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Acute Leukemias

VENETOCLAX SHOWS ROBUST AND SUBTYPE DEPENDENT PRECLINICAL ACTIVITY IN ACUTE LYMPHOBLASTIC LEUKEMIA MODELS CHARACTERIZED BY BCL2 DEPENDENCE

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Introduction: Despite advances in front-line chemotherapy and the introduction of targeted immunotherapies such as inotuzumab ozogamicin and blinatumomab, the long-term prognosis for patients with acute lymphoblastic leukemia (ALL) remains unsatisfactory, especially for relapsed or refractory cases. Venetoclax (Ven), a potent and selective BCL2 inhibitor, has shown preclinical and early clinical activity across B- and T-cell ALL subtypes, consistent with the central role of BCL2 in leukemic cells survival. Its established efficacy in acute myeloid leukemia (AML) supports its translational potential in lymphoid malignancies. Ponatinib (Pona), a third-generation tyrosine kinase inhibitor active against BCR-ABL1 and other kinases frequently altered in high-risk or Ph-like ALL, represents a rational partner for combination therapy. We therefore evaluated Ven single-agent activity and explored its interaction with Pona across a broad panel of ALL models.

Methods: A comprehensive preclinical panel included 19 cell lines (4 AML, 2 T-ALL, 12 B-ALL, plus one stabilized B-ALL line derived from a patient sample) and 32 primary specimens (27 B-ALL, 3 T-ALL, 2 mixed phenotype AL). Cell viability and proliferation were assessed using the RealTime-Glo luminescent assay (Promega).

Results: Within the AML subset, KMT2A-r MV4-11 and MOLM-13, as well as MONO-MAC-6, exhibited greater sensitivity to Ven than the non-KMT2A-r OCI-AML-3. In T-ALL, MOLT-4 was relatively sensitive (IC_{50} ≈ 0.84 µM), while JURKAT was less responsive (IC_{50} ≈ 8.37 µM). B-ALL models showed marked heterogeneity: FLT3-ITD$^+$ KASUMI-10, EP300-ZNF384$^+$ JIH-5, and ETV6-RUNX1$^+$ REH were the most sensitive (IC_{50} 0.001–0.002 µM), followed by cell lines with intermediate sensitivity including NALM-19 (Ph-), SUP-B15 (Ph+), HAL-01 (TCF-HLF), 697 (TCF3-PBX1), MHH-CALL-4 (Ph-like), NALM-6 (DUX4-r), RS4;11 (KMT2A-r), MUTZ-5 (Ph-like) and KOPN-8 (KMT2A-r) (Fig1A). Primary samples displayed highly heterogeneous Ven sensitivity (Fig1B). The Ven–Pona combination showed synergy in SUP-B15 and additive effects in other B-ALL models (Fig1C). Notably, primary BCL2L1–NRIP1$^+$ cells, with the fusion confirmed by Sanger sequencing, also exhibited strong synergy (Fig1D).

Conclusions: Ven demonstrates robust and subtype-dependent preclinical activity across a wide ALL panel, with particular potency in models characterized by BCL2 dependence or BCL2L1–NRIP1$^+$. The combination with Pona yields synergistic or additive anti-leukemic effects, notably in Ph$^+$ SUP-B15 cells and in primary BCL2L1–NRIP1$^+$ sample. These findings highlight the relevance of BCL2 pathway dysregulation in specific ALL subsets and provide a strong rationale for co-targeting apoptotic and kinase signaling to overcome resistance mechanisms. Overall, the data support further translational development and clinical evaluation of Ven–Pona combinations in high-risk, relapsed, or kinase-driven ALL subtypes.

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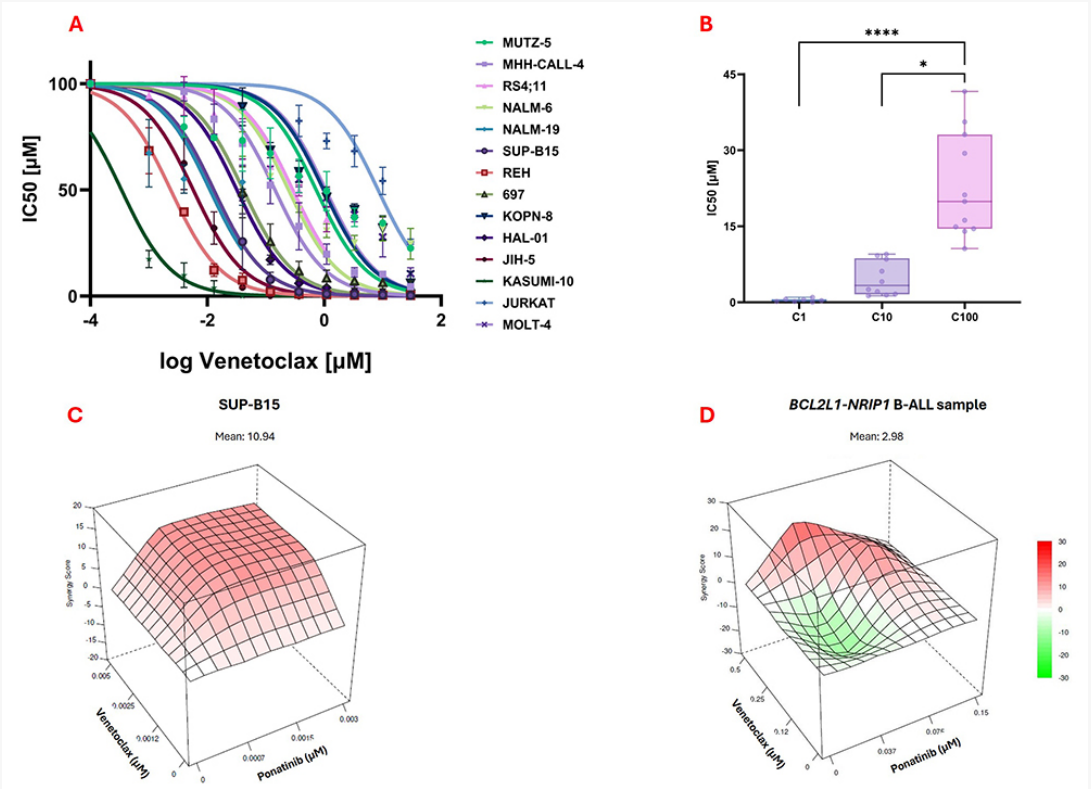

Fig. 1 (A) In vitro response assays to venetoclax at 72h showed higher sensitivity in B-ALL cell lines compared to T-ALL cell lines MOLT-4 and JURKAT. (B) Primary B- and T-ALL samples were divided into three groups according to their sensitivity to venetoclax. C1: IC50 < 1 µM; C10: 1–10 µM; C100: > 10 µM. The differences in IC50 between C1 and C100 ($p<0.0001$) and between C10 and C100 ($p<0.05$) are statistically significant. (C) The combination of venetoclax and ponatinib shows a synergistic effect in the SUP-B15 cell line. (D) In a primary B-ALL sample with the *BCL2L1-NRIP1* fusion, the combination of venetoclax and ponatinib showed an additive effect, and synergistic at two points. Synergy was calculated using the ZIP synergy model.