Menin inhibitor DS-1594b drives differentiation and induces synergistic lethality in combination with venetoclax in acute myeloid leukemia cells with rearranged mixed-lineage leukemia and mutated nucleophosmin-1

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Abstract

Mixed-lineage leukemia (MLL) rearrangements (*MLLr*) and nucleophosmin-1 (*NPM1*) mutations are associated with acute leukemias whose pathogenesis is critically influenced by protein-protein interactions between menin and MLL. We hypothesized that targeting the menin-MLL interaction using DS-1594b and blocking the anti-apoptotic BCL-2 protein using venetoclax may promote differentiation and enhance eradication of *MLLr* and *NPM1*-mutated leukemias models. We treated acute myeloid leukemia (AML) cell lines with *MLLr, NPM1* mutations, other leukemias and primary samples from AML patients with venetoclax alone, DS-1594b alone, and their combination. We measured proliferation, viability, apoptosis, and differentiation using a variety of cellular assays, western blotting, and BH3 profiling. Treatment with DS-1594b and venetoclax exerted significant synergy, resulting in enhanced differentiation and inhibited proliferation across several cell lines. In the *NPM1*-mutated AML patient-derived xenograft model, DS-1594b single-agent treatment significantly extended survival. Importantly, compared with DS-1594b monotherapy, the combination of DS-1594b and venetoclax more profoundly reduced leukemic burden and prolonged mouse survival. Menin inhibition was the primary driver of transcription changes in this model and impacted the expression of anti-apoptotic regulators, providing a mechanistic explanation for the synergy observed between these drugs. Overall, we observed synergistic effects on differentiation induction and proliferation inhibition, both *in vitro* and *in vivo*. Together, our studies underscore the promise of this combination strategy as a novel therapeutic approach for improving treatment outcomes in patients with these specific genomic alterations.

Introduction

Acute leukemias are a heterogeneous group of aggressive blood cancers characterized by the rapid proliferation of immature white blood cells in the bone marrow. Among these, mixed-lineage leukemia (MLL, *KMT2A*) rearrangements (*MLLr*) and nucleophosmin 1 (*NPM1*) mutations represent two distinct subtypes, each posing significant clinical challenges.[1,2] *MLLr* are a common genetic anomaly in pediatric hematologic malignancies, where they are found in up to 80% of infant acute lymphoblastic leukemia patients.[3] However, in adult acute myeloid leukemia (AML), they occur in only 5% to 10% of cases.[4] These rearrangements arise from translocations involving the *MLL* gene, producing fusion proteins that enhance proliferation, block differentiation, and drive aggressive leukemias.[5] Unfortunately, *MLLr* leukemias are notoriously resistant to conventional treatment approaches and associated with high early mortality, resulting in a distressingly low 5-year survival rate of only 35% in newly diagnosed, and <10% in relapsed/refractory (R/R) AML.[6]

In contrast, *NPM1* mutations are among the most common alterations in adult AML, present in ~30% of cases.[7] The *NPM1* gene encodes a nucleolar phosphoprotein involved in various cellular processes, including ribosome biogenesis and centrosome duplication. Mutations in *NPM1* cause aberrant cytoplasmic localization, disrupting normal functions and promoting leukemogenesis through *HOX* gene activation.[8,9] Although *NPM1*-mutated AML generally has a favorable prognosis in the absence of *FLT3*-internal tandem duplications (ITD) mutations[10] it remains a clinical challenge in relapse/refractory and elderly patients.[11]

Menin, encoded by *MEN1*, is a scaffold protein essential for regulating gene expression through its interactions with chromatin-modifying complexes and plays a crucial role in various cellular processes.[12] It was initially identified as the product of the *MEN1* gene, linked to multiple endocrine neoplasia type 1, a hereditary tumor syndrome.[13] Several studies have revealed the critical role of protein-protein interactions between menin, MLL, and MLL fusion proteins in the pathogenesis of *MLLr* leukemias.[14,15] Similarly, mutated NPM1 interacts with the MLL complex to regulate oncogenic signatures in *NPM1*-mutated AML.[16,17] Consequently, targeting the menin-MLL interaction with additional menin inhibitors has emerged as a promising therapeutic strategy in preclinical and clinical studies of both *MLLr* and *NPM1*-mutated AML.[18] Notably, the first menin inhibitor revumenib was recently approved by the Food and Drug Administration for the treatment of R/R acute leukemia with *KMT2A* translocations, marking a significant milestone in the treatment of these challenging leukemias.[19] Resistance mechanisms to menin inhibitors can include the appearance of specific point mutations that abrogate drug binding, but emerging evidence suggests that different inhibitors may have unique effects on the various pathways through which resistance develops.[20] Therefore, expanding preclinical data across a range of structurally distinct menin inhibitors remains an important task to refine therapeutic approaches.

Here, we investigated the preclinical potential of the novel menin-MLL inhibitor DS-1594b,[21] in combination with venetoclax, a selective inhibitor of the antiapoptotic BCL2 protein.[22] Venetoclax has shown promising activity in AML, making it an ideal partner for targeted therapies.[23] We and others have shown that acute lymphoblastic leukemia cells with the t(4;11) *MLL* translocation express high BCL2 levels and are highly sensitive to venetoclax, as the resulting MLL/AF4 fusion protein upregulates BCL2 via increased H3K79me2/3 at its locus.[24] Here, we hypothesized that targeting the menin-MLL interaction using DS-1594b in combination with venetoclax may promote cell differentiation and enhance lethality in acute leukemias, particularly in *MLLr* and *NPM1*-mutated AML. To test this hypothesis, we utilized both cell lines and patient samples harboring either *MLLr* or NPM1 mutations and a patient-derived xenograft (PDX) model of *NPM1*-mutated acute leukemia to assess the synergistic effects of DS-1594b and venetoclax on leukemic cell viability, apoptosis induction, and differentiation potential.

By evaluating this drug combination preclinically, our study aims to provide insights into a targeted therapeutic strategy for acute leukemias with *NPM1* mutations and *MLLr*,[25] potentially supporting new treatment options for these high-risk patients.

Methods

Cell lines and patient samples

AML cell lines with *MLLr* (OCI-AML2, MOLM-13, MOLM-14, MV4-11, MOLM-13 ven-res), *NPM1* mutations (OCI-AML3, IMS-M2), and without these alterations (U937, HL60) were obtained from DSMZ and the University of Perugia.[26] Cells and patient samples (2,000–150,000/well) were treated with DS-1594b (0-10 μM, 5-10 days; Daiichi Sankyo[21]) and/or venetoclax (0-500 nM, 5 days; LC Laboratories[22]), except MV4-11 cells, which were treated for 3 days due to their higher sensitivity. This study was approved by the institutional review board of The University of Texas MD Anderson Cancer Center (protocol LAB-01-473), and conducted in accordance with the Declaration of Helsinki; written informed consent was obtained from all participants.

Proliferation, viability, apoptosis, and differentiation assays

Cell proliferation was measured by quantifying ATP using a CellTiter-Glo Luminescent Cell Viability Assay (Promega). The effect of each treatment on the number of viable cells and apoptotic cells was evaluated by Annexin-V-DAPI assay with flow cytometry. To evaluate differentiation, cells were stained with CD14, CD15, CD11b, CD45, and CD33 antibodies (BD Biosciences) and analyzed with flow cytometry.

Western blotting

Immunoblotting was performed as detailed in Baran *et al.*[27] (*Online Supplementary Appendix*). The antibody panel used is summarized in *Online Supplementary Table S1*.

BH3 profiling

BH3 profiling was conducted as previously reported[28] (*Online Supplementary Appendix*).

Acute myeloid leukemia xenograft mouse study

Forty female NSG mice (8-10 weeks old; Jackson Laboratory, NOD.Cg-Prkdc^scid Il2rgtm1Wjl/SzJ) were inoculated via tail vein with 3×10^6 NPM1m PDX/luc/GFP cells in 100 μL. After leukemia engraftment was confirmed by bioluminescence, mice (N=10/group) were randomized to vehicle, venetoclax, DS-1594b, or the combination. DS-1594b (50 mg/kg) was given orally for 4 weeks starting 12 days post-injection; venetoclax was given orally at 50 mg/kg for 2 weeks, then 100 mg/kg for 2 weeks of a 28-day cycle. Mice were weighed weekly and sacrificed at endpoint per IACUC guidelines. Spleen PDX cells were barcoded and stained with met-

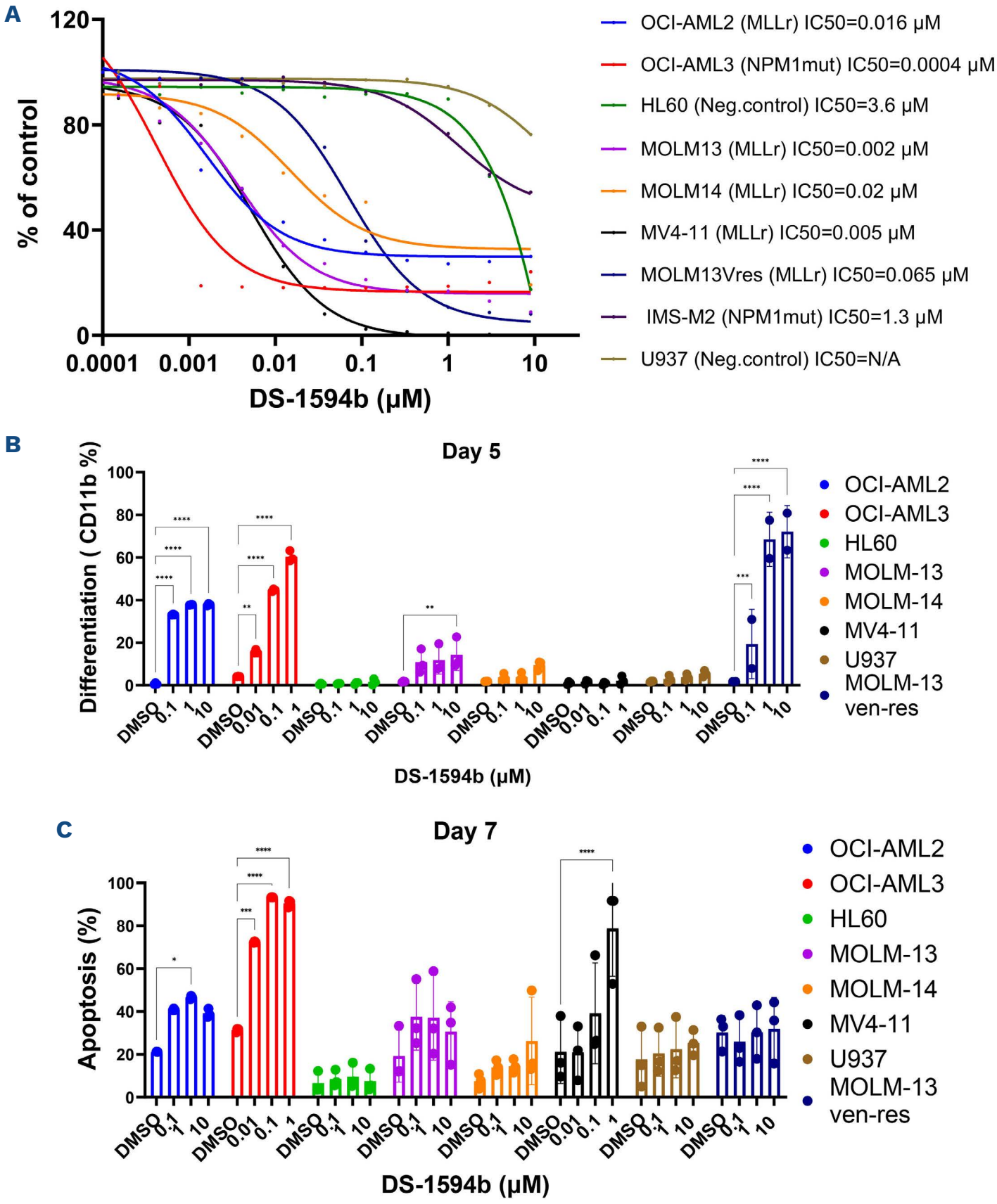

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Figure 1. DS-1594b alone promotes differentiation in *MLL*-rearranged and NPM1-mutant cell lines. (A) A proliferation assay was conducted by treating cell lines with *MLL* rearrangements (OCI-AML2, MOLM-13, MOLM-14, MV4-11, MOLM-13 venetoclax resistance [ven-res]) and *NPM1* mutations (OCI-AML3 and IMS-M2) and negative control (Neg.) cell lines (U937 and HL60) with DS-1594b alone at concentrations between 0.0001 μM and 9 μM for 7 days. Dose-response curves were analyzed using a curve-fitting routine based on non-linear regression to compute the half-maximal inhibitory concentration (IC50) value. (B) Cell lines were treated with vehicle (0.2% dimethyl sulfoxide [DMSO]) or 0.1, 1, or 10 μM (or 0.01, 0.1, and 1 μM) DS-1594b for 5 days. Differentiation effects were determined by flow cytometry using the CD11b marker. Two-way ANOVA was performed to determine statistical significance (**P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001). (C) Apoptotic cells were identified by flow cytometry using counting beads, Annexin-V, and DAPI after 7 days. Two-way ANOVA was performed to determine statistical significance (**P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001). (D) OCI-AML3, HL60, OCI-AML2, and IMS-M2 cells were treated with the indicated concentrations of DS-1594b for 5 or 7 days. Following this, total cell lysates were prepared, and BCA protein assay was performed, and 30 μg of protein was loaded for western blot analyses. The expression levels of β-actin in the lysates served as the loading control. N/A: not applicable.

al-conjugated antibodies for high-dimensional cytometry by time of flight (CyTOF).[29] Bioluminescence images were acquired every 7-10 days using the IVIS Lumina LT system.

RNA-sequencing analysis

FastQ files were quality checked using FastQC[30] and the reads were trimmed using Trim Galore! With the parameter --2colour 20. The trimmed reads were then mapped to hg38 reference genome using STAR.[31] Gene expression was then quantified using featureCounts.[32] DESeq2[33] was used to carry out differential gene analysis. Batch correction was carried out using RUVSeq.[34] Gene ontology enrichment analysis using biological process terms was performed using ClusterProfiler.[35]

Results

DS-1594b alone promotes differentiation in *MLL*-rearranged and *NPM1*-mutated cell lines

We first evaluated the impact of DS-1594b on the viability of various cell lines with *MLLr* (MOLM-13, MOLM-14, MV4-11) and *NPM1* mutations (OCI-AML3, IMS-M2) after 7 days of treatment. Our findings indicated that low μM concentrations of DS-1594b significantly reduced proliferation in these cell lines, while having no effect on non-*MLL*r/non-*NPM1*-mutated U937 and HL60 cells (Figure 1A). Given the frequency of venetoclax resistance in AML, we generated venetoclax-resistant (ven-res) AML cell lines to evaluate whether menin inhibition could provide an alternative therapeutic option. To this end, we exposed MOLM-13, OCI-AML2, and MV4-11 cells to increasing concentrations of venetoclax, starting at 10 nM and increasing to 1 μM (see *Online Supplementary Appendix*). Notably, the ven-res MOLM-13 cell line, along with the other two ven-res cell lines, OCI-AML2 and MV4-11, all of which harbor *MLL* rearrangements, showed varying responses to DS-1594b. MOLM-13 ven-res was sensitive to the treatment, while OCI-AML2 and MV4-11 ven-res did not respond (Figure 1A; *Online Supplementary Figure S1A*).

Given the known effects of menin inhibitors on inducing cell differentiation,[36] we assessed whether DS-1594b alone induced differentiation in the tested AML cell lines by examining differentiation markers (CD11b, CD14, CD15) using flow cytometry. Our results revealed that OCI-AML3,[37,38] OCI-AML2, MOLM-13 ven-res, and MOLM-14 cell lines began to show differentiation effects (CD11b positivity) after 5 days (Figure 1B), with the effects becoming more evident after 10 days of treatment (*Online Supplementary Figure S1B*). Of note, the differentiation marker CD15, expressed by neutrophils, was found to be upregulated only in the MOLM-14 cell line, while CD14, expressed by monocytes, was present only when CD11b was expressed after 10 days (*Online Supplementary Figure S1C, D*). No differentiation was observed in non-*NPM1*/non-*MLL*r cell lines like U937 or HL60, even at higher doses of DS-1594. Moreover, DS-1594b treatment induced apoptosis in OCI-AML2, OCI-AML3, and MV4-11 cells after 7 days (Figure 1C). Notably, apoptosis was also observed in MOLM-13 and MOLM-13 ven-res cell lines after 10 days of treatment (*Online Supplementary Figure S1E*). Western blot analysis performed after 5-day treatment with DS-1594b showed a reduction in menin protein levels across all leukemia cell lines, accompanied by decreased BCL-2 expression in OCI-AML3 and OCI-AML2, and reduced levels of the cell-cycle inhibitor p27 specifically in OCI-AML2 cells (Figure 1D). Interestingly, when treated with DS-1594b, MCL-1 was upregulated in OCI-AML3 but not in the other cell lines. In addition, CD11b upregulation was found in OCI-AML2 and OCI-AML3, consistent with results observed from flow cytometry analysis.

Next, using dynamic BH3 profiling, we tested whether menin inhibition enhanced cell dependency on the antiapoptotic BCL-2 family members for survival (see the *Online Supplementary Appendix*). MV4-11 cells were pre-treated with DS-1594b followed by exposure to different BH3 mimetic peptides, and the mitochondrial outer membrane permeabilization was measured by flow cytometric monitoring of cytochrome c release after 24 hours. We observed that in both cell lines, inhibition of menin increased cell priming to the pan-activator and sensitizer hBIM, hBID-Y, PUMA, and Bmf-Y peptides (*Online Supplementary Figure S2A, B*), and only OCI-AML3 cells were additionally primed to MCL-1 targeting mNoxaA and MS1 peptides. This pattern indicates that while in MV4-11 cells, DS-1594b enhanced cell dependency on BCL-2, in OCI-AML3 cells the drug additionally increased their dependence on the anti-apoptotic MCL-1 for survival.

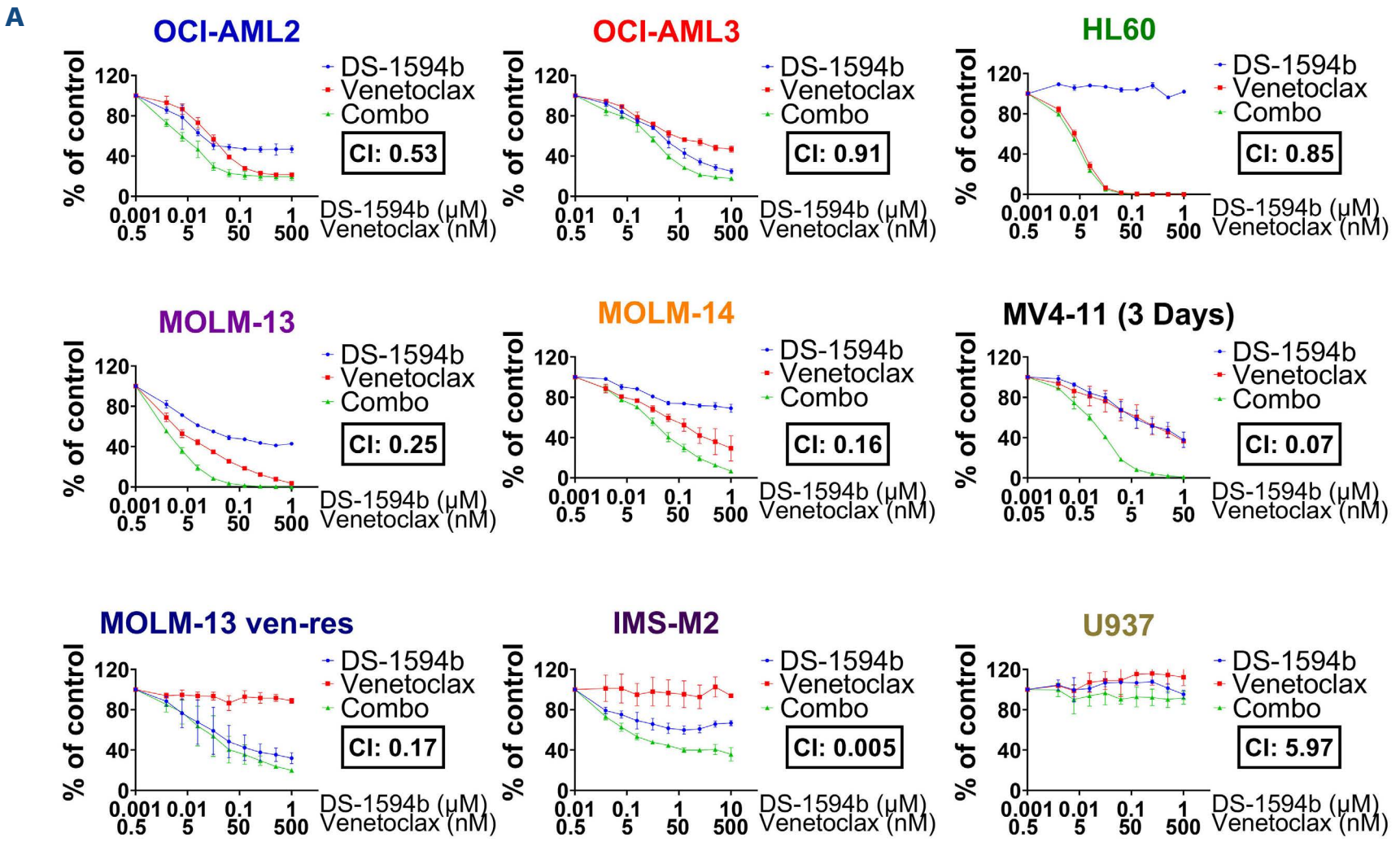


Figure 2. Co-treatment with DS-1594b and venetoclax exerts synergistic *in vitro* lethality in acute myeloid leukemia cells expressing *MLL* rearrangements or *NPM1* mutations. (A) Proliferation assay was conducted by treating cell lines with *MLL* rearrangements (OCI-AML2, MOLM-13, MOLM-14, MV4-11, MOLM-13 venetoclax resistance) and *NPM1* mutations (OCI-AML3 and IMS-M2) and negative control cell lines (U937 and HL60) with DS-1594b (DS) alone, venetoclax (Ven) alone, or a combination treatment with the indicated concentrations in a fixed ratio for 5 days (5d). MV4-11 was treated for 3 days. The combination index (CI), based on the Chou-Talalay method, was determined by CalcuSyn software (version 2.0). (B) Apoptosis assay was conducted by treating cells lines for 5d, except for MV4-11, which was treated for 3d, with the indicated concentrations. Apoptotic cells were determined by flow cytometry using counting beads, Annexin-V, and DAPI. Two-way ANOVA was performed to determine statistical significance between dimethyl sulfoxide (DMSO) and combination (combo) treatment (**P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001). (C) OCI-AML2, OCI-AML3, IMS-M2, MV4-11, and U937 cells were treated with the indicated concentrations of DS-1594b and venetoclax for 3d or 5d. Following this, total cell lysates were prepared, BCA protein assay was performed, and 30 μg of proteins were loaded for western blot analyses. The expression levels of β-actin in the lysates served as the loading control.

Overall, our results demonstrate that DS-1594b induces differentiation of AML cells, consistent with a similar effect reported for other menin inhibitors in the literature,[39] as well as blocking cell proliferation. Additionally, we observed significant apoptosis induction after prolonged treatment (7-10 days) in several cell lines. Importantly, menin inhibition primed AML cells to become more dependent on BCL-2 for survival.

Co-treatment with DS-1594b and venetoclax exerts synergistic *in vitro* lethality in acute myeloid leukemia cells expressing *MLL* rearrangements or *NPM1* mutations

Our findings of increased survival BCL-2 dependency upon menin inhibition led us to explore the possibility that targeting BCL-2 with clinically used venetoclax may enhance the anti-AML efficacy of DS-1594b in cells expressing *NPM1* mutant proteins or MLL fusion proteins.

To this end, we tested the efficacy of combined DS-1594b and venetoclax treatment in the same *MLLr* and *NPM1*-mutated cell lines described previously. These combination experiments were performed using a 5-day treatment schedule (except for MV4-11, treated for 3 days), which was selected to capture the full range of drug responses and potential synergistic effects, especially given the delayed activity typically observed with Menin inhibitors in AML. Combination treatment significantly reduced proliferation in all MLLr and NPM1-mutant lines, while sparing control lines (HL60, U937) (Figure 2A). Notably, the MV4-11 cell line displayed significant inhibition after just 3 days of treatment (combination index [CI]=0.07), suggesting heightened sensitivity to the drug combination, as did the MOLM-13 and MOLM-14 cell lines after 5 days of treatment (CI=0.25 and CI=0.16, respectively). Moreover, the *NPM1*-mutated IMS-M2 cell line exhibited inhibition only when treated with the drug combination, not when treated with either drug alone (CI=0.005). In addition, Bliss synergy score analysis revealed synergy of the combined treatment in MOLM-14, but not in U937 cells (*Online Supplementary Figure S2C*), confirming efficacy of both drugs in *MLLr* AML cell lines.

Next, we analyzed the effects of co-treatment with venetoclax and DS-1594b on apoptosis using flow cytometry for Annexin-V and a western blot assay. All tested cell lines, except the negative control U937, underwent apoptosis following combined treatment (*Online Supplementary Figure S3A*). Notably, in OCI-AML2 cells, the combination efficacy is primarily driven by venetoclax. Additionally, the western blot analysis (Figure 2B) demonstrated increased levels of PARP-C and decreased level of total caspase-3, both well-known apoptosis hallmarks. CD11b was upregulated in OCI-AML3, and menin was downregulated in all cell lines. The expression of MCL-1 persisted in OCI-AML3 cells after treatment with the combination for 3 days, consistent with increased priming by BH3 profiling, yet was reduced after 5 days likely due to a change in cell state due to differentiation. In addition, P27 is downregulated in all cell lines except for the U937 cell line control. These outcomes were contrary to what was observed when DS-1594b was used alone.

These findings collectively confirm that DS-1594b and venetoclax combination treatment effectively inhibits proliferation and induces apoptosis in cell lines with *MLLr* and *NPM1* mutations, achieved through the activation of the PARP-c and caspase-3-c pathways.

DS-1594b and venetoclax combination therapy promotes differentiation and shows enhanced lethality in primary acute myeloid leukemia patient samples harboring *MLL* rearrangements or *NPM1* mutations

Next, we investigated the potential of a combination DS-1594b and venetoclax treatment to induce differentiation and lethality in primary samples from AML patients that harbor *MLLr* or *NPM1* mutations. Our findings provide evidence that the combined treatment exerted a moderate synergistic effect, in four of six tested patient samples (Figure 3A; *Online Supplementary Figure S4A*). Importantly, among these, three of five patient samples with *MLLr* exhibited synergistic inhibition of viability as shown by Bliss synergy score, indicating a favorable response to menin/BCL-2 inhibition. Sample from patient 3 (PT3) however, displayed resistance to menin inhibition. Additionally, dual combination demonstrated a slight synergistic effect in patient sample PT6 with an *NPM1* mutation (Figure 3A; *Online Supplementary Figure S4A*). In turn, DS-1594b alone led to a substantial increase in the differentiation of AML cells, particularly in PT2 and PT6 (Figure 3B), and less so in other patient samples treated with DS-1594b alone.

Overall, our results suggest that the combination therapy of a menin inhibitor and venetoclax may be a promising treatment strategy for AML patients with *MLLr* or *NPM1* mutations. Furthermore, our findings highlight the potential of using DS-1594b as a single agent to promote AML cell differentiation.

In vivo efficacy of the combination of DS-1594b with venetoclax in patient-derived xenografts with *NPM1* mutations

After observing moderate synergy between DS-1594b and venetoclax against AML cells with *MLLr* or *NPM1* mutations *in vitro*, next we assessed antileukemia efficacy of dual combination *in vivo* using NSG mice engrafted with *NPM1*-mutated AML cells in a PDX luciferase-expressing model. We tested DS-1954b and venetoclax individually and in combination at well-tolerated doses. We found that co-treatment with DS-1594b and venetoclax for 4 weeks resulted in a greater reduction in AML burden compared with treatment with either single-agent treatment or the vehicle control. Bioluminescence imaging demonstrated the efficacy of the combination treatment (Figure 4A, B). Importantly, the weight of the mice in the combination group was not significantly affected, indicating good tolerance, whereas venetoclax and control groups experienced significant weight reduction (Figure 4C). Interestingly, there was no difference in weight between the DS-1594b and combination groups. Furthermore, the com-

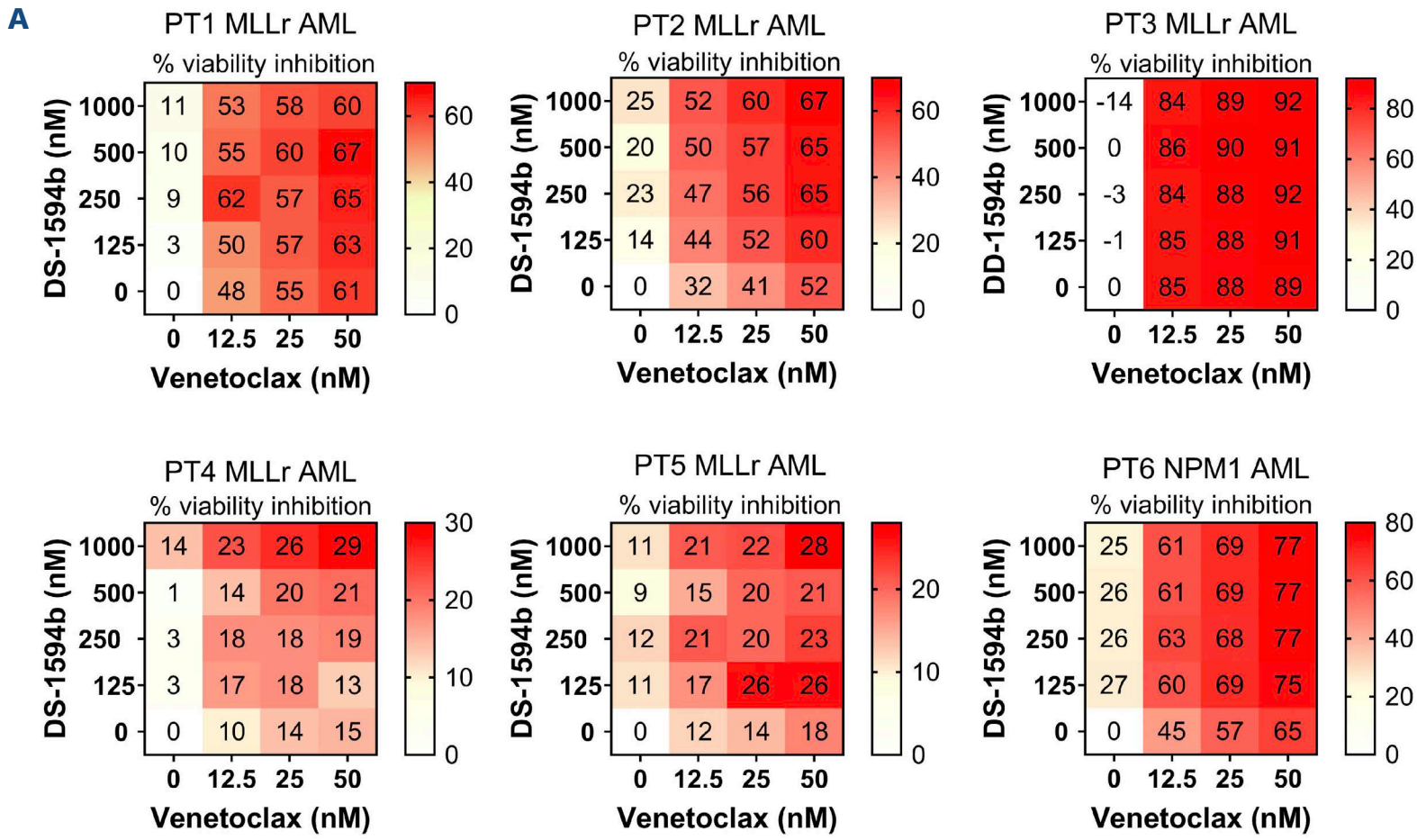
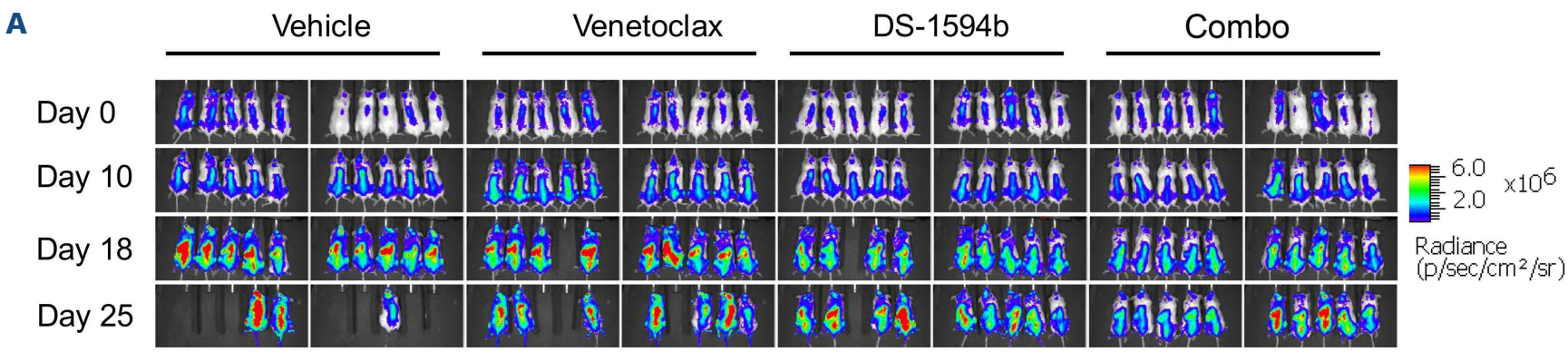
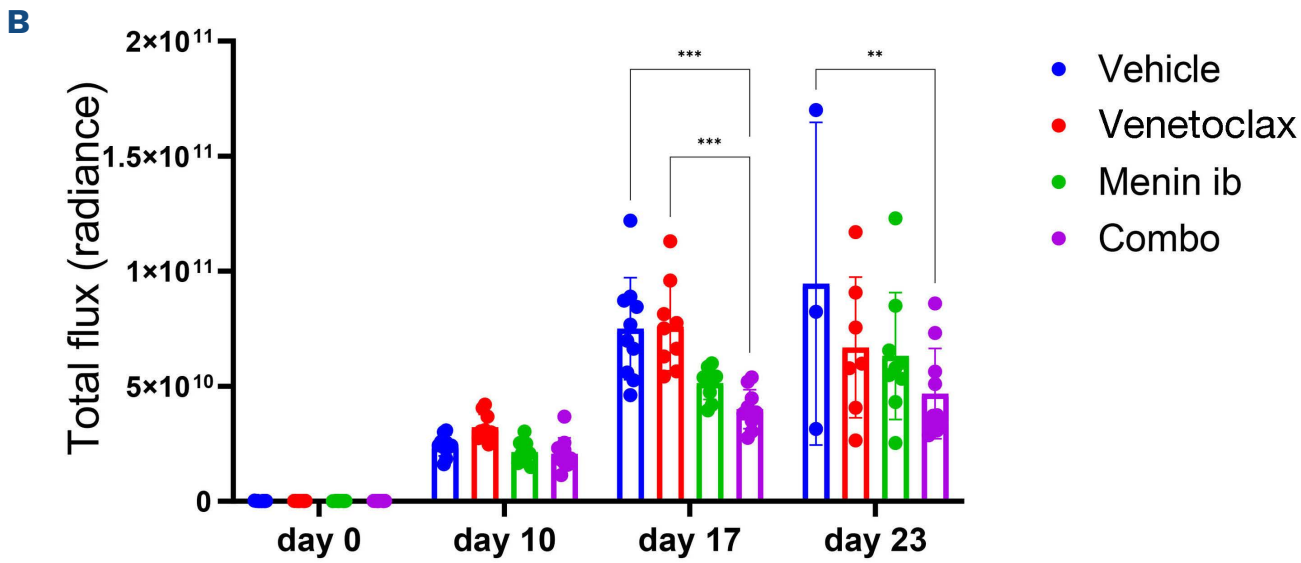
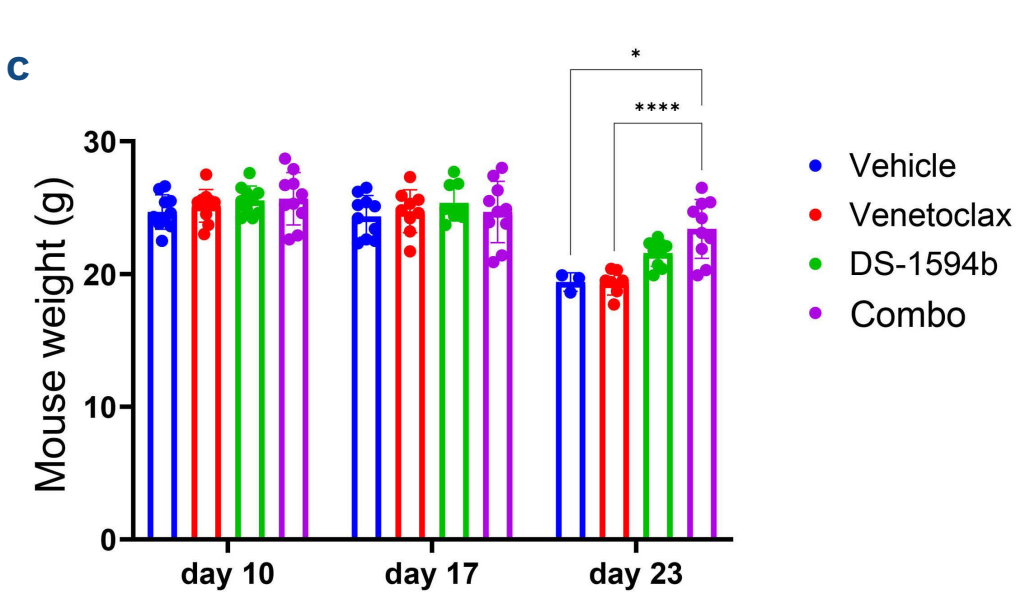
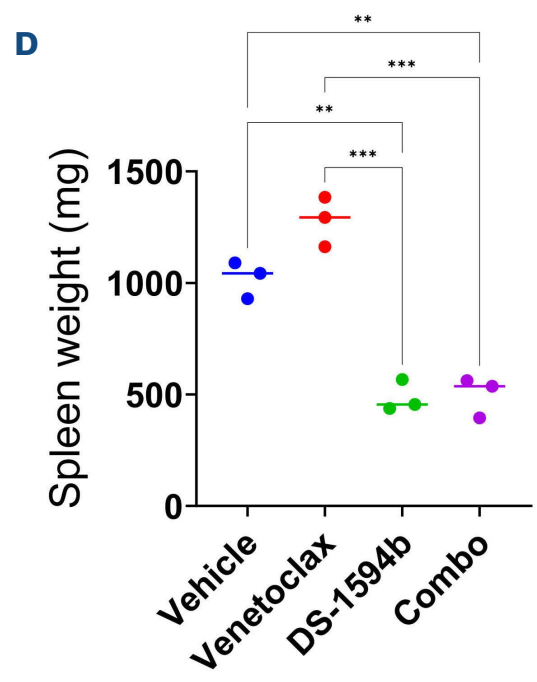


Figure 3. Combination therapy promotes differentiation and shows enhanced lethality in primary acute myeloid leukemia patient samples harboring *MLL* rearrangements or *NPM1* mutations. (A) Patient cells with *MLL* rearrangements (MLLr) or *NPM1* mutations were treated with the indicated concentrations of DS-1594b and venetoclax for 3 days. Viable cell numbers were measured by quantifying ATP using a CellTiter-Glo Luminescent Cell Viability Assay. (B) Four patients' cells were treated with vehicle (0.2 % dimethyl sulfoxyde [DMSO]) or 0.1 or 1 μM DS-1594b for 5 to 7 days. Differentiation effects were determined by flow cytometry using the CD11b marker. Single experiments were conducted due to the limited number of cells from the patients. AML: acute myeloid leukemia; PT: patient.









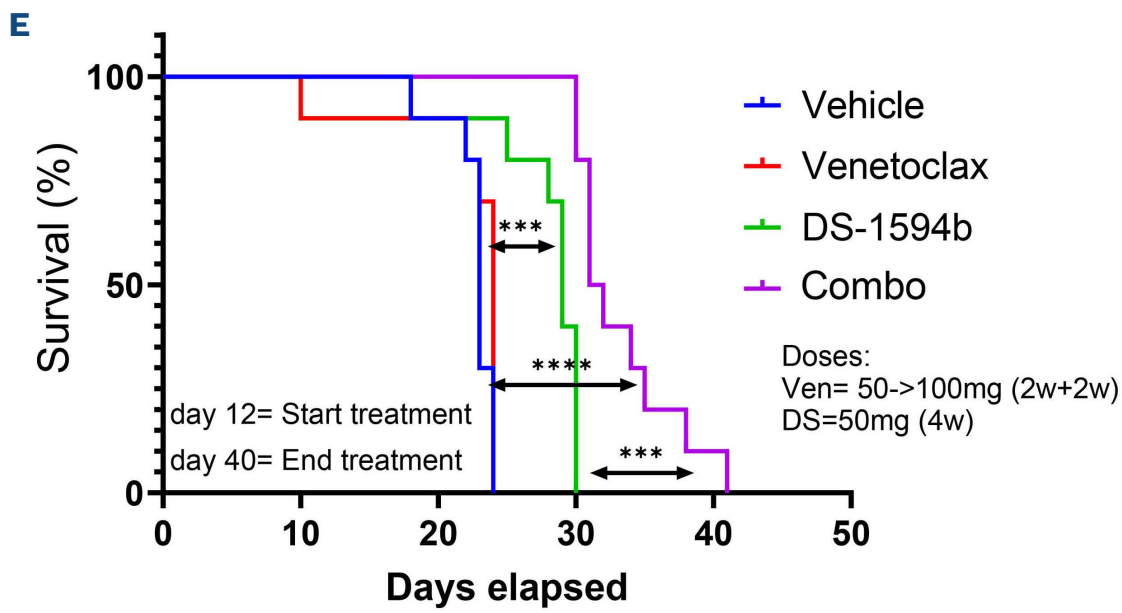


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Figure 4. *In vivo* efficacy of the combination of DS-1594b with venetoclax in *NPM1*-mutated patient-derived xenografts. (A) Bioluminescence imaging of tumor burden. Mice were inoculated via the tail vein with *NPM1*m PDX/luc/GFP; 3.0×10^6 cells/100 µL/mouse). Once leukemia engraftment was confirmed by bioluminescence imaging (day 0), mice (N=10/group) were randomized to 4 treatment arms: vehicle; venetoclax (Ven) alone, DS-1594b alone, and venetoclax/DS-1594b (Combo). Bioluminescence imaging was performed at days 0, 10, 18, and 25 with IVIS Lumina LT *In Vivo* Imaging System. (B) Total flux radiance of mice every 7 to 10 days from bioluminescence imaging data. Two-way ANOVA was performed to determine significance (**P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001). (C) Body weight was measured at days 10, 17, and 23. Two-way ANOVA was performed to determine statistical significance (**P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001). (D) The spleen weight of 3 mice selected randomly from each treatment group was recorded. Two-way ANOVA was performed to determine statistical significance (**P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001). (E) Kaplan-Meier survival curves of mice according to treatment arm (N=10/group). Treatment started on day 12 and ended on day 40. Venetoclax was administered at 50 mg/kg for 2 weeks (2w) followed by 100 mg/kg for 2w; DS-1594b (DS) was given at 50 mg/kg for 4w. Overall survival was estimated using the Kaplan-Meier method, and differences between groups were assessed using the Gehan-Breslow-Wilcoxon test (****P*<0.001; *****P*<0.0001).

bination and single-agent DS-1594b group had a reduced spleen weight compared with the other groups indicative of a significant suppression of AML progression in the treated groups. (Figure 4D; *Online Supplementary Figure S5A*). No differences were observed in bone marrow engraftment (*Online Supplementary Figure S5B*). The survival curve clearly demonstrated the benefits of the combination treatment, with the DS-1594b group showing some benefit but the combination group showing the greatest benefit (Figure 4E). Notably, this PDX appeared resistant to venetoclax, as demonstrated by the survival curve and bioluminescence images.

Next, we tested whether the addition of venetoclax further enhanced leukemia differentiation compared to menin inhibition alone. To this end, we performed CyTOF using a comprehensive panel of surface and intracellular markers to assess changes in protein expression across multiple pathways, with a particular focus on markers associated with myeloid and monocytic differentiation (Figure 5A). This approach enabled a detailed phenotypic characterization of leukemic cells following *in vivo* treatment. For this analysis, cells from the PDX spleen were stained with anti-human antibodies against differentiation markers and leukemia markers (*Online Supplementary Table S2*). We found that single-agent DS-1594b as well as combined treatment led to the emergence of a population of cells (pop1) with elevated expression of CD33, CD13, and CD44, which are well-known markers of myeloid cell differentiation[40-42] (Figure 5B, C; *Online Supplementary Figure S5C*). Importantly, this population of cells did not significantly increase in the combined treatment compared to DS-1594b alone, suggesting that the observed differentiation of AML cells was driven mainly by DS-1594b.

Menin inhibition potentiates venetoclax treatment via transcriptional mechanisms

To better understand the molecular mechanisms underlying the impact of the combined venetoclax/menin treatment, we performed RNA-sequencing on PDX spleen cells harboring *NPM1*c, DNMT3A and *FLT3*-ITD mutations[43] after 4 weeks of treatment *in vivo*. Comparing across single and combination treatments, it was apparent that most differences in gene expression were driven by the DS-1594b-mediated inhibition of menin, with few additional gene expression changes induced by the combined treatment (Figure 6A). Classic menin targets, such as *MEIS1*, *FLT3* and *HOXA9*, had decreased expression (*Online Supplementary Figure S5D*). Cluster 1 and 4 genes (decreased expression in DS-1594b and combination) were enriched for DNA replication, cell division, and RNA processing, whereas Cluster 5 genes (decreased expression with venetoclax and combination treatment) were enriched for interferon response and response to virus (*Online Supplementary Figure S5E*).

Interestingly, there was a small subset of genes that were further downregulated or upregulated in the combination treatment compared to menin inhibition alone (Figure 6B, clusters 3 and 4). Based on this we hypothesized that menin inhibition might drive the downregulation of anti-apoptotic factors, which could be further potentiated by co-treatment with venetoclax. To explore this possibility, we focused on key anti-apoptotic genes and found that DS-1594b suppressed expression of MCL-1 (Figure 6C). Importantly, this effect was significantly augmented by combined treatment with venetoclax. Given that upregulation of MCL-1 is a well-defined factor underlying AML resistance to venetoclax,[44] such profound effect of treatment on MCL-1 level could account for the synergy of combined therapy observed in the tested PDX model.

We performed additional RNA-sequencing in the *NPM1*-mutant cell line OCI-AML3 and the MLL-AF4 cell line MV4-11 and similarly observed that menin inhibition drives the majority of transcriptional changes both alone and in combination with venetoclax (*Online Supplementary Figure S6A, B*), including downregulation of known menin targets (*Online Supplementary Figure S6C, D*) and specific anti-apoptotic genes. We found that OCI-AML3 cells (*Online Supplementary Figure S6E*) specifically downregulated BCL2 in response to treatment with menin inhibition and with the combination. MV4-11 cells (*Online Supplementary Figure S6F*) exhibit statistically significant downregulation of BCL2 and BCL2L10 with Menin inhibitor and combination treatment, along with subtle (but not significant) decreases in BCL2L12 and MCL1. This suggests that the specific anti-apoptotic genes affected by Menin inhibition may depend on the AML context. Chromatin immunoprecipitation sequencing (ChIP-

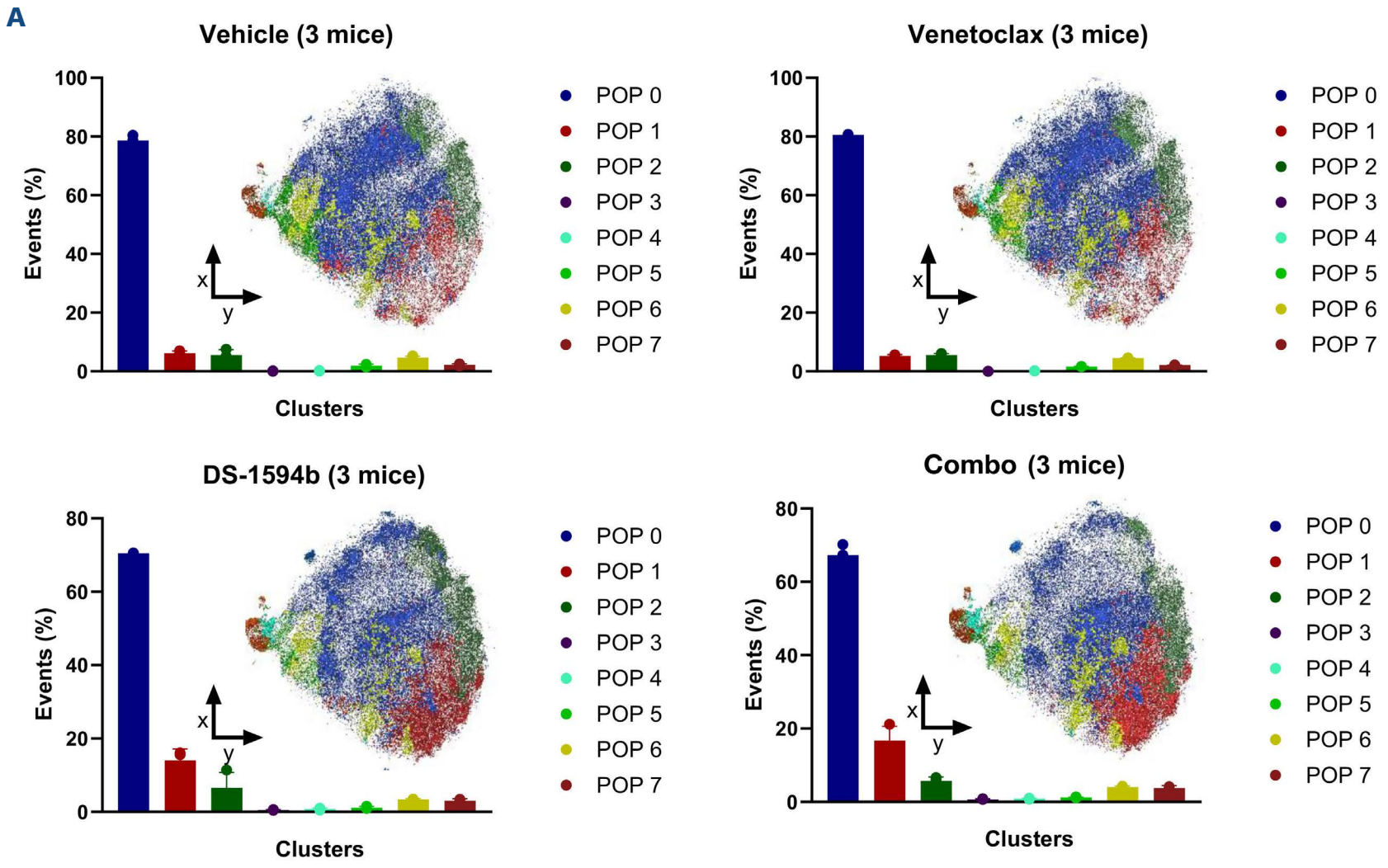

Figure 5. DS-1594b drives differentiation in patient-derived xenograft model. (A) Human patient-derived xenograft (PDX) cells were collected from the spleens of 3 mice in each treatment group after 4 weeks of treatment. These cells were then stained for time of flight cytometry (CyTOF) analysis. Dimensionality reduction was performed using the *t* distributed stochastic neighbor embedding method. Processed data were subjected to negative value pruned inverse hyperbolic sine transformation and clustered based on the PhenoGraph algorithm (k 22) using all cell surface markers listed in *Online Supplementary Table S2*. X- and Y-axes respresent first and second t-SNE dimensions (tSNE_1 and tSNE_2), reflecting similarity in surface marker expression among single cells. (B) Percentage of pop1 population events across the different group treatment *P* values. (C) The expression levels of each protein within each population cluster. CD44, CD33, CD13 differentiation markers are highlighted. NS: not significant; (**P*<0.05; ***P*<0.01); Combo: combination venetoclax/DS-1594b.

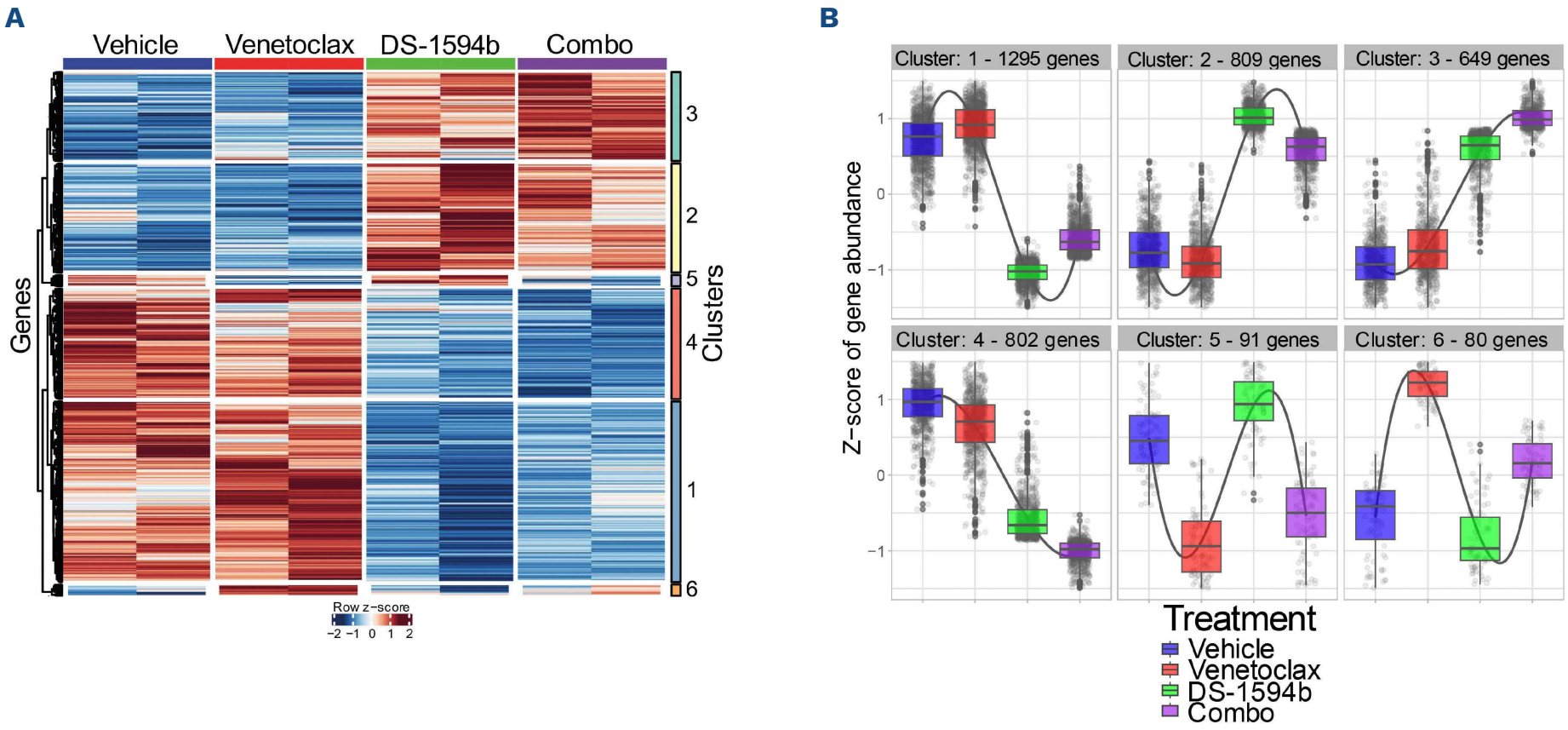

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Figure 6. Menin inhibition potentiates venetoclax treatment via transcriptional mechanisms. (A) Clustered heatmap of differentially expressed genes (adjusted *P* value [*P*-adj] <0.05) in patient-derived xenograft (PDX)-derived splenic leukemia cells from mice treated for 4 weeks with vehicle control (Veh), venetoclax, menin inhibitor (MENi) or a combination (Combo). (B) Boxplots representing the patterns of expression (z-scored) of differentially expressed genes (*P* adj<0.05) from PDX-derived splenic leukemia cells treated with Veh, venetoclax, MENi, or Combo. (C) Expression (CPM) of anti-apoptotic factors in PDX-derived splenic leukemia cells from mice treated with Veh, venetoclax, MENi or Combo. Statistical significance was determined using one-way ANOVA followed by Tukey's *post hoc* test. Significance levels are indicated as follows: ***P adj <1×10^{-3}; **P adj <1×10^{-2}; *P adj <5×10^{-2}; NS, not significant (P adj >5×10^{-2}). (D) RNA-sequencing in PDX-derived splenic leukemia cells from mice treated with venetoclax compared to Veh control. Genes with the lowest adjusted *P* value are labelled. (E) GO:BP enrichment analysis of genes downregulated (*P* adjust<0.05) with venetoclax treatment.

seq) for Menin showed that Menin binds directly to some anti-apoptotic genes in both our PDX models, primary patient cells from an *NPM1*-mutant AML, and cell lines (*Online Supplementary Figure S6G*), MV4-11 data were obtained from publicly available GEO dataset GSE196036), suggesting that these genes are directly regulated by menin binding.

Although menin inhibition appears to drive the majority of transcriptional changes in the combination treatment, we nonetheless wanted to determine if any gene expression changes were driven specifically by venetoclax. To better clarify the differences between the individual treatments with menin, venetoclax, and the combination, we compared differentially expressed genes in each pairwise comparison: venetoclax *versus* vehicle, DS-1954b *versus* vehicle, and combination *versus* vehicle (*Online Supplementary Figure S7A*). The largest overlap of differentially expressed genes was between downregulated genes with menin inhibition and combination treatment. Of the genes that are downregulated with the combination but not menin inhibition, only five genes are also downregulated with venetoclax alone, suggesting that the addition of venetoclax to DS-1954b induces these changes. In a pairwise comparison of vehicle *versus* venetoclax treated cells, there were 76 downregulated and 73 upregulated genes (Figure 6D). A gene ontology (GO) enrichment analysis of the genes downregulated in venetoclax-treated cells revealed that they were related to apoptosis, although it is likely that this regulation is indirect (Figure 6E), given that venetoclax primarily functions as a BCL-2 inhibitor rather than directly influencing gene transcription.

These data indicate that venetoclax and menin inhibitors act through distinct mechanisms, with menin inhibition mainly impacting transcriptional programs, while synergy between the two agents occurs through modulation of anti-apoptotic pathways. Overall, our findings support the combination of DS-1594b and venetoclax as a promising therapeutic strategy with potent anti-leukemic activity *in vivo* for patients with *Mllr* and *NPM1* mutations.

Discussion

In this study, we investigated the potential of combining the menin inhibitor DS-1594b with the BCL-2 antagonist venetoclax in AML. We assessed its ability to promote differentiation and enhance lethality in AML cell lines and primary patient samples harboring *MLLr* or *NPM1* mutations. Additionally, we assessed the *in vivo* efficacy of this combination therapy using a PDX mouse model. Overall, DS-1594b alone primarily inhibited growth and promoted differentiation both *in vitro* and *in vivo*. Moreover, when combined with venetoclax, it effectively induced apoptosis in AML cell lines and *NPM1*-mutated AML PDX mouse model, presenting a promising treatment approach for patients with acute leukemias. These results are consistent with previous studies reporting synergistic anti-leukemic effects of venetoclax in combination with other menin inhibitors.[45,46] The decreased expression of menin and BCL-2 family members, along with the activation of apoptotic pathways, highlights a potential mechanism for the observed effects. Notably, the MV4-11 and MOLM-13 cell lines displayed heightened sensitivity to treatment with DS-1594b and venetoclax, emphasizing the therapeutic potential of this combination in AML subtypes with *FLT3*-ITD mutations.

Our investigation extended to primary AML patient samples harboring *MLLr* or *NPM1* mutations. Encouragingly, the combination treatment synergistically inhibited cell proliferation in most tested samples, particularly those with *MLLr*. These results underscore the potential clinical relevance of DS-1594b and venetoclax combination therapy. However, we also observed a lack of response in certain patient samples, indicating the need for further investigation into potential mechanisms of resistance and underscoring the importance of developing strategies to overcome resistance for more effective therapeutic outcomes in AML patients.[47]

Our *in vivo* study using a PDX mouse model corroborated our *in vitro* findings, as mice who were treated with DS-1594b and venetoclax had a significantly reduced AML burden compared with those who were treated with single agents or vehicle control. Importantly, the combination therapy did not adversely affect mouse weight, suggesting that the regimen was well-tolerated.

RNA-sequencing analysis revealed that while most differences in gene expression were driven by the menin inhibitor, only a small subset of genes exhibited further modulation upon combination treatment. Specifically, we observed a significant downregulation of antiapoptotic MCL-1 in our PDX model and direct menin binding at anti-apoptotic factor loci, including MCL1, suggesting an added complementary mechanism for the observed synergy between the two treatments. Furthermore, our CyTOF analysis revealed increased ex-

pression of differentiation markers in the DS-1594b alone and combined treatment groups.[48] This finding supports that treatment with both DS-1594b and venetoclax may positively impact leukemic cell differentiation *in vivo*.

The observed synergistic effects on differentiation and apoptosis, *in vitro* and *in vivo*, have important clinical implications. However, while the study demonstrates efficacy in a subset of patient samples, the observed resistance in some cases underscores the AML clonal heterogeneity and complexity of finding universally effective treatments, in patients treated at the time of relapsed/refractory disease. These findings are particularly relevant in light of recent early-phase clinical trial data indicating promising activity of menin inhibitor/venetoclax combinations in the R/R setting[49] and high response rates with a triple combination of azacitidine/venetoclax and menin inhibitors in the R/R and older frontline AML patients.[50] Therefore, further studies are needed to explore the mechanistic underpinnings of this synergy and identify potential biomarkers of patient response and resistance. In conclusion, these results underscore the potential of DS-1594b and venetoclax as a targeted combination therapy, offering a promising and novel approach to specifically counteract the survival and differentiation blockades in AML patients with *MLLr* and *NPM1* mutations, and laying the groundwork for more personalized and effective treatment regimens in this patient population.

Disclosures

TAM is a paid consultant for and shareholder in Dark Blue Therapeutics Ltd. MK serves on advisory boards for AbbVie, Auxenion GmbH, Dark Blue Therapeutics, Legend, MEI Pharma, Menarini/Stemline Therapeutics, Novartis, and Syndax; she also provides consulting for AbbVie, Adaptive, AmMax, Curis, Janssen, Kyowa Kirin, Menarini/Stemline Therapeutics, Novartis, Sanofi Aventis, Servier, and Vincerx; she has received research funding from AbbVie, Janssen, and Klondike Biopharma. ND discloses consultancy fees from Bristol-Myers Squibb, Daiichi, Pfizer, Gilead, Servier, Genentech, Astellas, AbbVie, ImmunoGen, Amgen, Trillium, Jazz, Syndax, Sumitomo, Kura, AROG, Servier, Shattuck labs, Sanofi, Arcellx, Caribou, Debiopharm, Aptos, Astra-Zeneca, StemLine and VincerX; research funding from Hanmi, Trovagene, FATE, Novimmune, Glycomimetics, BMS, Astellas, Daiichi, Abbvie, Immunogen, Shattuck labs, Sanofi, Arcellx, Caribou, Debiopharm, Aptos, Astra-Zeneca, StemLine, VincerX, Nerviano, FATE therapeutics, Sumitomo and Kura. MPM discloses speaker honoraria/scientific advisory board consultancy for Abbvie, Amgen, Astellas, Be-One, BMS, Delbert, Gilead, Janssen, Jazz Pharmaceuticals, Novartis, Pfizer, Roche and Servier. BC received research funding from REPARE Therapeutics and AmMax. PT in a scientific advisory board member at 65 Therapeutics.

Contributions

VC designed and performed experiments, analyzed data, and wrote the manuscript. VS and AS contributed to experimental work and design, data analysis, and manuscript review. CC contributed to experimental work and design, as well as data analysis. NB contributed to experimental work and manuscript review. ZZ provided essential experimental tools and methodological guidance. CR and SC assisted with experimental work. ND provided clinical insights and contributed to manuscript review. BC provided cell lines and experimental support during revision. PT supported the project by facilitating experiments and providing reagents. MPM and TAM provided conceptual guidance, scientific discussions, and manuscript editing. MK supervised the project, provided funding, and critically reviewed the manuscript.

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Data-sharing statement

All high throughput data have been deposited in the Gene Expression Omnibus (GEO) under accession number GSE282741.

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