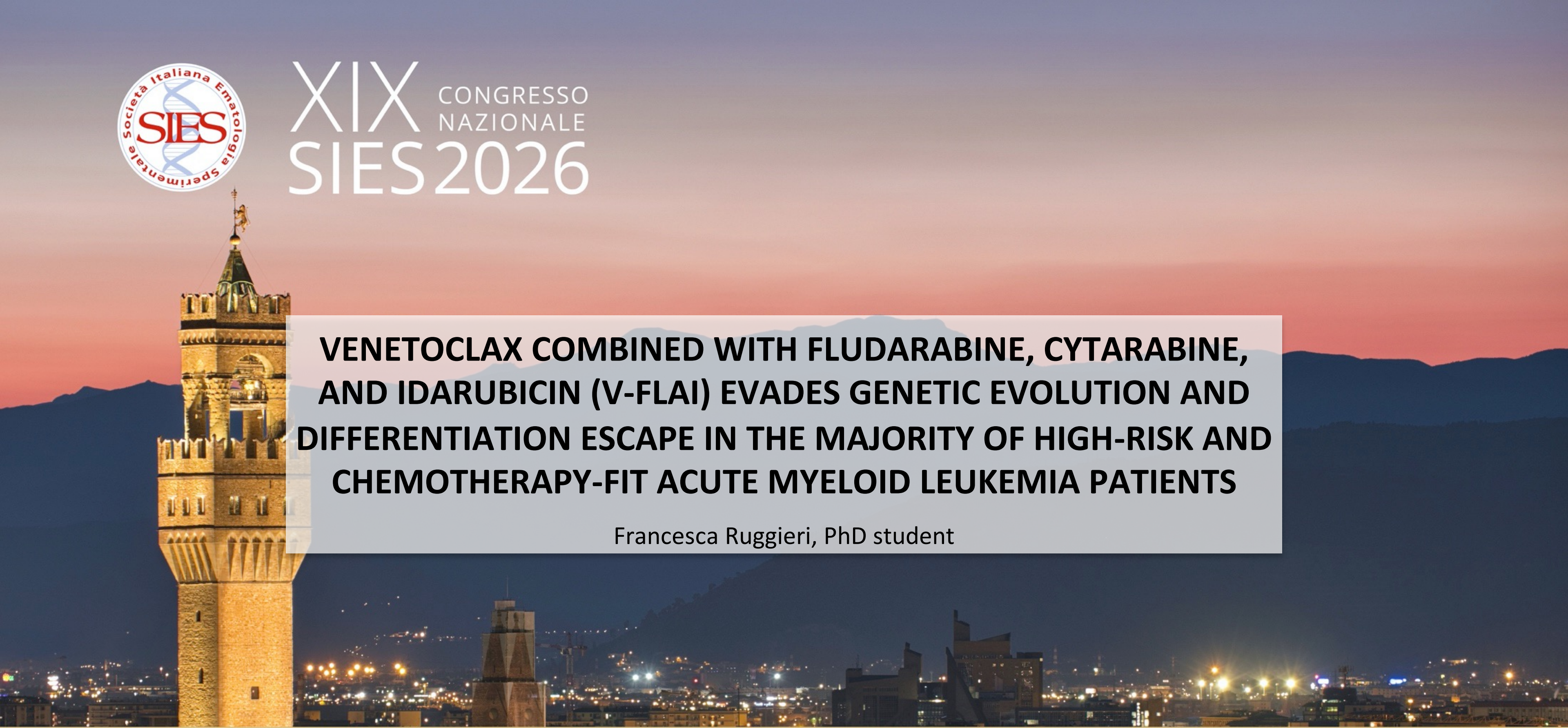


XIX CONGRESSO NAZIONALE
SIES 2026

VENETOCLAX COMBINED WITH FLUDARABINE, CYTARABINE, AND IDARUBICIN (V-FLAI) EVADES GENETIC EVOLUTION AND DIFFERENTIATION ESCAPE IN THE MAJORITY OF HIGH-RISK AND CHEMOTHERAPY-FIT ACUTE MYELOID LEUKEMIA PATIENTS

Francesca Ruggieri, PhD student

Firenze | **4-6 marzo 2026**
Palazzo degli Affari

Disclosures of Francesca Ruggieri

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Intermediate/high-risk AML: the need for novel induction strategies

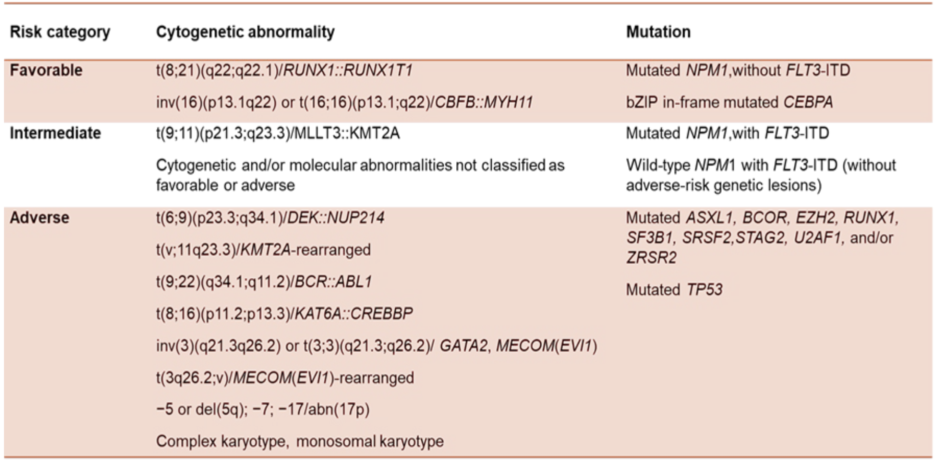
- The frontine therapy of fit acute myeloid leukemia (AML) patients is the induction chemotherapy regimen

- The first line remission rate of non-low risk AML is ~50%

- Novel induction regimes are under investigation: the combination of venetoclax and chemotherapy is emerging as a promising approach (FLAG-IDA+Ven)

DiNardo et al. *Leukemia.* 2025
DiNardo et al. *Am J Hematol.* 2022
DiNardo et al. *JCO* 2021
Rausch et al. *Leukemia.* 2023

ELN 2022 risk stratification



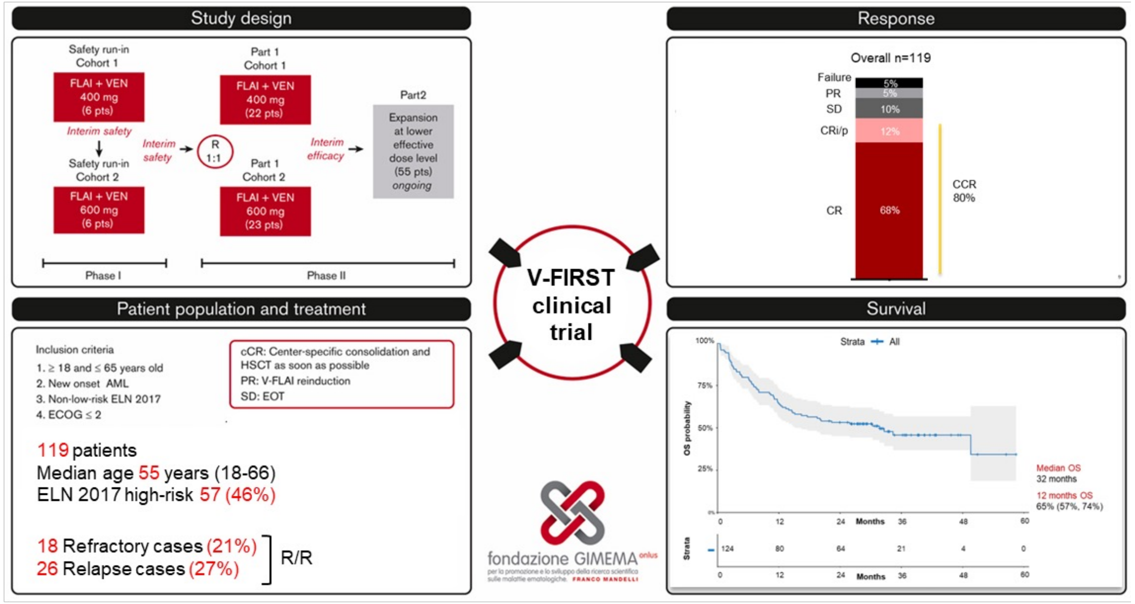
Risk category	Cytogenetic abnormality	Mutation
Favorable	t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*	Mutated *NPM1*,without *FLT3*-ITD
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*	bZIP in-frame mutated *CEBPA*
Intermediate	t(9;11)(p21.3;q23.3)/MLLT3::KMT2A	Mutated *NPM1*,with *FLT3*-ITD
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse	Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions)
Adverse	t(6;9)(p23.3;q34.1)/*DEK::NUP214*	Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2,STAG2, U2AF1,* and/or *ZRSR2*
	t(v;11q23.3)/*KMT2A*-rearranged	Mutated *TP53*
	t(9;22)(q34.1;q11.2)/*BCR::ABL1*	
	t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*	
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2, MECOM*(*EVI1*)	
	t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged	
	−5 or del(5q); −7; −17/abn(17p)	
	Complex karyotype, monosomal karyotype	

Döhner et al. *Blood* 2022

The V-FIRST (GIMEMA AML1718) trial

A Safety Run-In and Phase 2, Open-Label, Multicentre Study investigating Safety, Tolerability and Effectiveness of venetoclax add in combination at fludarabine, cyratabine and idarubicine (FLAI) in induction therapy of new onset Non-M3 Acute Myeloid Leukemia

Venetoclax/fludarabine, cytarabine, idarubicin (V-FLAI)



Inclusion criteria
1. ≥ 18 and ≤ 65 years old
2. New onset AML
3. Non-low-risk ELN 2017
4. ECOG ≤ 2

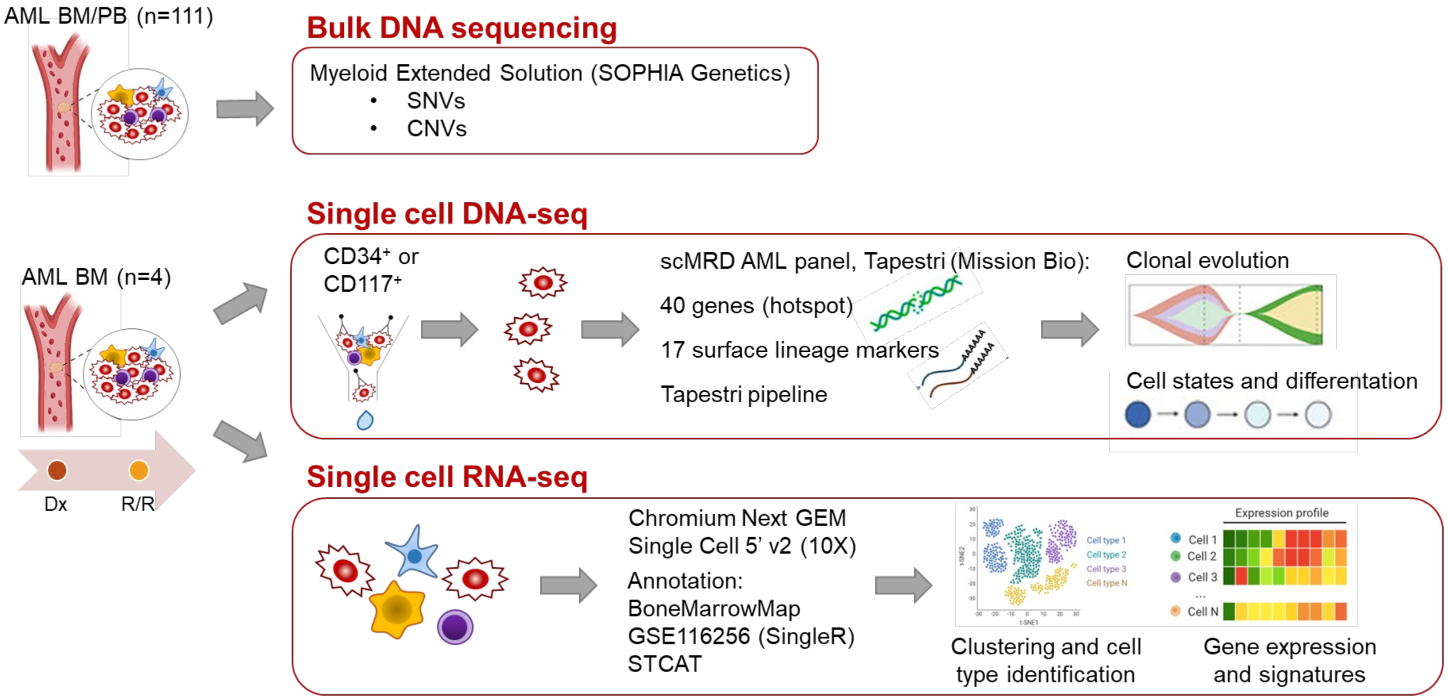
cCR: Center-specific consolidation and HSCT as soon as possible
PR: V-FLAI reinduction
SD: EOT

119 patients
Median age 55 years (18-66)
ELN 2017 high-risk 57 (46%)

18 Refractory cases (21%)
26 Relapse cases (27%)
R/R

adjusted from Marconi et al. *Blood Adv.* 2025

Genetic and transcriptomic analyses of the V-FIRST cohort



AML BM/PB (n=111)

Bulk DNA sequencing

Myeloid Extended Solution (SOPHIA Genetics)
- SNVs
- CNVs

AML BM (n=4)

Dx
R/R

Single cell DNA-seq

CD34$^+$ or CD117$^+$

scMRD AML panel, Tapestri (Mission Bio):

40 genes (hotspot)

17 surface lineage markers

Tapestri pipeline

Clonal evolution

Cell states and differentation

Single cell RNA-seq

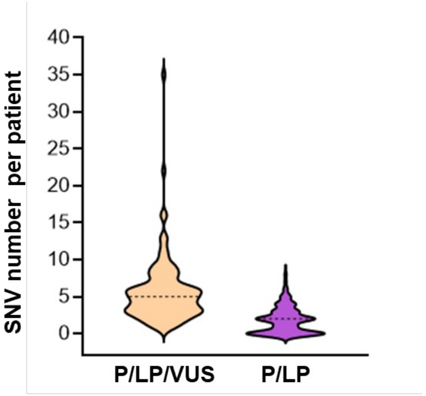
Chromium Next GEM Single Cell 5' v2 (10X)

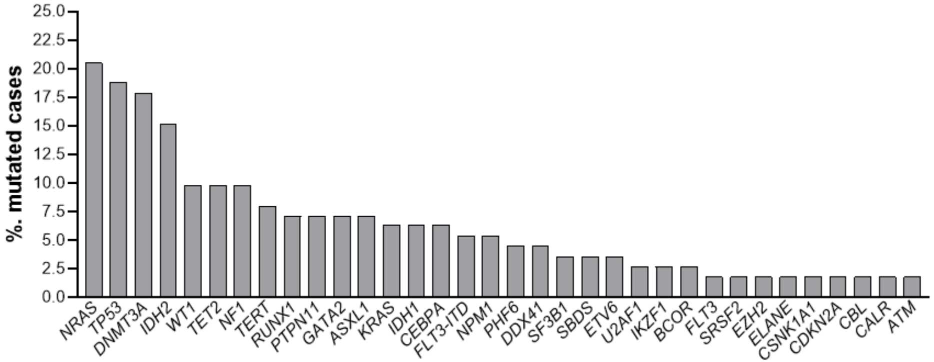
Annotation:
BoneMarrowMap
GSE116256 (SingleR)
STCAT

Clustering and cell type identification

Gene expression and signatures

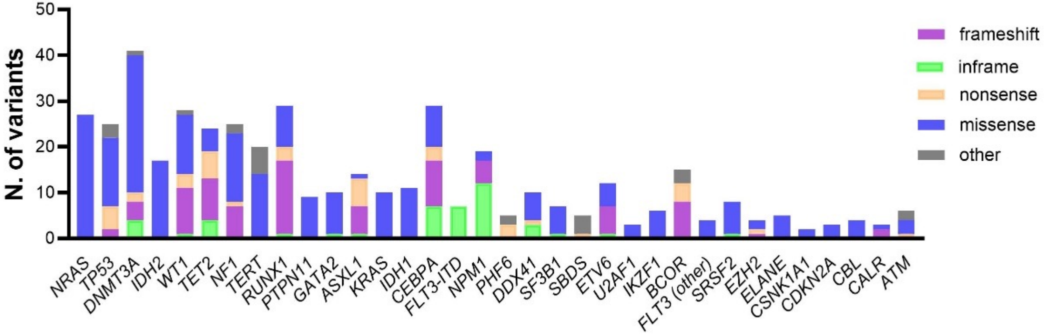
The mutational landscape of the V-FIRST cohort





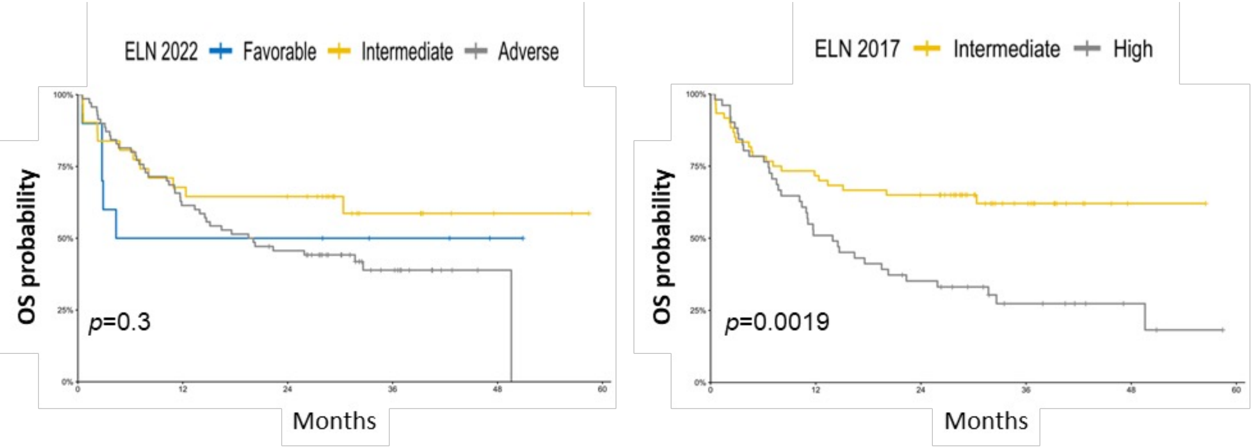
Median n. P/LP variants: 2 (0-7)
Median n. P/LP/VUS variants: 5 (0-35)

P= pathogenic
LP= likely pathogenic
VUS= variant of undetermined significance

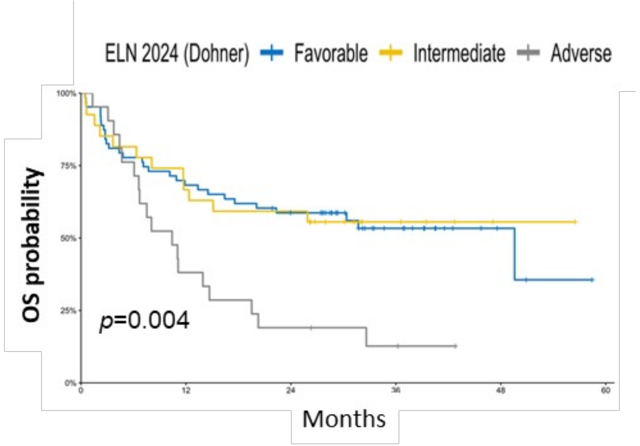


The current AML risk classification for intensively-treated patients is not predictive of clinical outcome to V-FLAI

Chemotherapy regimens



Less-intensive therapies

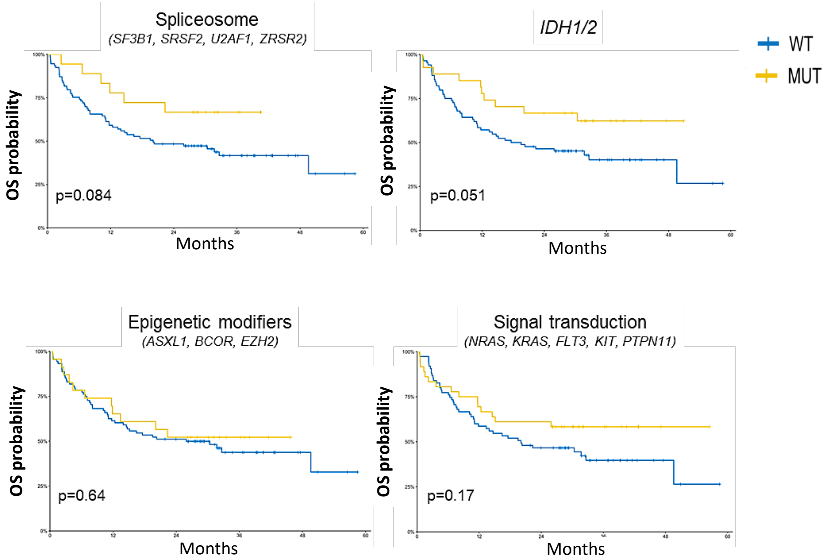


Patients carrying mutations in *IDH1*/2, splicing/epigenetic regulators and signal transduction genes respond to V-FLAI

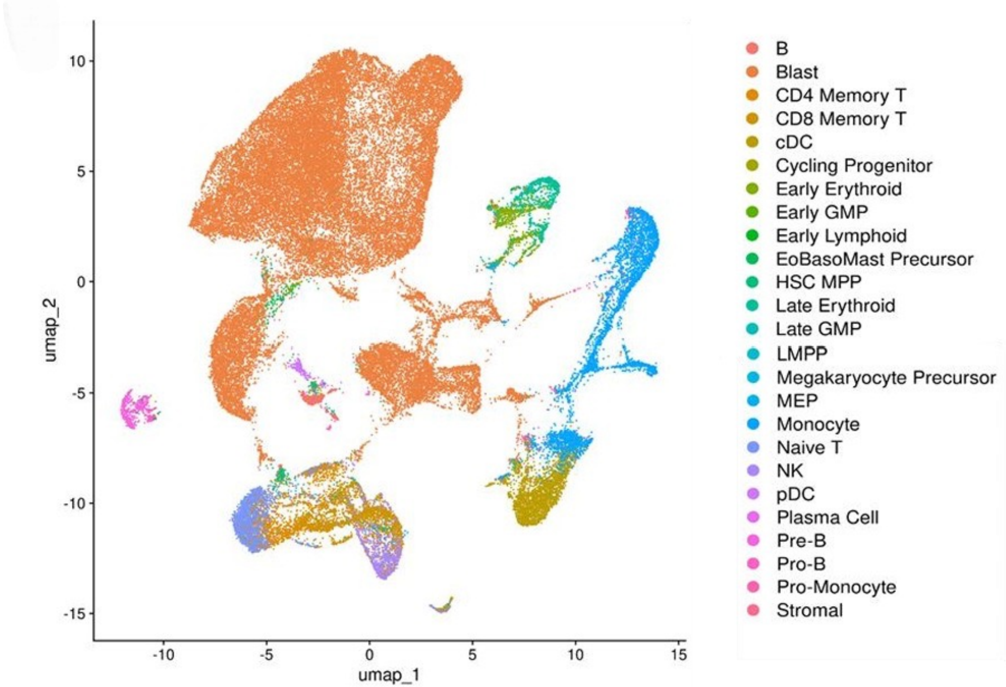
Response (cycle 1+2)

	Multivariable Logistic Regression Model		
	OR	**95% CI**	**p-value**
Signal transduction genes	1.04	0.39, 2.93	>0.9
Epigenetic modifiers	1.96	0.57, 9.07	0.3
Spliceosome genes	1.91	0.43, 13.6	0.4
***MECOM*-r**	0.03	0.00, 0.26	**0.005**
***CEBPA*-inframe-bZIP**	0.73	0.09, 15.5	0.8
***FLT3*-ITD**	1.91	0.29, 37.9	0.6
***NPM1* (*FLT3*-wt)**	0.57	0.17, 2.07	0.4
IDH1/2	1.42	0.48, 4.87	0.5
***KMT2A*-r**	1.22	0.25, 8.97	0.8
Monosomy 5/DEL5q	0.23	0.08, 0.69	**0.008**
Monosomy 7	0.23	0.05, 0.94	**0.039**
***TP53*-mut/del**	0.23	0.08, 0.66	**0.007**

Overall survival

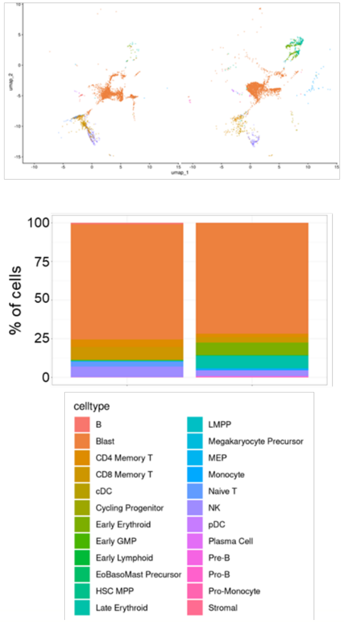


Single-cell RNA sequencing reveals dynamic remodeling of leukemic blast states during AML R/R to V-FLAI



Single-cell RNA sequencing reveals dynamic remodeling of leukemic blast states during AML R/R to V-FLAI

#4512



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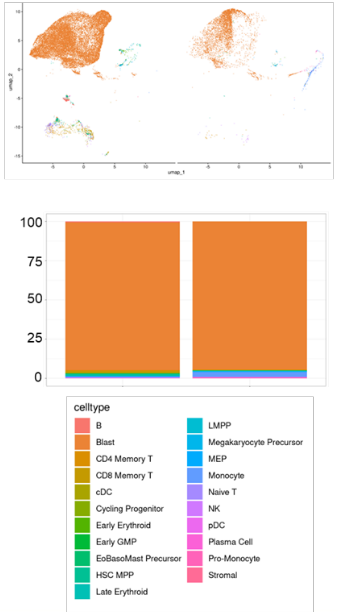

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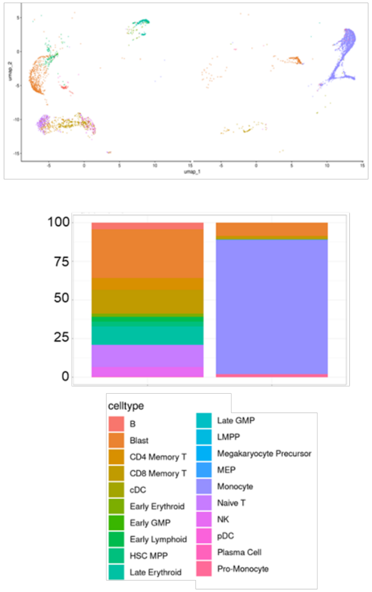

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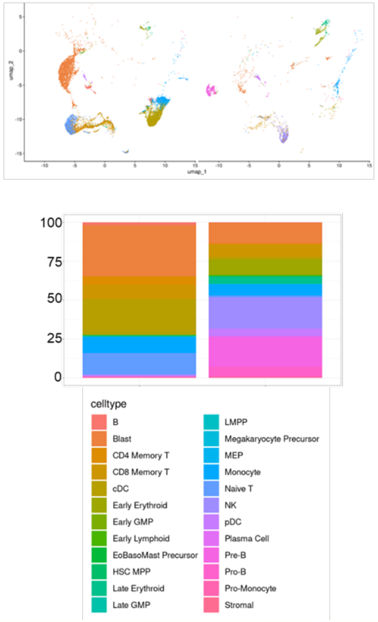
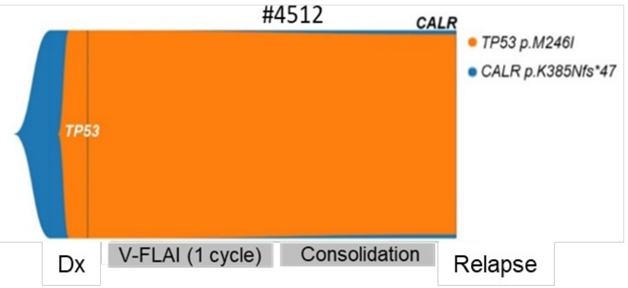
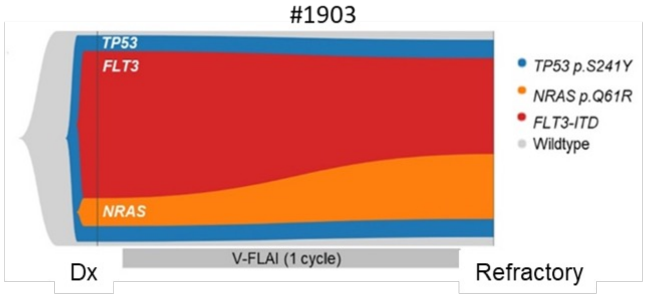
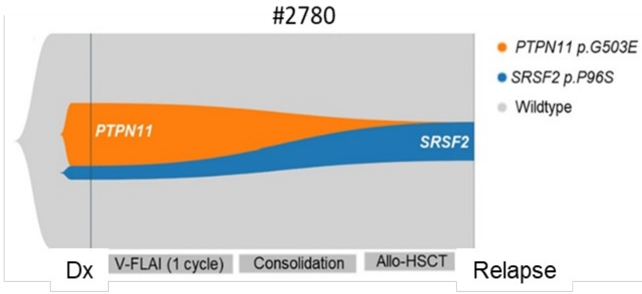
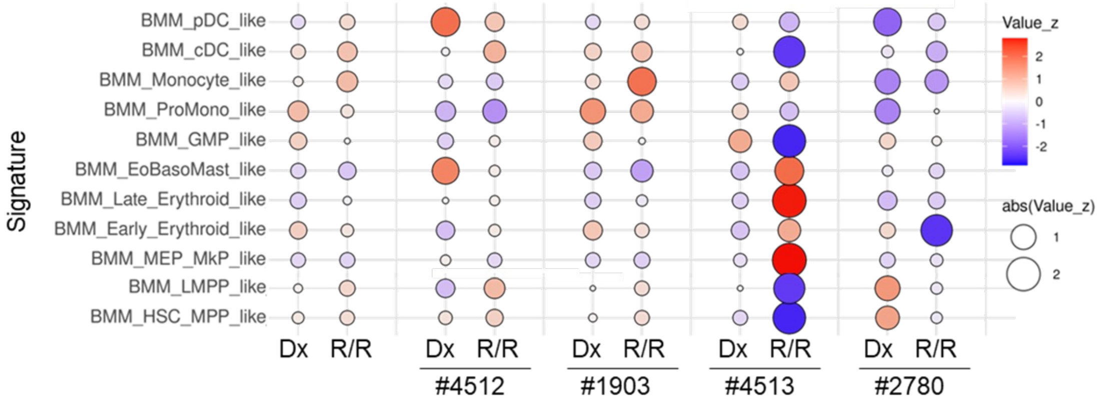


Clonal and differentiation trajectories driving R/R

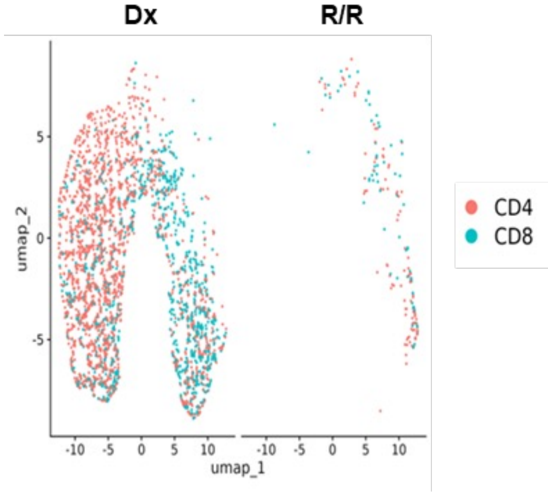


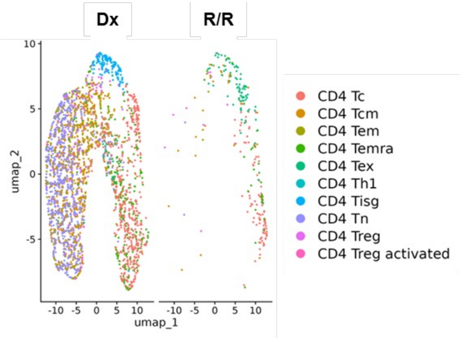


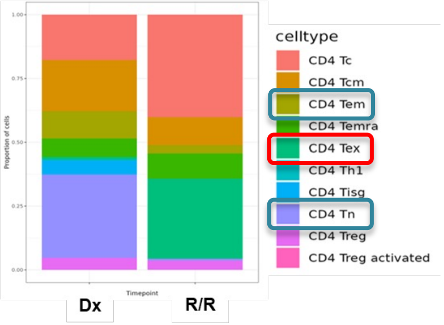


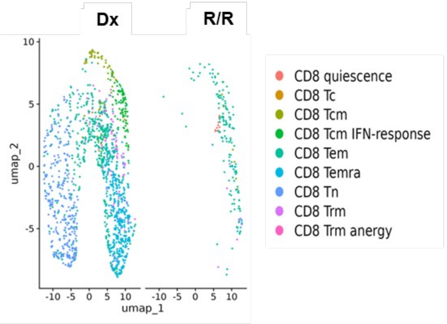


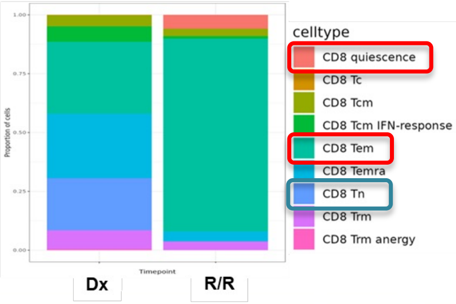
V-FLAI resistance is associated with immune compartment reshaping and T-cell exhaustion





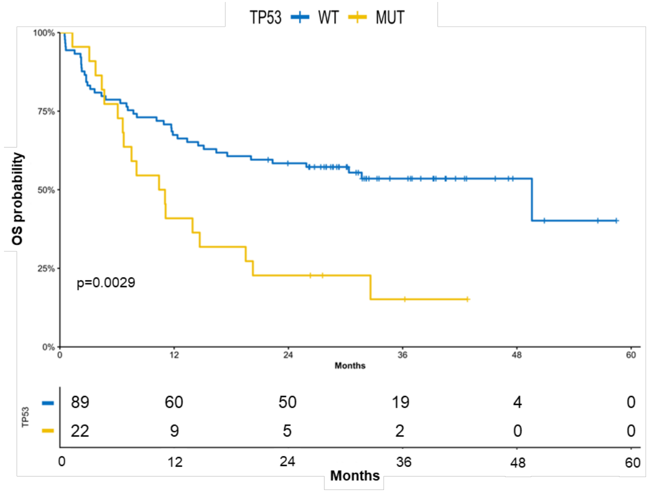




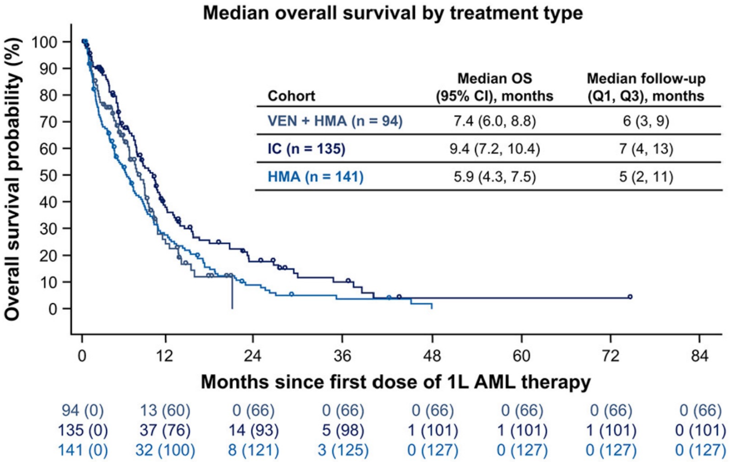


Conclusions

- Promising outcome of patients with mutations in signal transduction genes, splicing and epigenetic regulators
- Disease persistence and poor prognosis in *TP53*-mutated and *MECOM*-rearranged cases



Median OS: 11 months (7, 20)

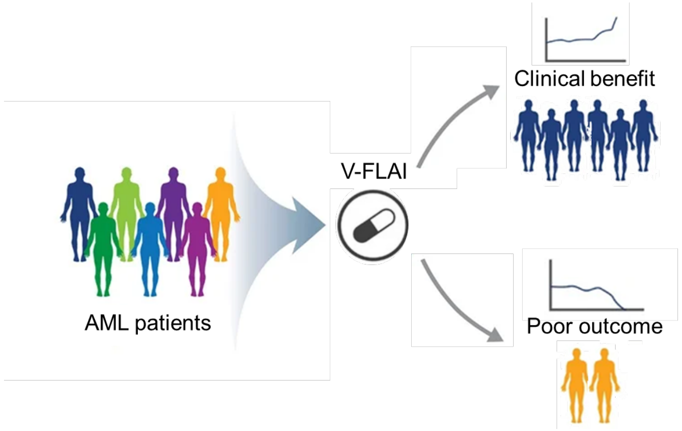


Cohort	Median OS (95% CI), months	Median follow-up (Q1, Q3), months
VEN + HMA (n = 94)	7.4 (6.0, 8.8)	6 (3, 9)
IC (n = 135)	9.4 (7.2, 10.4)	7 (4, 13)
HMA (n = 141)	5.9 (4.3, 7.5)	5 (2, 11)

Daver et al. Ann. Hematol. 2023

Conclusions

- Promising outcome of patients with mutations in signal transduction genes, splicing and epigenetic regulators
- Disease persistence and poor prognosis in *TP53*-mutated and MECOM-rearranged cases
- Lineage skewing contributes to V-FLAI resistance
- V-FLAI shapes the T cell response that is weakened at R/R



Re-definition of AML patients' risk

Converging mechanisms of Venetoclax and FLAI resistance

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per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

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