data Table 3 | Measurable residual disease and cytogenetic responses**

| Response | Efficacy population (N = 60) | *KMT2Ar* (n = 46) | Mutated *NPM1* (n = 14) |
|---|---|---|---|
| MRD* neg. rate within CR/CRh | 14/18 (78%) | 11/15 (73%) | 3/3 (100%) |
| Median time to MRD* neg. among patients with CR/CRh (range), months | 1.9 (0.9–4.9) | 1.9 (0.9–4.9) | 1.9 (1.0–2.8) |
| MRD* neg. rate among patients with CR/CRh/CRp | 18 (78%) | 15 (75%) | 3 (100%) |
| Median time to MRD* neg. in CR/CRh/CRp (range), months | 1.9 (0.9–4.9) | 1.9 (0.9–4.9) | 1.9 (1.0–2.8) |
| CCyR† by FISH among patients with CR/CRh/CRp/MLFS | NA | 16/25 (64%) | NA |
| Median time to CCyR† in CR/CRh/CRp/MLFS (range), months | NA | 1.9 (0.9–2.8) | NA |

*MRD, minimal or measurable residual disease assessed at participating sites by multicolor flow cytometry or by polymerase chain reaction. MRD status percentage is based on patients with non-missing MRD status out of the responders. MRD-negative rates are shown as n (%).

†CCyR denotes complete cytogenetic remission in which *KMT2A* fusions were not detectable by fluorescence in situ hybridization in evaluable patients assessed at participating sites.

CR, complete remission; CRh, complete remission with partial haematologic recovery; CRi, complete remission with incomplete haematologic recovery; CRp, complete remission with incomplete platelet recovery; FISH, fluorescence in situ hybridization; MLFS, morphologic leukaemia free state; MRD, minimal or measurable residual disease; NA, not applicable given absence of disease defining cytogenetic abnormalities.

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# Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

## Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

| n/a | Confirmed |
|---|---|
| ☐ | ☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☒ | ☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ The statistical test(s) used AND whether they are one- or two-sided<br>*Only common tests should be described solely by name; describe more complex techniques in the Methods section.* |
| ☐ | ☒ A description of all covariates tested |
| ☐ | ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted<br>*Give P values as exact values whenever suitable.* |
| ☒ | ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☒ | ☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated |

*Our web collection on statistics for biologists contains articles on many of the points above.*

## Software and code

Policy information about availability of computer code

| | |
|---|---|
| Data collection | The clinical data were captured in Medidata Classic Rave® 2021.2.0 |
| Data analysis | SAS version 9.4 was used to analyze clinical data, and GraphPad Prism version 8.0. Changes in gene expression |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

## Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Syndax Pharmaceuticals, Inc. (Syndax) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. Syndax is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. Upon submission of a request to datarequest@syndax.com, Syndax will provide an outline of the process and requirements for submitting a data request. Feasible

requests will be reviewed by a committee of Syndax subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with Syndax before Syndax may grant data access. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent Syndax from sharing requested data, including country or region-specific regulations. If Syndax declines the request, it will communicate the decision to the investigator. Access to genetic or exploratory biomarker data requires a detailed statistical analysis plan that is collaboratively developed by the requestor and Syndax subject matter experts.

## Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

| | |
|---|---|
| Reporting on sex and gender | Sex and gender-based analyses were not performed given the lack of statistical power to infer meaningful conclusions in subgroup analyses of this first-in-human phase 1 study. |
| Population characteristics | Key eligibility criteria include age 30 days or older; relapsed or refractory acute leukemia with KMT2A rearranged or mutated NPM1 performed at each participating site; have Eastern Cooperative Oncology Group (ECOG) performance status score 0–2 (if aged ≥18 years); Karnofsky Performance Scale of ≥50 (if aged ≥16 years and <18 years); Lansky Performance Score of ≥50 (if aged <16 years); have adequate organ function. Extended data table 1 summarizes the baseline demographics and disease characteristics for the overall population enrolled. More details are available in the protocol. |
| Recruitment | Patients were recruited in participating centers (City of Hope, Duarte, CA; Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; Memorial Sloan Kettering Cancer Center, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Chicago, Chicago, IL; University of Iowa, Iowa City, IA; Washington University School of Medicine in St. Louis, St. Louis, MO; Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA) in the United States according to the full protocol eligibility criteria without bias. |
| Ethics oversight | The study protocol and all amendments were approved by the institutional review board or ethics committee at The University of Texas MD Anderson Cancer Center, City of Hope, Washington University School of Medicine in St. Louis, Dana-Farber Cancer Institute, Winship Cancer Institute, Emory University School of Medicine, University of Chicago, Florida Cancer Specialists/Sarah Cannon Research Institute, University of Iowa, and Memorial Sloan Kettering Cancer Center. |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

# Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

# Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

| | |
|---|---|
| Sample size | Dose escalation in this phase 1 study employed a Rolling 6 trial design (Skolnik 2008). The study included two parallel dose escalation cohorts, for patients not taking (Arm A) or taking (Arm B) strong CYP3A4 inhibitors, where 2 to 6 patients can be concurrently enrolled into a dose level, dependent upon (1) the number of patients enrolled at the current dose level; (2) the number of patients who have experienced dose-limiting toxicity (DLT) at the current dose level; and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of 6 has enrolled or when the study endpoints have been met. A dose cohort in either arms may be expanded to 12 patients. |
| Data exclusions | No data from the specified efficacy or safety populations were excluded from analysis. |
| Replication | This is a phase 1 clinical trial which enrolled eligible human subjects with appropriate sample size calculation, therefore replication of data is not applicable for analysis of trial results. |
| Randomization | This is a phase 1 clinical trial, no randomization of subjects performed between arms (with and without a CYP3A inhibitor) in order to allow patients to receive the anti-fungal that fits best their clinical need. |
| Blinding | This is a single arm study, blinding is not applicable. |

# Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

## Materials & experimental systems

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ Antibodies |
| ☐ | ☒ Eukaryotic cell lines |
| ☒ | ☐ Palaeontology and archaeology |
| ☒ | ☐ Animals and other organisms |
| ☐ | ☒ Clinical data |
| ☒ | ☐ Dual use research of concern |

## Methods

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ ChIP-seq |
| ☒ | ☐ Flow cytometry |
| ☐ | ☐ MRI-based neuroimaging |

# Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

| | |
|---|---|
| Cell line source(s) | MOLM-13 were acquired from DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH). |
| Authentication | The cells were not authenticated. |
| Mycoplasma contamination | Cells tested negative for mycoplasma contamination. |
| Commonly misidentified lines (See ICLAC register) | No commonly misidentified cell lines were used in this study. |

# Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

| | |
|---|---|
| Clinical trial registration | ClinicalTrials.gov, NCT04065399 |
| Study protocol | Available in the supplementary information section. |
| Data collection | Data were collected at participating centers in the United States between November 5, 2019, and March 31, 2022 (City of Hope, Duarte, CA; Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; Memorial Sloan Kettering Cancer Center, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Chicago, Chicago, IL; University of Iowa, Iowa City, IA; Washington University School of Medicine in St. Louis, St. Louis, MO; Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA). The data cutoff date for this analysis was March 31, 2022. |
| Outcomes | The primary endpoints of the this phase 1 trial are: (1) To determine the safety, tolerability, the maximum tolerated dose (MTD), or, if different, the recommended phase 2 dose (RP2D) in arms A (without strong CYP3A4 inhibitors), and B (with strong CYP3A4 inhibitors). (2) To characterize the pharmacokinetic parameters of SNDX-5613. Exploratory objectives included assessment of the antileukemic activity of SNDX-5613 and an evaluation of the relationship between clinical or pharmacodynamic biomarkers with safety and efficacy. Dose-limiting toxic effects were defined as non-hematologic toxic effects of grade 3 or higher during cycle 1 or hematologic toxicities directly attributed to study drug and not to the underlying disease. Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Clinical efficacy was assessed by the investigators with the use of a modified version of the 2017 European LeukemiaNet response criteria including complete remission with partial hematologic recovery (CRh). More details are available in the protocol. |

# Magnetic resonance imaging

## Experimental design

| | |
|---|---|
| Design type | Not applicable |
| Design specifications | Not applicable |
| Behavioral performance measures | Not applicable |

## Acquisition

Imaging type(s) — *Specify: functional, structural, diffusion, perfusion.*

Field strength — *Specify in Tesla*

Sequence & imaging parameters — *Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.*

Area of acquisition — *State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.*

Diffusion MRI ☐ Used ☐ Not used

## Preprocessing

Preprocessing software — *Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*

Normalization — *If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.*

Normalization template — *Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.*

Noise and artifact removal — *Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).*

Volume censoring — *Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.*

## Statistical modeling & inference

Model type and settings — *Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).*

Effect(s) tested — *Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.*

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016) — *Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.*

Correction — *Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).*

## Models & analysis

| n/a | Involved in the study |
|---|---|
| ☐ | ☐ Functional and/or effective connectivity |
| ☐ | ☐ Graph analysis |
| ☐ | ☐ Multivariate modeling or predictive analysis |

Functional and/or effective connectivity — *Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).*

Graph analysis — *Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).*

Multivariate modeling and predictive analysis — *Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.*