

Menin Inhibition Decreases Bcl-2 and Bcl-xL and Enhances Venetoclax Activity in NPM1/FLT3-mutated AML

Bing Z. Carter,¹ Wenjing Tao,¹ Po Yee Mak,¹ Duncan Mak,¹ Lauren Ostermann,¹ Peter Ordentlich,² Gerard McGeehan,² and Michael Andreeff.¹ ¹Section of Molecular Hematology and Therapy, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ²Syndax, Waltham, MA, USA.

INTRODUCTION

Nucleophosmin (NPM1) is the most commonly mutated gene in adult AML (approximately 30%), which results in its aberrant cytoplasmic localization (NPM1c). The interaction of mixed-lineage leukemia (MLL1) with menin in NPM1 mutated AML shares a common HOX gene signature and dependencies as that of MLL-rearrangements (MLL1-r) with menin. Inhibition of menin has demonstrated anti-leukemia activity in both NPM1c and MLL-r AML. NPM1 mutations in AML frequently occur in patients with other mutations, such as FLT3-ITD and FLT3 tyrosine kinase domain (TKD) mutations. Menin inhibition was reported to target FLT3 and co-inhibition of menin and FLT3 has demonstrated enhanced anti-leukemia activity in MLL-r/FLT3- and NPM1c/FLT3-mutated AML.

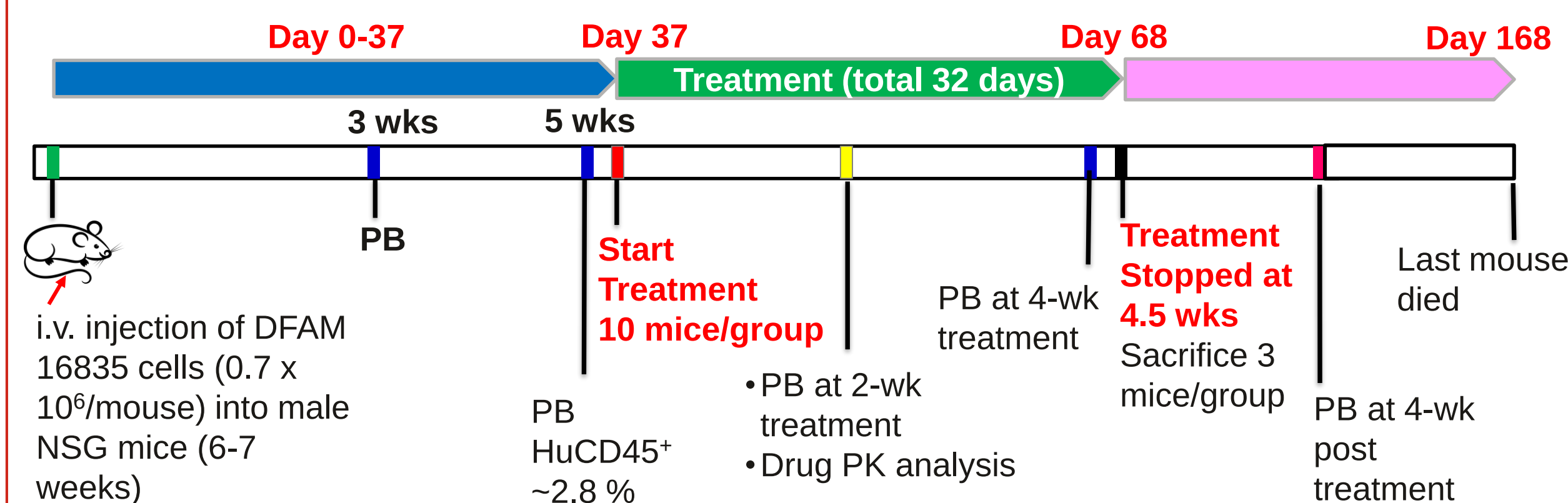
Targeting Bcl-2, a critical factor for AML cell and AML stem/progenitor cell survival, has emerged as an effective therapeutic option for elderly patients with AML. However, despite the major improvement of combining the Bcl-2 inhibitor venetoclax with hypomethylating agents, most patients develop resistance and ultimately relapse.

OBJECTIVE(S)

To investigate the anti-leukemic activity and potential synergism and mechanisms of the combination of the menin-MLL1 inhibitor SDNX-50469, an equipotent surrogate of the clinical compound SDNX-5613, and venetoclax *in vivo* in an NPM1c/FLT3-ITD/TKD patient-derived xenograft (PDX) model.

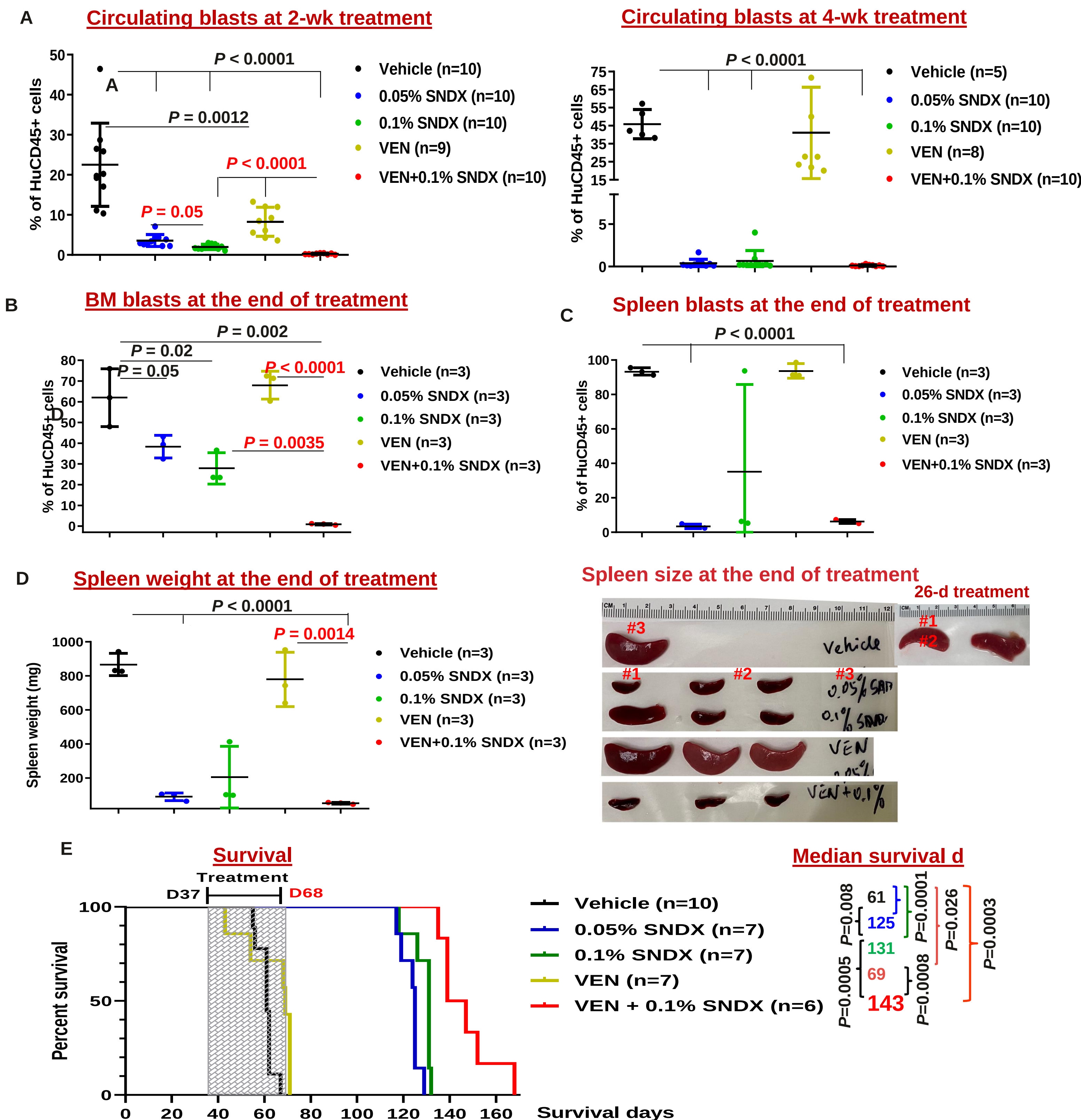
METHOD(S)

- PDX cell engrafted NSG mice were treated with 0.05 or 0.1% SDNX-50469-spiked chow, venetoclax (50 mg/kg), or 0.1% SDNX-50469 plus venetoclax for one month.
- Engraftment and disease progression were assessed by flow cytometric measurement of human CD45⁺ cells in mouse peripheral blood. Survival was monitored.
- The treatment effects on various leukemia cell populations and their protein expression levels were determined by CyTOF mass cytometry.

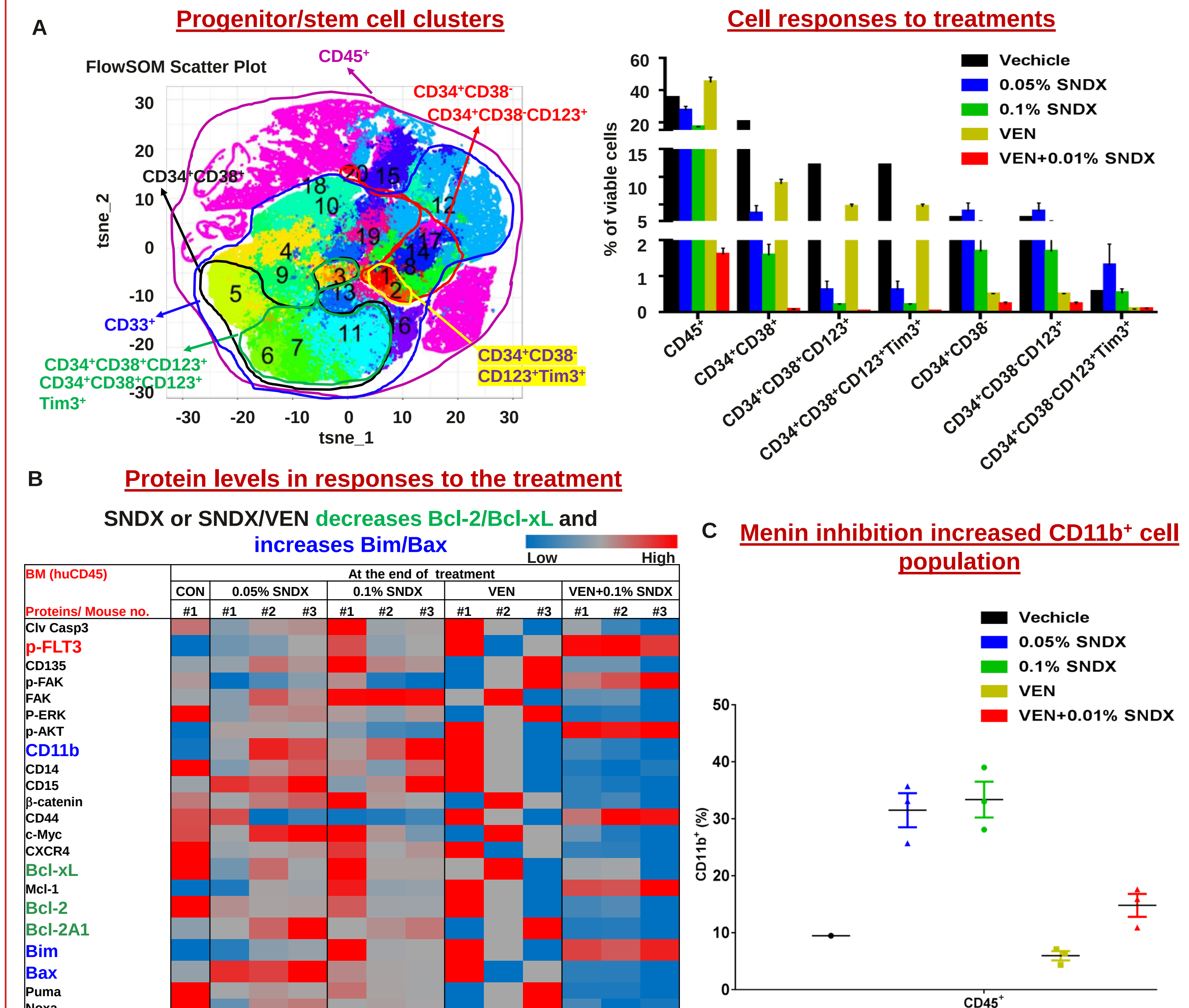


RESULTS

1. Menin inhibition exerted anti-leukemia activity and prolonged survival, which was further enhanced by Bcl-2 inhibition in an NPM1c/FLT3-ITD/TKD PDX model



2. Menin and Bcl-2 inhibition targeted leukemia cells and stem/progenitor cells and modulated Bcl-2 protein levels by CyTOF analysis in BM cells at the end of the treatment



CONCLUSION(S)

- Menin is a valid therapeutic target in NPM1/FLT3 mutant AML.
- Menin inhibition decreases antiapoptotic Bcl-2 and Bcl-xL proteins.
- Combined inhibition of Menin and Bcl-2 targets leukemia blasts and stem/progenitor cells and prolonged survival in a NPM1/FLT3-mutated AML PDX model, which warrants further clinical evaluation.
- Inhibition of FLT3 may further enhance the therapeutic efficacy of menin and Bcl-2 co-targeting in NPM1 and FLT3 mutated AML.