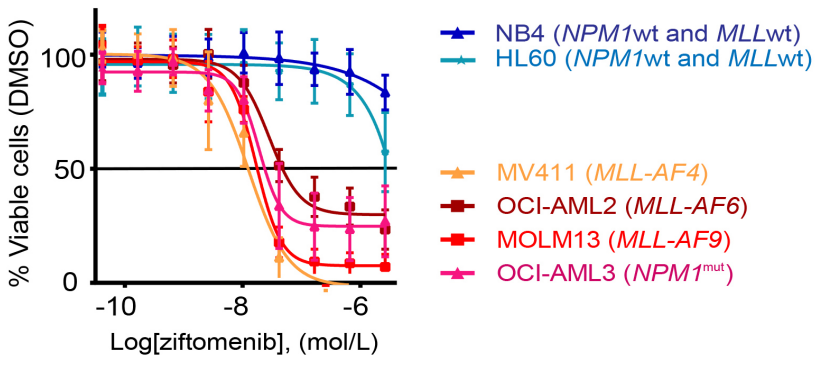
# Menin inhibitor ziftomenib (KO-539) synergizes with drugs targeting chromatin regulation or apoptosis and sensitizes acute myeloid leukemia with *MLL* rearrangement or *NPM1* mutation to venetoclax

Acute myeloid leukemia (AML) represents a genetically heterogeneous group of myeloid neoplasms derived from early hematopoietic progenitors. Mutations in the *NPM1* gene and chromosomal rearrangements of the gene encoding the histone 3 lysine 4 (H3K4) methyltransferase *MLL* (KMT2A) represent recurrent genetic abnormalities that define distinct AML subtypes and predict treatment outcomes.[1,2] Both genetic alterations in AML are associated with activating a particular leukemogenic transcriptional program, including the aberrant expression of the self-renewal associated homeobox (*HOX*), *MEIS1*, and *PBX3* transcription factor genes and their target genes *FLT3* and *BCL2*.[3] The interaction of MLL with the adaptor protein menin is required for *MLL*-rearranged (*MLL*-r) leukemogenesis,[3] and we discovered that *NPM1*$^{mut}$ AML also depends on the menin binding motif in MLL.[4] Small-molecule inhibitors that block the menin-MLL interaction cause downregulation of leukemic gene expression, induce differentiation, and have anti-leukemic activity against NPM1$^{mut}$ and *MLL*-r leukemia models (reviewed in[5]). Ziftomenib is one of five menin inhibitors currently assessed in clinical phase I/II trials (*clinicaltrials.gov. Identifiers: NCT04067336, NCT04065399, NCT05153330, NCT04811560, NCT04988555*) with explorative single-agent efficacy of ziftomenib reported in relapsed or refractory AML.

Here, we selectively screened for synergistic treatment partners using a combinatorial drug screen and deciphered synergistic effects of ziftomenib on *MLL*-r and *NPM1*$^{mut}$ AML. In order to characterize the single-drug treatment effects of ziftomenib, we first assessed its anti-proliferative activity in various M*LL*-r (MOLM13, MV411, OCI-AML2) and *NPM1*$^{mut}$ (OCI-AML3) human AML cell lines. Similar to other menin inhibitors such as VTP-50469, we observed strong and dose-dependent inhibitory effects in all *MLL*-r and *NPM1*$^{mut}$ AML at low nanomolar concentrations upon 7 days of treatment (half-maximal inhibitory concentration [$IC_{50}$] <25 nM; Figure 1A, B). HL60 and NB4 AML cells with-

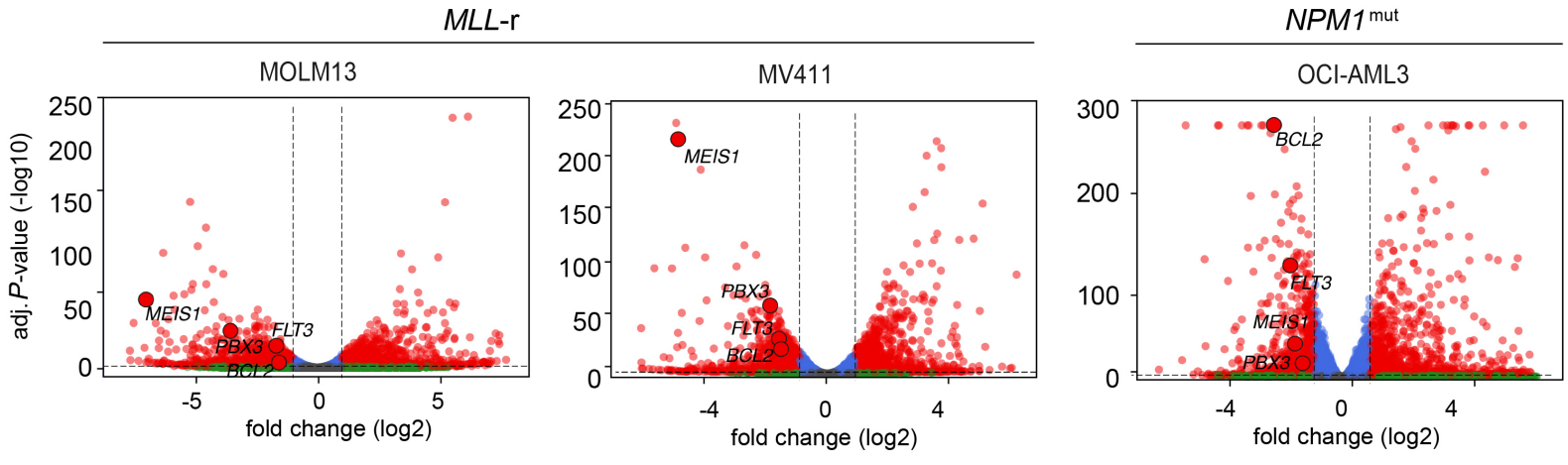
**A** **Ziftomenib treatment: 7 days**




**B** **$IC^{50}$ Ziftomenib**

| Human cell line | *MLL / NPM1* | IC50 [nM] |
|---|---|---|
| MV411 | *MLL-AF4* | 14 |
| MOLM13 | *MLL-AF9* | 19 |
| OCI-AML2 | *MLL-AF6* | 32 |
| OCI-AML3 | *NPM1*$^{mut}$ | 21 |
| HL60 | wildtype | >2500 |
| NB4 | wildtype | >2500 |

**C** **RNA sequencing data of Ziftomenib *vs.* DMSO**

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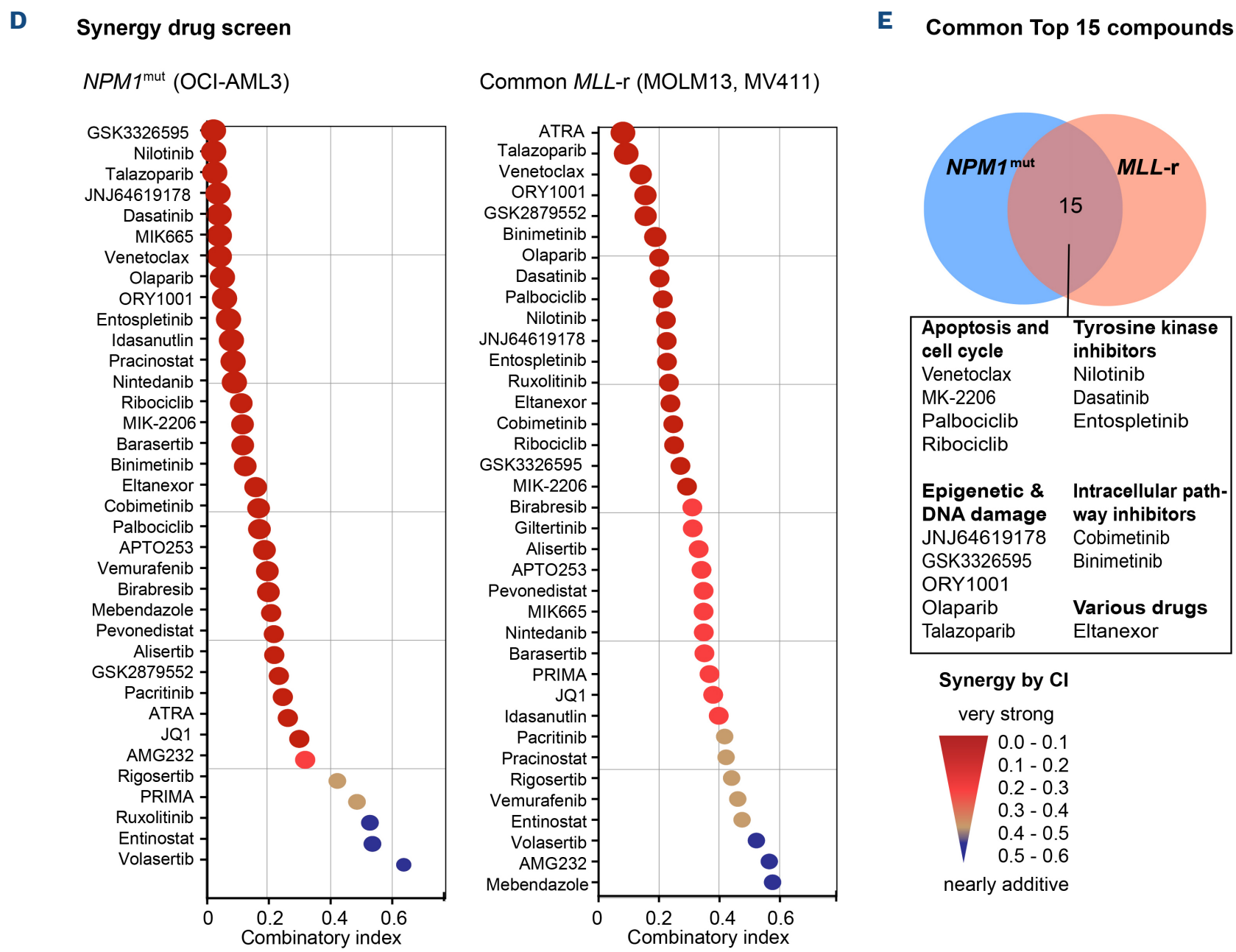
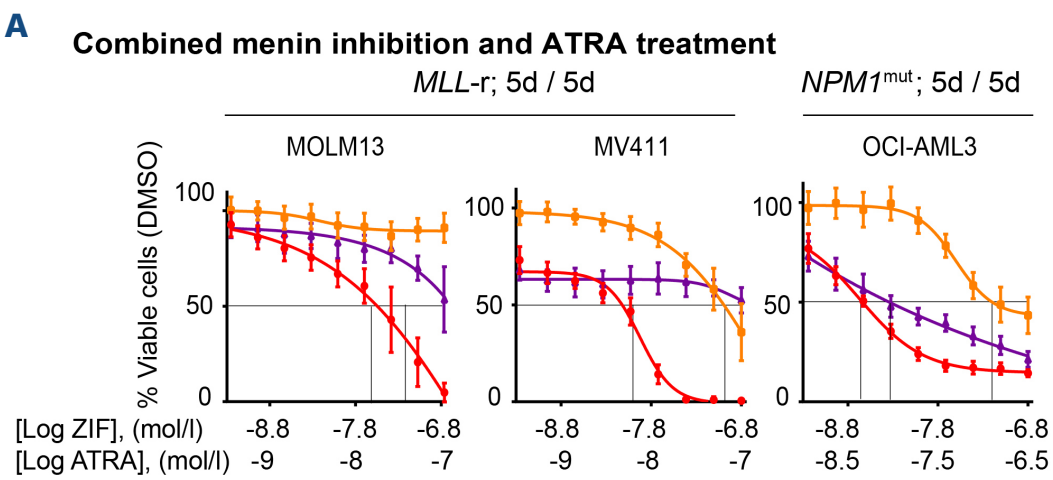


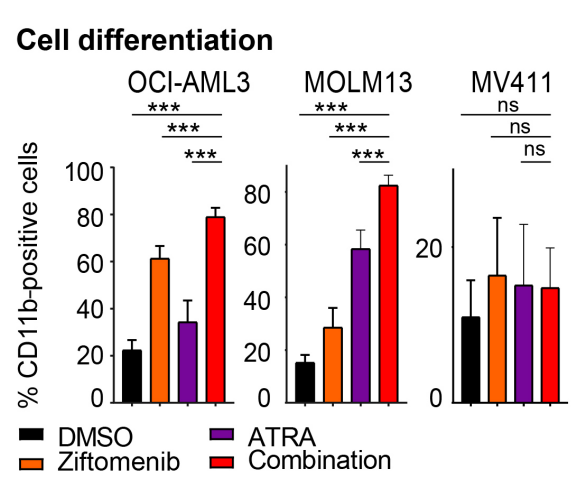

**Figure 1. Ziftomenib acts highly selective in *MLL*-r and *NPM1*$^{mut}$ acute myeloid leukemia and synergizes with a variety of targeted drugs *in vitro*.** (A) Dose-response curve from cell viability assays in human acute myeloid leukemia (AML) cell lines after 7 days of treatment. (B) Ziftomenib half-maximal inhibitory concentration ($IC_{50}$) values determined after 7 days of treatment by GraphPad Prism software. (C) Volcano plots of RNA-sequencing data after 150 nM ziftomenib treatment in OCI-AML3, MOLM13 (4 days) and MV411 (3 days). Negative log2 values represent downregulated genes with ziftomenib compared with dimethyl sulfoxide (DMSO). Selected MLL targets are labeled. (D) Drug synergy screen of ziftomenib with 37 targeted drugs. Depicted are weighted combination indices (CI) calculated after 2 days pretreatment with ziftomenib followed by 2.5 days combined treatment with small molecule inhibitors. Viable (DAPI-negative) cells were assessed by flow cytometry. CI values were calculated using CompuSyn software and weighted for $IC_{75}$, $IC_{90}$ and $IC_{95}$ values ($(1xIC_{75}+2xIC_{90}+3xIC_{95})/6$) based on recommendations from Chou Talalay for anti-cancer drugs because strong inhibitory effects are a necessity in the treatment of cancer. For *MLL*-r cell lines, the mean CI of MV411 and MOLM13 was calculated. (E) Venn-Diagram of common top 15 synergistic drugs based on highest CI values. Data in panels (A, B) represent the mean of 3 independent experiments, each in technical triplicates, error bars represent standard deviation. RNA sequencing of each cell line was performed in triplicates. The drug screens were performed twice in each cell line, CI values represent the mean of these independent experiments.

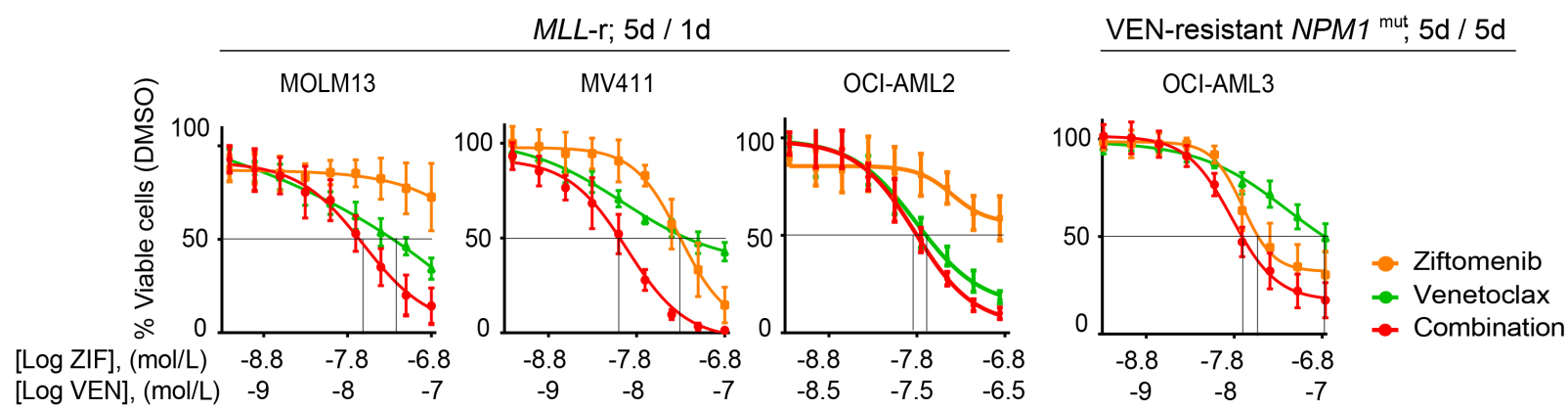
out *MLL*-r or *NPM1*$^{mut}$ served as negative controls and exhibited only minor responses to very high concentrations ($IC_{50}$ >2,500 nM) consistent with a high selectivity of ziftomenib (Figure 1A, B). Next, we assessed gene expression changes by RNA sequencing. Ziftomenib uniformly induced transcriptional downregulation of *MEIS1*, *PBX3*, *FLT3*, and *BCL2* in all *NPM1*$^{mut}$ and *MLL*-r cells (Figure 1C; *Online Supplementary Figure S1A*) and demonstrated high consistency with the effects of other menin inhibitors[3,6–10] (*Online Supplementary Figure S1E*). Ziftomenib also induced differentiation as evidenced by upregulation of the monocytic cell surface markers CD11b and CD14 and cytomorphologic analysis (*Online Supplementary Figure S1B, C*). Also, the genes upregulated with ziftomenib treatment were highly enriched for genes associated with hematopoietic cell differentiation (*Online Supplementary Figure S1D*).

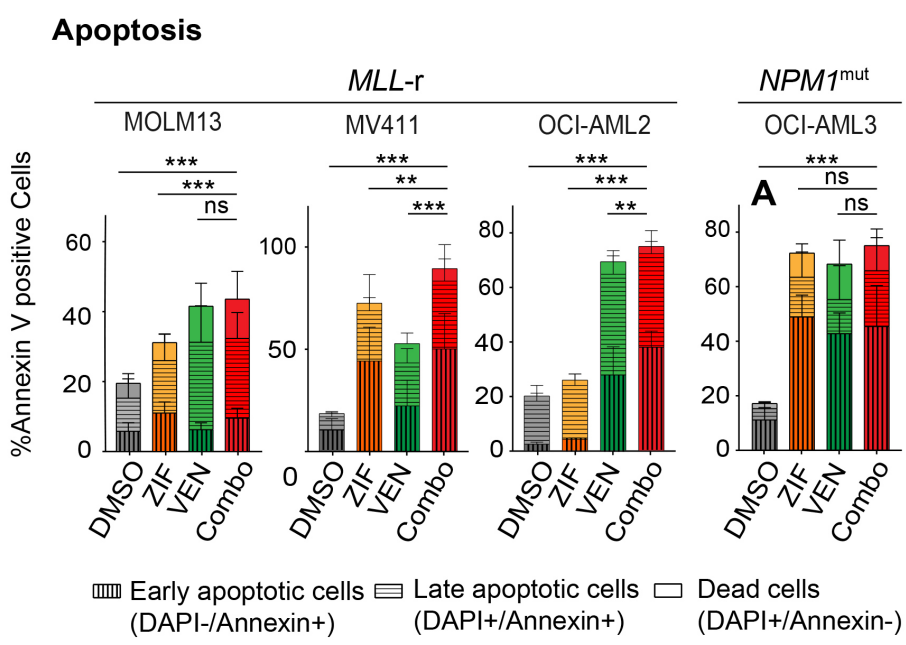
As single-drug treatment is generally unlikely to induce long-term remissions in AML, we sought to screen ziftomenib for effective drug combination partners. Therefore, we designed a screen assessing single and combined drug effects of ziftomenib and 37 targeted compounds, each at four concentrations in a constant 1:4 ratio. Com-

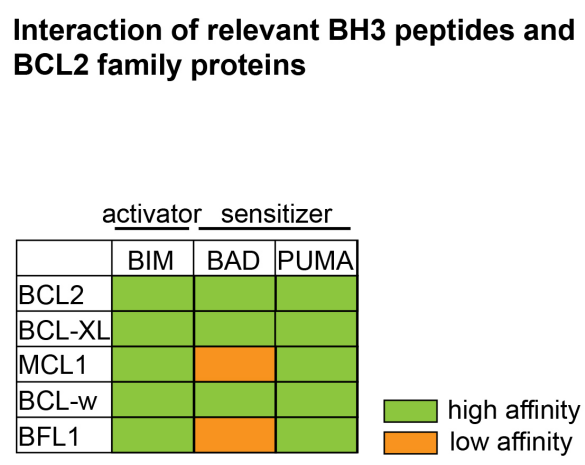
pounds were selected based on previously reported (pre)clinical activity against AML (*Online Supplementary Figure S2A*). Because treatment with menin inhibitors affect proliferation with a latency of several days,[4,8] we pretreated leukemic cells with ziftomenib for 2 days and then added the other compounds for another 2.5 days. Drug synergy was calculated based on viable cell count as previously described[9] (*Online Supplementary Figure S2B*). The screen revealed synergistic effects of ziftomenib with many of the preselected drugs. There was a strong overlap of most synergistic combination partners between *MLL*-r and *NPM1*$^{mut}$ AML subtypes. Of the top 20 synergistic compounds from each AML subtype, 15 overlapped and were enriched for agents targeting epigenetic regulation and DNA damage (e.g., LSD1 [ORY-1001], PRMT5 [GSK3326595, JNJ-64619178], and PARP [olaparib, talazoparib]) as well as apoptosis and cell cycle (e.g., BCL2 [venetoclax], AKT [MIK-2206], and CDK4/6 [ribociclib, palbociclib]) (Figure 1D, E; *Online Supplementary Figure S2C, D*). All-*trans*-retinoic acid (ATRA) was highly synergistic in both AML subtypes, which was confirmed in cell viability assays. The combination induced strong differentiation as evidenced by upregulation of CD11b (Figure 2A, B; *Online Supplementary Figure S2E)*. As previously reported, menin inhibitors synergize with the FLT3 kinase inhibitor gilteritinib.[9] This was confirmed for ziftomenib against the *MLL*-r AML cells

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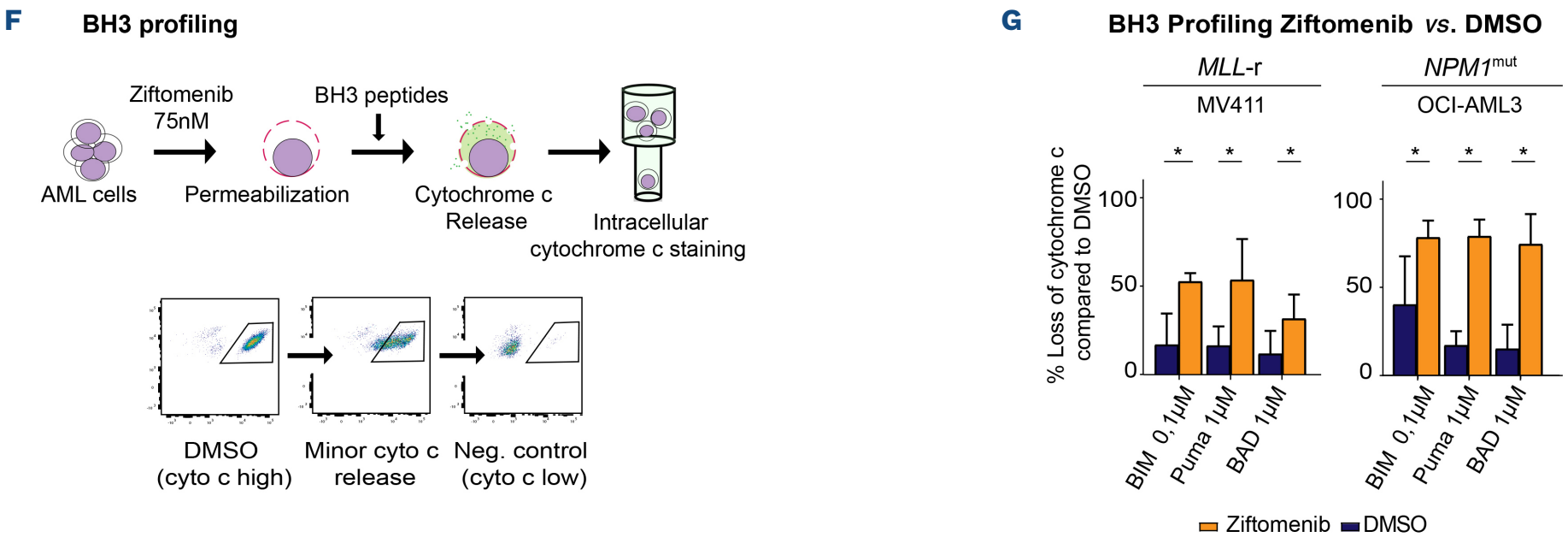



**Figure 2. Characterization of the highly synergistic effects of ziftomenib shows differentiation with ATRA and a pro-apoptotic signature with venetoclax.** (A) Dose-response curves from combinational cell viability assays of MV411, MOLM13, and OCI-AML3 comparing 150 nM ziftomenib (5 days), 100 nM ATRA (5 days), and combinational treatment (5 days / 5 days). (B) Surface CD11b expression of all viable cells was assessed by flow cytometry after treatment described in (A). (C) Dose-response curves from combinational cell viability assays of MV411, MOLM13, and OCI-AML2 comparing ziftomenib (5 days), venetoclax (24 hours), and combinational treatment (4 days ziftomenib pretreatment and additional 24 hours combined treatment with venetoclax). For OCI-AML3, treatment duration was 5 days with both drugs. (D) Percentage of apoptotic (Annexin V) and dead (DAPI-stained) cells after single and combinational treatment with ziftomenib (150 nM) and venetoclax (100 nM; OCI-AML3 500 nM, OCI-AML2 25 nM) in human cell lines. (E) Affinity of BCL2 proteins to different BH3 activating or sensitizing peptides. (F) Schematic of BH3 profiling: After permeabilization with 0.002% digitonin, cells were exposed to BH3-peptides and then fixed. As readout, loss of cytochrome c was evaluated by flow cytometry as surrogate for apoptotic priming. (G) BH3 profiling was conducted in cells treated with 75 nM ziftomenib for 48 hours. Cells were exposed to the BH3-peptides (BIM 0.1 µM, BAD 1 µM, PUMA 1 µM). Panels (A-D, G) represent the mean of 3 independent experiments, each performed in technical triplicates. Error bars represent standard deviation.

harboring an *FLT3*-internal tandem duplication (ITD) mutation (MOLM13 and MV411) in our screen and in more detailed cellular assays (*Online Supplementary Figure S2F*). As mentioned above, *BCL2* was uniformly downregulated with ziftomenib, and the specific BCL2 inhibitor venetoclax appeared among the top synergistic combination partners in our screen (Figure 1C, D).

In order to explore this combination in more detail, we first assessed venetoclax in single-agent treatment assays to determine $IC_{50}$ values across the respective AML cell lines. We found remarkable growth inhibition in the *MLL*-r cells and resistance of the *NPM1*$^{mut}$ OCI-AML3 cells (*Online Supplementary Figure S3A*), as previously described.[11] Assessment of combined venetoclax and ziftomenib treatment in cellular response assays confirmed synergistic growth inhibition in the *MLL*-r cells and also less pronounced in the *NPM1*$^{mut}$ OCI-AML3 cells (Figure 2C) as reported.[12–14] No growth inhibition was detected in the *NPM1* and *MLL* wild-type NB4 cells (*Online Supplementary Figure S3B, C*). It is of interest to note that drug synergy in OCI-AML3 cells was only observed with a prolonged 5-day combined drug exposure of ziftomenib and venetoclax (Figure 2C). No synergy was found in OCI-AML3 when venetoclax was added for 24 hours (h) (including much higher concentrations) after a four-day ziftomenib pretreatment (*Online Supplementary Figure S3D, E*). In order to confirm the enhanced anti-leukemic activity of menin targeting with venetoclax treatment, we knocked down *MEN1* (menin) using two validated small hairpin RNA (shRNA) in *MLL*-r MOLM13 cells (*Online Supplementary Figure S3F*). *MEN1* knock-down increased venetoclax-mediated cell killing, phenocopying the effects of pharmacological menin inhibition. Next, we performed Annexin V staining demonstrating substantial apoptosis induction with venetoclax that was even more pronounced in the combination (significant in 2 of 4 cell lines) (Figure 2D). In order to assess potential apoptotic priming of ziftomenib we performed selected BCL2 homology (BH) 3 screening exemplarily in the *MLL*-r MV411 and *NPM1*$^{mut}$ OCI-AML3 cells. Therefore, cells were treated with ziftomenib for 48 h *versus* vehicle control and then exposed to different concentrations of various BH3-peptides (Figure 2E, F). We found a significantly enhanced cytochrome c release in ziftomenib-treated cells in response to the pro-apoptotic peptides BIM, PUMA and BAD (Figure 2G). This may partially be explained by the downregulation of BCL2 leading to an increased sensitivity to venetoclax. It is worth mentioning that apoptotic priming was only detected at higher BIM concentrations (0.1 uM), which may explain discrepancies with published data assessing other menin inhibitors, where lower peptide concentrations were used.[10] While more detailed studies are required to determine the net response of BCL2 family proteins upon ziftomenib treatment, these findings suggest that apoptotic priming may contribute to drug synergy with venetoclax in these leukemias.

**A** **Patient characteristics**

| ID | #1 | #2 | #3 | #4 |
|---|---|---|---|---|
| Sex | male | female | female | female |
| Age in years at diagnosis | 55 | 78 | 64 | 24 |
| % BM blasts | 60-70 | 80 | 80 | 90 |
| WBC count / nL | 42 | 87 | 15 | 227 |
| Karyotype | 46,XY | 47,XX, t(4;11)* | 46,XX | 46,XX |
| *NPM1* | Type A | Type A | Type A | Type A |
| *FLT3*-ITD | neg. | neg. | pos.** | pos.** |
| *FLT3*-TKD | neg. | neg. | neg. | neg. |
| *CEBPA* | WT | WT | WT | WT |
| *IDH1* | WT | WT | WT | R132H |
| *IDH2* | R140G | WT | WT | WT |
| *TP53* | WT | n.d. | WT | WT |
| *ASXL1* | WT | n.d. | WT | WT |
| *RUNX1* | WT | n.d. | WT | WT |
| *BCOR* | WT | n.d. | WT | n.d. |
| *EZH2* | WT | n.d. | WT | n.d. |
| *SF3B1* | WT | n.d. | WT | n.d. |
| *SRSF2* | WT | n.d. | WT | n.d. |
| *STAG2* | WT | n.d. | WT | n.d. |
| *U2AF1* | WT | n.d. | WT | n.d. |

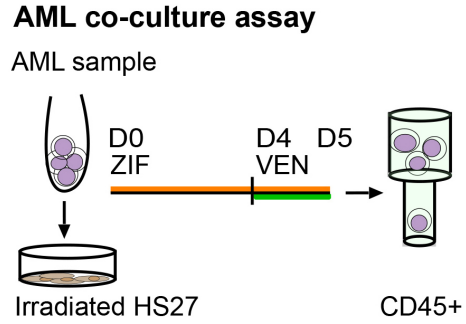
| ID | #1 | #2 | #3 | #4 |
|---|---|---|---|---|
| *DNMT3A* | R882 | n.d. | R882 | n.d. |
| *PTPN11* | MUT | n.d. | WT | n.d. |
| *ZRSR* | WT | n.d. | WT | n.d |
| *BCR::ABL* | WT | WT | WT | WT |
| *RUNX1::RUNX1T1* | WT | WT | WT | WT |
| *KMT2A::MLL3* | WT | WT | WT | WT |
| *CBF::MYH11* | WT | WT | WT | WT |
| *PML::RARA* | WT | WT | WT | WT |

WT = wildtype n.d. = no data available

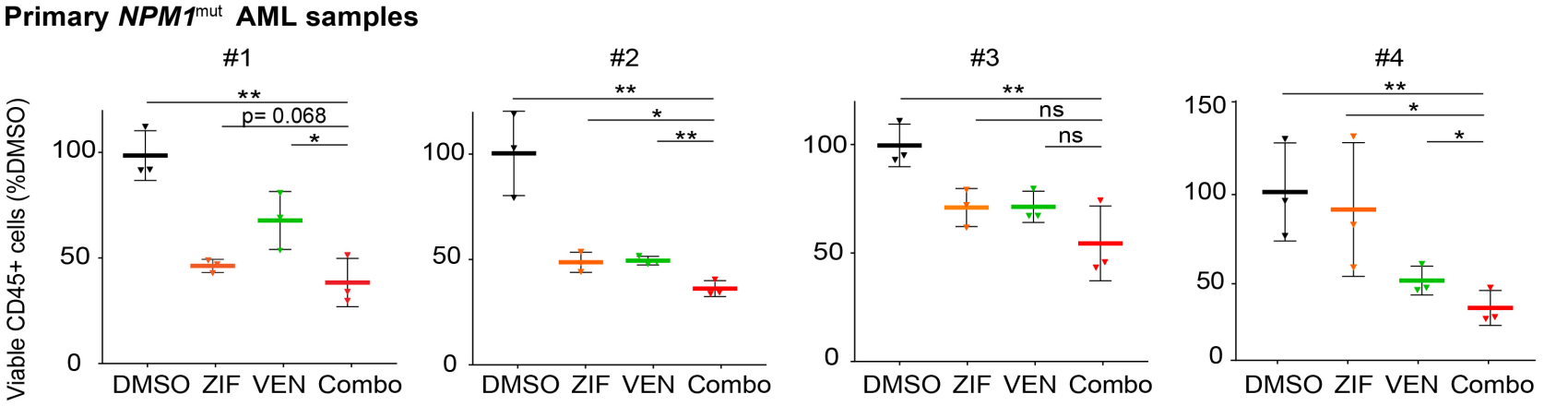
* 47, XX,t(4;11)(q3?1;q?21),+der(4)t(4;11)(pq3?1;q21) [11]/ 46,XX[7] FiSH t(4;11)(FGFR3+;KMT2A+;KMT2A-),der(4)t(4;11)(q3?1;q?21)(FGFR3+,KMT2A+)

** high [ratio>0.6]; (#3 0.61; #4 0.869)

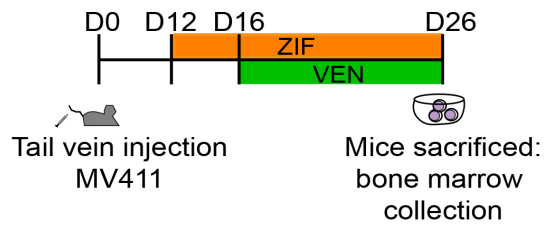
**B** **AML co-culture assay**



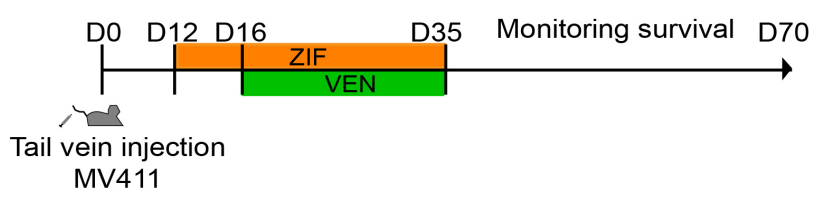

**C** **Primary *NPM1*$^{mut}$ AML samples**



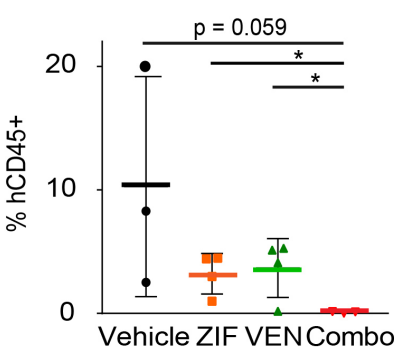

**D** **Leukemia burden: Disseminated MV411 xenograft model**




**F** **Overall survival: Disseminated MV411 xenograft model**




**E** **Leukemia burden MV411 xenograft model**




**G** **Overall survival MV411 xenograft model**

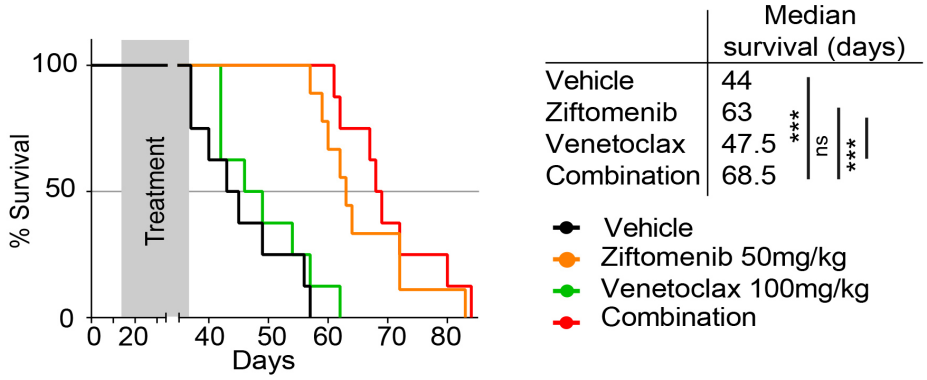



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**Figure 3. The combination of ziftomenib and venetoclax demonstrates efficacy in *NPM1*$^{mut}$ primary patient samples and *in vivo*.** (A) Patient characteristics of *NPM1*$^{mut}$ acute myeloid leukemia (AML) patient samples. (B) AML patient samples were seeded with irradiated HS27 cells and treated with dimethyl sulfoxide (DMSO), ziftomenib (75 nM, 5 days), venetoclax (10 nM, 24 hours), or both compounds. Readout was flow cytometry based human CD45-positive, viable cell count compared to DMSO. (C) Viable human CD45-positive cells upon drug treatment of *NPM1*$^{mut}$ AML samples as described above. (D) Experimental design of the assessment of leukemia burden in MV411-derived leukemic xenograft mice (N=4). Engraftment was confirmed on day 11 by flow cytometry before start of treatment. (E) Assessment of leukemia burden defined as human CD45-positive bone marrow cells (N=3 and 4 mice/group) upon treatment with drug vehicles, ziftomenib (50 mg/kg; by mouth [PO]; once daily), venetoclax (100 mg/kg; PO; once daily), or combination. (F) Experimental design of the assessment of overall survival (N=8). Engraftment was confirmed on day 11 by flow cytometry before start of treatment. (G) Kaplan-Meier estimates of MV411-derived leukemic xenograft mice (N=8 mice/group) upon treatment with drug vehicles, ziftomenib (days 12-35, 50 mg/kg; PO; once daily), venetoclax (days 16-35, 100 mg/kg; PO; once daily) or both. The log-rank (Mantel-Cox) test was used to calculate *P* values from the Kaplan-Meier estimates. In panels (C, E) significance was calculated by one-sided student *t* test. Error bars represent standard deviation.

We next investigated combinatorial ziftomenib and venetoclax treatment in four primary *NPM1*$^{mut}$ AML patient samples (Figure 3A-C). We selected AML samples harboring this particular gene mutation as - unlike the venetoclax-resistant *NPM1*$^{mut}$ OCI-AML3 cells - *NPM1*$^{mut}$ patients responded particularly well to venetoclax-based treatment in clinical trials.[15] *NPM1*$^{mut}$ AML cells were treated for 5 days in a human stromal cell co-culture assay as previously described[9] (Figure 3B). All four samples showed an enhanced reduction of viable AML cells with combinatorial *versus* single-drug treatment with statistical significance in two samples (Figure 3C).

In order to assess the therapeutic potential of combined ziftomenib and venetoclax treatment *in vivo*, we used a disseminated *MLL*-r MV411 xenotransplantation model. We transplanted MV411 cells into NSG mice via tail vein injection and randomly assigned the animals into four groups to receive either drug vehicle, ziftomenib (50 mg/kg), venetoclax (100 mg/kg), or their combination. Treatment was initiated on day 12 after transplantation. In order to assess leukemic burden - as defined by the percentage of human CD45-positive cells in the bone marrow - the animals were euthanized on day 26. We observed a significant reduction within the combination-treated animals compared to venetoclax and ziftomenib single-drug treatment (Figure 3D, E). In a separate experiment, we explored the survival of MV411 xenograft mice. Treatment was started on day 12 and continued until day 35. Animals receiving venetoclax and ziftomenib exhibited the most extended median survival across all treatment groups. The survival benefit of the combination was significant compared to treatment with drug vehicle or venetoclax alone but not to single-agent ziftomenib, potentially due to the small sample size, the long interval after the end of treatment, and the high potency of ziftomenib alone (Figure 3F, G). When assessing the combination treatment in a murine xenotransplantation model of the venetoclax-resistant OCI-AML3 cells, we found a trend toward superior reduction of leukemic burden compared to single-drug treatment. While these results are consistent with the above-reported *in vitro* data, this trend did not reach statistical significance. Of interest, the ziftomenib-treated animals exhibited strong differentiation effects in nearly all engrafted AML cells (*Online Supplementary Figure S3G, H*).

In summary, the menin inhibitor ziftomenib has significant activity against *NPM1*$^{mut}$ and *MLL*-r AML, suppresses specific leukemogenic gene expression, and induces differentiation. Ziftomenib exhibited synergistic leukemia cell killing in combination with drugs from various classes, many of them targeting chromatin regulation and DNA damage as well apoptosis and cell cycle. While additional studies will be required to characterize these combinations in detail, we have focused here on the promising combinations with ATRA and venetoclax, the latter being currently considered the standard of care for non-fit AML patients. Consistent with published data,[12–14] we demonstrated that ziftomenib has profound anti-proliferative activity in combination with venetoclax against *MLL*-r and *NPM1*$^{mut}$ AML and is already available for assessment in clinical trials. Our data suggest that ziftomenib may induce apoptotic priming and (re-)sensitize AML cells to venetoclax. If confirmed, this finding could support further evaluation as a potential treatment option for AML patients harboring these genotypes that failed venetoclax-based regimens and have few further treatment options.

## Authors

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**Disclosures**

MWMK receives honoraria and is a consultant for Pfizer, Kura Oncology, Jazz Pharmaceuticals, Bristol-Myers Squibb / Celgene and Abbvie; is on the speakers bureau of Gilead and receives travel support from Daiichi Sankyo. JR has received travel support from Abbvie. LK and FB are employed by Kura Oncology and are current equity holders. DS receives honoraria from Bristol-Myers-Squibb, Astra Zeneca and Abbvie. KD receives honoraria and is on the advisory board of Novartis, Janssen, BMS/Celgene, Daiichi Sankyo, Jazz and Roche; is member of advisory board of Abbvie and receives research funding from Novartis, BMS/Celgene, Agios and Astellas. The remaining authors have no conflicts of intererest to disclose.

**Contributions**

MWMK designed the research, analyzed and interpreted the data, wrote and revised the manuscript, and supervised the study. JR performed the experiments, analyzed and interpreted the data, wrote the original draft of the manuscript and edited the manuscript. MMD and ND performed experiments, analyzed and interpreted the data. SRB provided experimental support for BH3 profiling and revised the manuscript. KK, CL and HLS performed experiments and analyzed the data. DS analyzed and interpreted the RNA-sequencing data. FB und LK provided the menin-MLL inhibitor ziftomenib and revised the manuscript. HE provided NSG mice and revised the manuscript. MT and TK provided administrative support and revised the manuscript. KD provided genetic characterization of AML samples.

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**Data-sharing statement**

The RNA-sequencing data reported in this article have been deposited on Gene Expression Omnibus database (accession number GSE228307). Original data and methods are available by email request to the corresponding author.

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