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Inhibition of CSF1R-CSF1 axis with Axatilimab effectively targets leukemia stem cells and monocytes in BH3 mimetics-resistant AML

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INTRODUCTION

- BCL2 inhibitor venetoclax (VEN)/HMA combinations are highly effective in inducing remissions in AML
- Most patients relapse due to
  - the activation of oncogenic signaling pathways that stabilize MCL1, a key resistance factor to VEN
  - downregulation of pro-apoptotic proteins by mutant *TP53*
- Monocytic cells in AML express high levels of MCL1 and are insensitive to VEN, which by itself induces elevated levels of MCL1
- Leukemic myeloblasts undergo monocytic differentiation under selection pressure as shown by CyTOF pseudo time analysis
- We previously reported that combined MCL1 and BCL2 inhibition is highly synergistic in AML resistant to VEN or MCL1 inhibitor monotherapy[1,2]
- Importantly, cells developing resistance to combined BCL2 and MCL1 inhibition *in vivo* display increased cytokine expression, such as CSF1[3]

AIM

Investigate if AML cells resistant to BH3 mimetics are sensitive to CSF1R-CSF1 axis blockage

METHOD

- Protein/cytokine levels were determined by Western blot or flow cytometry
- BCL2, MCL1, and CSF1R were inhibited by VEN, AZD5991, or CSF1R antibody SNDX-6352 (Axatilimab), respectively
- Viable cells and apoptosis were determined by flow cytometric measurements of Annexin V/7-aminoactinomycin D or by CyTOF in phenotypically defined cell populations
- PDX cells developed from a VEN/Decitabine resistant AML patient were treated *in vivo* with VEN/AZD5991, which significantly extended survival. Leukemia cells were collected from these VEN/AZD5991 treated mice at moribund stage, injected into NSG mice, and treated with SNDX-6352, VEN/AZD-5991, or both
- The effects on cytokines, AML blasts, stem cells, and monocytes were determined

CONTACT INFORMATION

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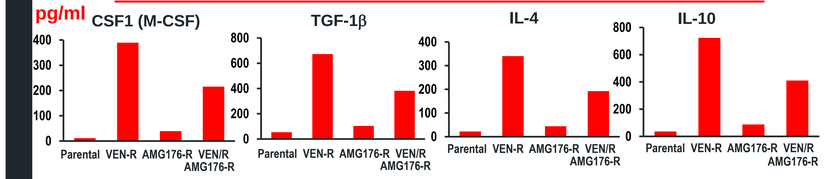
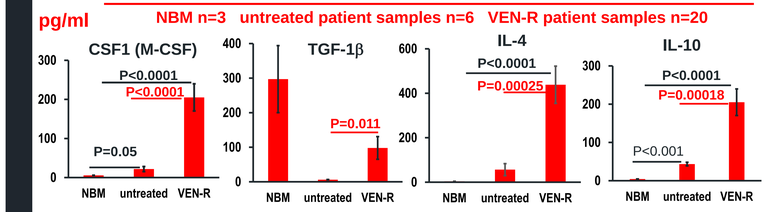
RESULTS

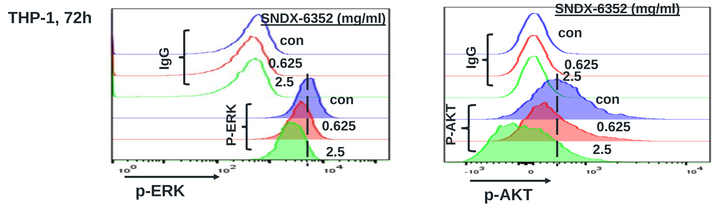
1. MV4-11 Cells with Acquired Resistance to BH3 Mimetics Targeting BCL2 or MCL1 Express Higher Levels of Cytokines Compared to Parental Cells



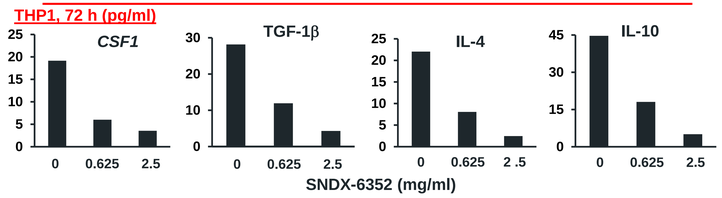
2. High Plasma Cytokine Levels in AML Patient Samples vs. NBM Massively Increased in VEN-R AML: highly inflammatory microenvironment



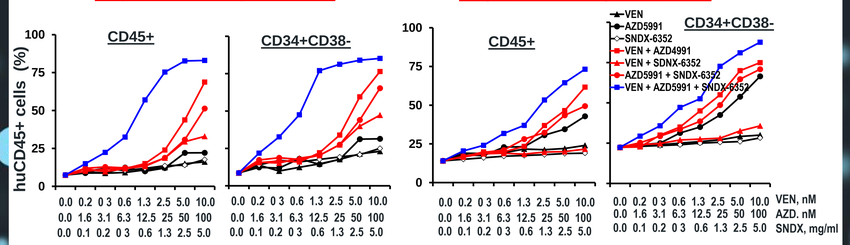
3. SNDX-6352 Suppresses ERK and AKT Signaling in Monocytic Leukemia Cell Lines



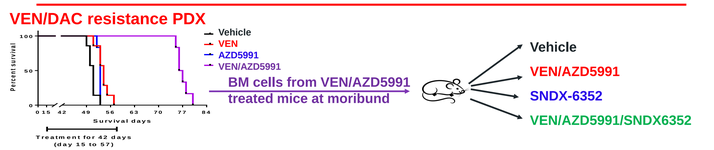
4. SNDX-6352 Decreases Secreted Cytokines in Monocytic Leukemia Cell Lines



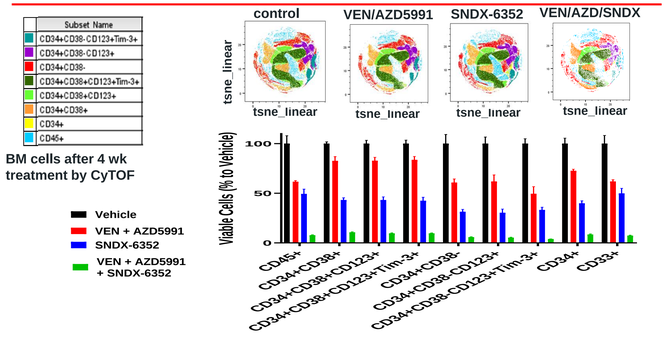
5. SNDX-6352/VEN/AZD5991 Combination More Effectively Kills AML Blasts and Stem/progenitor Cells from VEN-R Patients than Single or Two Drug Combinations



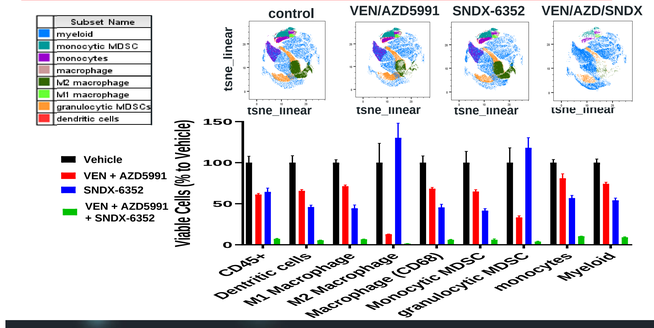
6. Targeting CSF1-CSF1R Axis *in vivo* in a BCL2i/MCL1i/HMA Resistant PDX Model



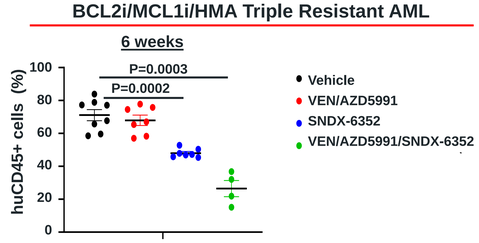
7. SNDX-6352 and its Combination with VEN/AZD5991 Significantly Decreases Leukemia Cells and Stem/Progenitor Cells in Triple Resistant AML PDX



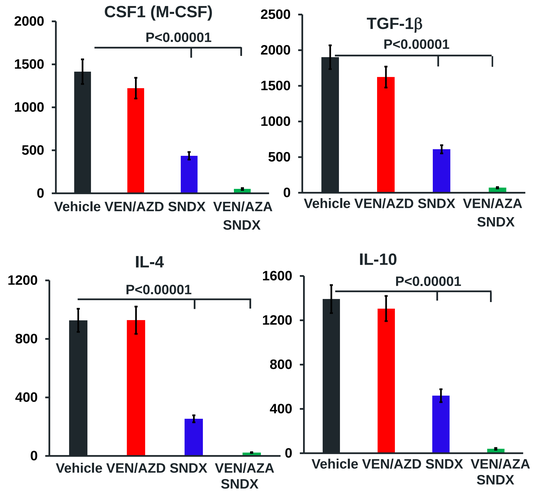
8. SNDX-6352 Alone Decreases and in Combination with VEN/AZD5991 Eliminates Immuno-suppressive MDSC and Monocytic Cells



9. CSF1R Blockade (SYNDX-6352) Alone or in Combination with BCL2i+MCL1i Is Effective in BCL2i/MCL1i/HMA Triple Resistant AML

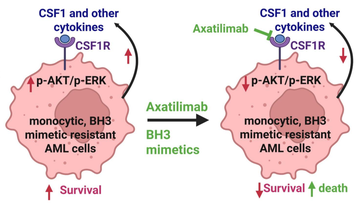


10. SNDX-6352, More Effectively when Combined with VEN/AZD5991 Decreases Mouse Serum Human Cytokine Levels



CONCLUSIONS

- CSF1, TGF-β, IL-4, IL-10, and numerous other cytokines are increased in BH3 mimetic resistant AML cell lines and patient samples
- Targeting CSF1-CSF1R axis with antibody against CSF1R inhibits ERK and AKT signaling



- Inhibition of CSF1R enhances the activities of BH3 mimetics against BCL2 or MCL1, and it is most active when combined with both BH3 mimetics in AML and AML stem/progenitor cells resistant to VEN (as MCL1 inhibitors are not available, MCL1 inhibition can be achieved by CDK9 inhibition, kinase inhibition, homoharringtonine, or others)
- CSF1R antibody (SNDX-6352) suppressed multiple inflammatory cytokine production *in vitro* and *in vivo*, has significant antileukemia activity in a triple (VEN/AZD5991/HMA) resistant PDX model

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1. Carter BZ, Mak PY, Tao W, et al. Targeting MCL-1 dysregulates cell metabolism and leukemia-stroma interactions and resensitizes acute myeloid leukemia to BCL-2 inhibition. *Haematologica*. 2020;23(10):260331.

2. Carter BZ, Mak PY, Tao W, et al. Maximal Activation of Apoptosis Signaling by Cotargeting Antiapoptotic Proteins in BH3 Mimetic-Resistant AML and AML Stem Cells. *Mol Cancer Ther*. 2022;21(6):879-889.

3. Zhang X, Tao W, Mak PY, et al. Cytokine Crosstalk Within the Bone Marrow Microenvironment as a Novel Resistance Mechanism of Bcl-2/Mcl-1 Inhibitor Resistance in AML. Clinical Lymphoma, Myeloma, & Leukemia 2020, Vol 20, supplement 1