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New technologies and multiomics analysis

INTEGRATING PHARMACOGENOMICS AND MICROENVIRONMENT PROFILING IN HIGH-RISK LEUKEMIAS

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Introduction: Ex vivo drug response profiling (DRP) in Acute Leukemia (AL) tests primary leukemia cells with therapeutic agents to assess sensitivity and guide personalized therapy. DRP can be performed within an actionable timeframe and predicts in vivo response. Integration with mutational and metabolomic profiling improves prognostic accuracy and complements risk stratification.

Methods: We established a network under the AL-TOMICA trial (NCT0662689), including eight Hematology Units across Emilia Romagna, to centralize relapsed/refractory (R/R) AL patients (pts). Within this framework, we performed high-throughput screening of nearly 200 drugs, NGS for recurrent mutations (30 myeloid and 114 lymphoid genes), and profiling of bone marrow extracellular vesicles (EVs) (37 surface epitopes). These methods were integrated with standard diagnostics for comprehensive disease characterization.

Results: We enrolled 122 pts; 83 (68%) -69 AML, 8 B-ALL, 4 T-ALL, 2 MPAL (Table 1)- were eligible for DRP. The main reason for exclusion was the low blast percentage. In 30% sampling was adequate for the complete combined analysis. As expected, we observed an enrichment of high-risk (HR) molecular aberrancies (Table 1), confirming the aggressive nature of these cases. To perform unbiased clustering of DRP profiles, we applied a normalized IC_{50} metric to rank responses (Figure 1a). We identified six clusters, from highly resistant (C1) to sensitive (C6) phenotypes. C1–3 included most cases with HR genetic features (42/56, 75%) (Figures 1b–c, Table 1), indicating that chemosensitivity may represent an intrinsic property of leukemia subsets. We suggest that functional profiling can define HR pts, including those lacking conventional markers (5 in our cohort). To identify new therapeutic options, we analyzed DRP according to mutational status or drug mechanism of action (MOA) in our AML cohort, which included primary cases (47), and secondary AMLs evolved from MDS (15), MPN (5), and MDS/MPN (2). As expected, TP53-mut pts exhibited resistance to MDM2 modulators, whereas FLT3-mut samples displayed sensitivity to ABL inhibitors (Figure 2a–b), suggesting that predicting shifts in kinase dependencies may guide therapy in R/R settings. When clustering by MOA, we observed greater sensitivity to PI3K/AKT/mTOR pathway inhibition in post-MDS AML, supporting the role of DRP in revealing pathway impairments even in absence of known mutations (Figure 3). Finally, we compared DRP with EVs' signature to predict markers of response. Among observations, only CD14 expression was negatively correlated with response to apoptotic modulators (Fig4), suggesting its potential as a biomarker for VEN sensitivity.

Conclusions: We established a functional platform that provided therapeutic guidance to R/R AL pts and outperformed the ESCAT-ESMO scale in terms of clinical actionability of molecular targets. Across all pts we identified at least one druggable pathway, compared with 51% identified based on genetic mutations alone.

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Figure 1a

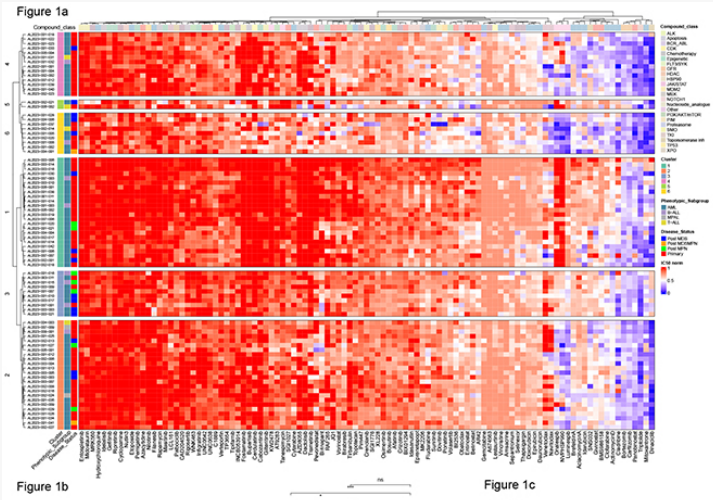

Table 1: Complete Cohort

Diagnosis	Hystory	Main genetic lesions	n of pts	AML ELN 2022
AML	Primary	MECOMr	3	Unfavorable
		MECOMr JAK2	1	Unfavorable
		MECOMr FLT3ITD	1	Unfavorable
		MECOMr TP53	1	Unfavorable
		TP53	9	Unfavorable
		TP53 JAK2	1	Unfavorable
		TP53 KMT2Aamp	1	Unfavorable
		KMT2Ar	1	Unfavorable
		Other HMR	17	Unfavorable
		FLT3ITD	7	Intermediate
		FLT3ITD NPM1	2	Intermediate
		FLT3ITD KMT2Aamp	1	Intermediate
		KMT2A::MLL	1	Intermediate
		KMT2A amp	1	Intermediate
		JAK2	1	Intermediate
		Other	2	Intermediate
		NPM1	2	Favorable
		CBF	2	Favorable
		WT	3	Favorable (if primary)
		UNK	5	UNK
AML	Post MPN	JAK2	3	Unfavorable
		JAK2 TP53	1	Unfavorable
		CALR	1	Unfavorable
AML	Post MDSMPN	MECOMr TP53	1	Unfavorable
		FLT3ITD NPM1	1	Unfavorable

Diagnosis	Hystory	Classification	n of pts	ALL ELN 2023
B-ALL	Primary	Ph pos	6	Unfavorable
		Ph neg	2	Intermediate
T-ALL	Primary	ETP	2	Unfavorable
		Pre-T	1	Unfavorable
		Cortical	1	Favorable
MPAL	Primary	T/My	1	(Unfavorable)
		B/My	1	(Unfavorable)

Figure 1b

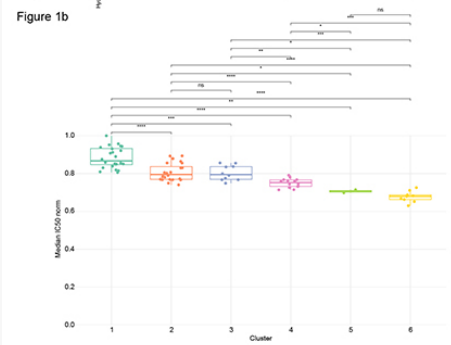

Figure 1c

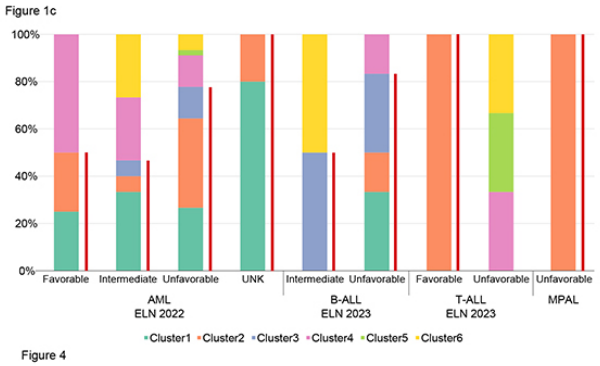

Figure 2a

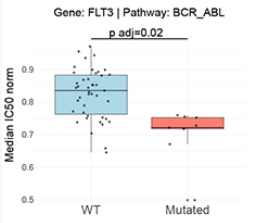

Figure 2b

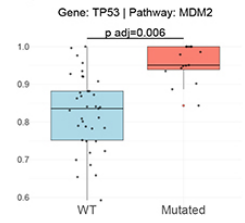

Figure 3

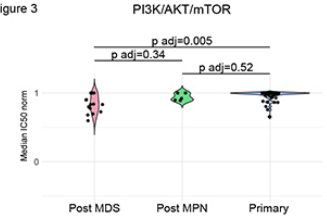

Figure 4