ADAM17-Driven NKG2D Ligand Shedding Defines a Leukemia-Intrinsic Immune Evasion Program That Predicts Venetoclax Resistance and Reveals MEK and PI3K as Therapeutic Vulnerabilities in AML

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Background

Venetoclax–based combinations have transformed (AML) therapy, yet primary resistance remains common. The shedding of NKG2D ligands from the blast surface may represent a resistance mechanism that shapes innate immune escape and downstream survival signaling.

Methods

- **9-gene NK immune evasion signature:** ADAM17, TIMP3, ULBP1/2/3, MICB, TGFB1, SMAD3, HLA-E, grounded in the ADAM17/TIMP3 sheddase–inhibitor axis.
- **Scoring:** ssGSEA computed per-patient NK evasion scores.
- **Drug mapping:** Differential sensitivity across 270 drugs by Wilcoxon test with Benjamini-Hochberg correction.

Patients & Outcomes

707 BeatAML samples: signature validation.

367 matched specimens: drug-response correlation.

142 TCGA-LAML: independent validation.

Primary measure: ex vivo venetoclax AUC vs NK evasion score; overall survival by Kaplan-Meier (score-dichotomized).

Key Findings

▶**NK score ↔ venetoclax AUC**

Spearman r = 0.48, p < 0.01 (n = 367): higher evasion, greater resistance.

▶**Worse survival**

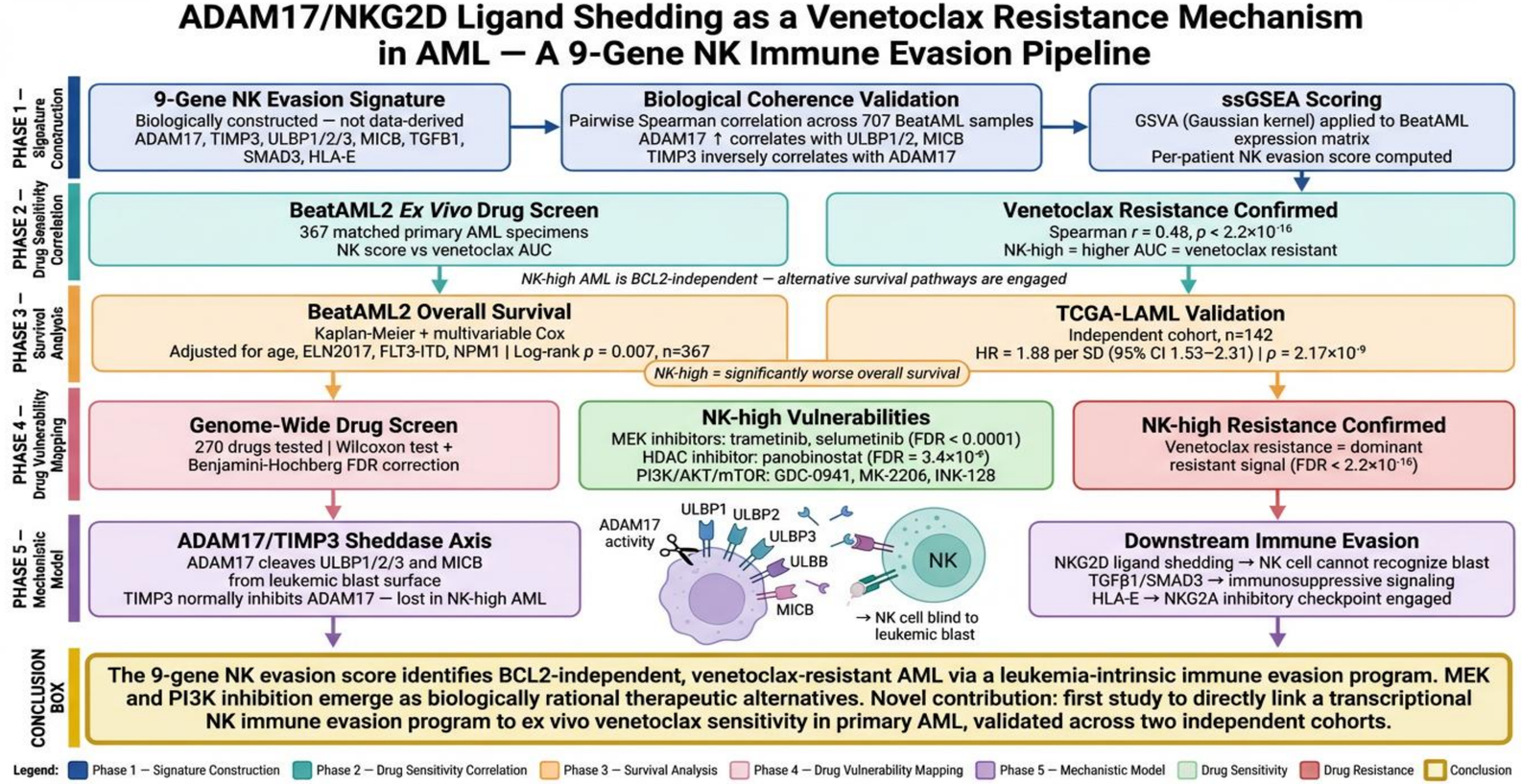
NK-high inferior OS in BeatAML (p= 0.007).
TCGA-LAML: HR = 1.88 per SD (95% CI 1.53–2.31, p=2.17×10^{-9}).

▶ **NK-high vulnerabilities:**

MEK inhibitors trametinib, selumetinib (FDR < 0.0001);

HDAC inhibitor (Panobinostat) & PI3K/AKT/mTOR inhibitors (FDR = 3.4×10^{-6})

Results



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References

1. Bottomly D, et al. Integrative analysis of drug response and clinical outcome in AML. Cancer Cell. 2022 (BeatAML2).
2. Ley TJ, et al. Genomic and epigenomic landscapes of adult de novo AML. N Engl J Med. 2013;368:2059–74 (TCGA-LAML).