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REDEFINING *FLT3* IN B-ALL: NOVEL FINDINGS AND THERAPEUTIC OUTLOOK

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Introduction: The prognosis for relapsed B-ALL patients (pts) remains poor, underscoring the need for new therapeutic strategies. Recent studies have identified FLT3 as a major oncogenic hub in ALL, where its deregulation extends beyond canonical ITD/TKD mutations to include non-canonical and regulatory mechanisms acting on the FLT3 locus, ultimately driving its aberrant expression and oncogenic potential (Lo Schiavo et al., Ferrari A, Mol Cancer, 2025). Despite this, the potential of FLT3 inhibitors (FLT3i) in adult B-ALL has been rarely explored.

Methods: We analyzed 215 adult B-ALL samples using RNA-seq panel (Pan-Cancer, Illumina; 1385 genes): 51 Ph+ or carrying t(4;11)/t(1;19) and 148 Triple-Negative (TN) cases, plus 15 donors. 14 available samples underwent additional DNA sequencing (Extended Myeloid Solution; 98 genes, FLT3 full coding). In vitro testing with 6 FLT3i [Gilteritinib (Gil), Midostaurin, Crenolanib, Sorafenib, Quizartinib, Ponatinib (Pon)] and Venetoclax (Ven) was performed on primary samples (n=29; FLT3-mut=5), 11 B-ALL wt lines, 2 B-ALL mut (NALM-6-mut, KASUMI-10), and 4 AML lines (OCI-AML3 wt; MV-4-11, MOLM-13, MONO-MAC6 FLT3-mut).

Results: RNA-seq revealed FLT3 as the third most mutated gene after TP53 and KMT2A. We detected 16 FLT3-mut samples (15/148 TN; 1/51 Ph+), mostly in the JM and TK domains. Overall, 10.1% of TN and 2% of Ph+ were FLT3-mut, with 68.8% affecting TKD (50%) or ITD (20%) domains, both potentially targetable by FLT3i. FLT3 expression was increased in 13/16 mutated cases compared to donors and wt pts, with higher levels in ZNF384r, KMT2Ar, and CEBPEr B-ALL. Over one-third of FLT3-mut cases showed an IKZF1--plus profile, ~50% harbored cohesin/CTCF alterations, and most carried epigenetic gene mutations, suggesting multi-layered deregulation. From our results we observed that REH and JIH-5 (Ph_TN) were highly sensitive to Pon. NALM-6 cells engineered with FLT3-ITD showed enhanced sensitivity to all FLT3i, resembling FLT3-mut KASUMI-10. Interestingly, MHH-CALL4 wt (Ph-like model) was more sensitive to Gil than OCI-AML3 wt, comparable to FLT3-mut MV-4-11. In 29 primary B-ALL samples, midostaurin, sorafenib, and quizartinib were most effective in FLT3-mut cases, while all inhibitors also showed measurable activity in wt, albeit with generally higher IC50 values. Notably, gil displayed comparable IC50 in both FLT3-mut and wt cells. Based on Gil efficacy in Ph-like contexts and the clinical use of Pon, we tested Gil+Ven and Pon+Ven combinations in B-ALL cell lines and 10 primary samples (n=1 mut). Both combinations showed synergistic or additive effects across models.

Conclusions: Newly emerging data show that FLT3 alterations identify a novel Ph-neg B-ALL subgroup with therapeutic relevance. Responses in both FLT3-mut and wt models suggest FLT3i may offer broader benefit to adult B-ALL patients.

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