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Abstract #655

Genomic and Phenotypic Impact of FHD-286–Induced Inhibition of SMARCA4/2 in Patients With Relapsed/Refractory Myeloid Malignancies

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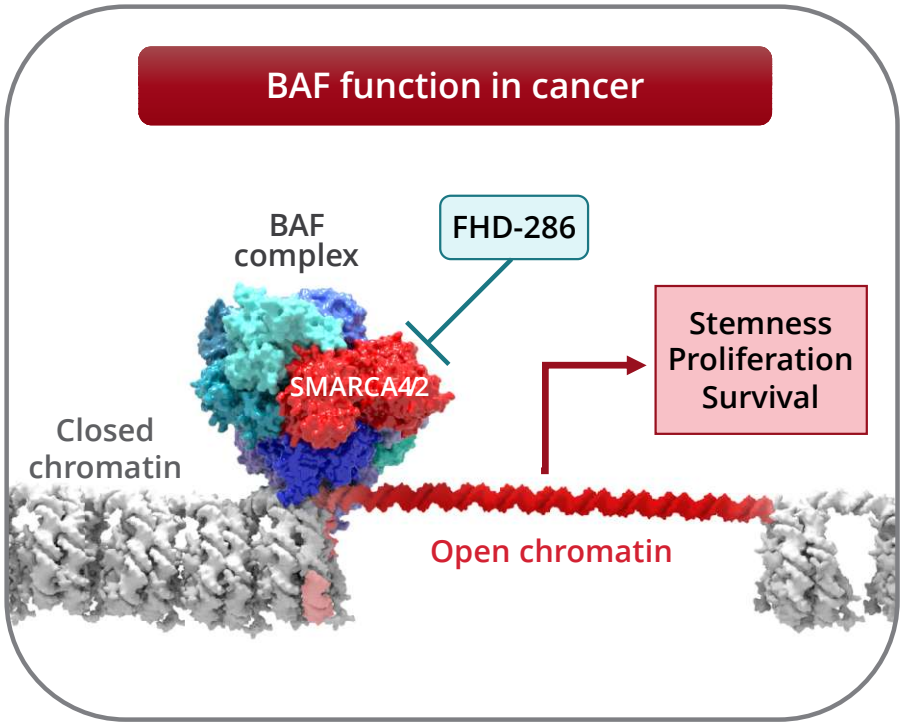
Introduction

- FHD-286 is a first-in-class dual inhibitor of the BAF ATPase subunits SMARCA4/2 (BRG1/BRM)
- BAF (SWI/SNF) is a chromatin remodeling complex that regulates gene expression
- Preclinically, BAF activity is a key dependency in multiple hematological malignancies
- FHD-286 monotherapy induced myeloid differentiation in patients with R/R AML or MDS[1]; FHD-286 + decitabine produced objective responses[2]
- Objective: Understand the molecular basis of clinical activity of FHD-286



[1]DiNardo, CD, et al. *Clin Cancer Res.* 2025. [2]DiNardo, CD, et al. Presented at EHA 2025.
AML, acute myeloid leukemia; ATP, adenosine triphosphate; MDS, myelodysplastic syndrome; R/R, relapsed/refractory.

Patients and methods

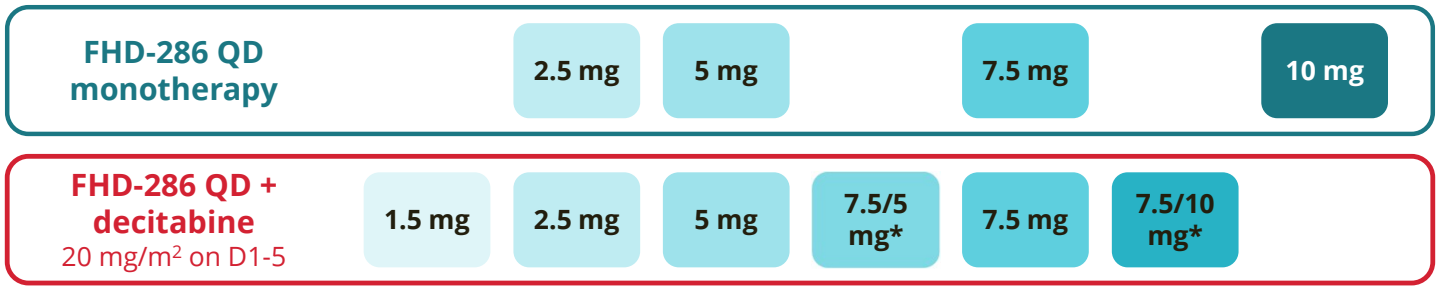
Design

- **Study**: Multicenter, open-label, Phase 1 dose escalation trial of FHD-286 ± decitabine given in 28-day cycles
- **Patients**: R/R AML (n=78), MDS (n=8), or CMML (n=1)
  - 81/87 (93%) received prior hypomethylating agent therapy
- **Samples**: Longitudinal bone marrow aspirate (BMA)
  - Time points: Screening, C1D15 (combination only), day 1 of subsequent cycles, end of treatment

Analysis

- Multiparameter flow cytometry
  - 135 samples from 51 patients (AML: 45; MDS: 5; CMML: 1)
- Single-cell RNA sequencing (scRNA-seq)
  - 90 samples from 40 patients (AML: 35; MDS: 4; CMML: 1)

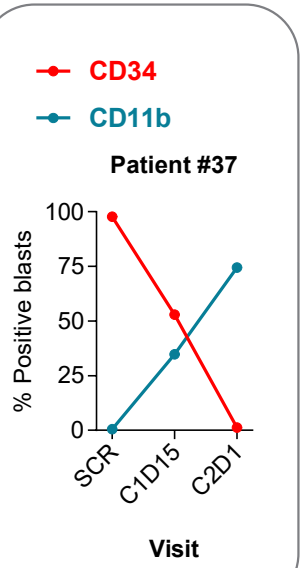
FHD-286-C-002 (NCT04891757) study design



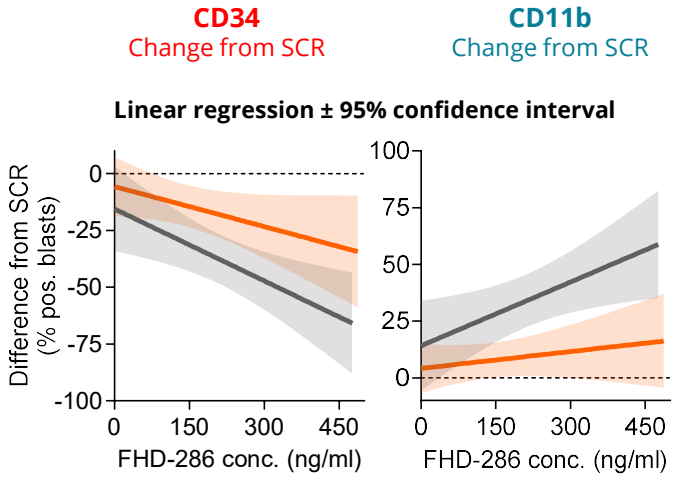
*Interval dosing: First dose given for first 2 weeks of each cycle; second dose given for second 2 weeks of each cycle.
CMML, chronic myelomonocytic leukemia; CxDy, Cycle x Day y; D, Days; QD, once daily.

FHD-286 promotes myeloid differentiation, but decitabine combination appears to dampen this effect

Longitudinal analysis
Individual patients

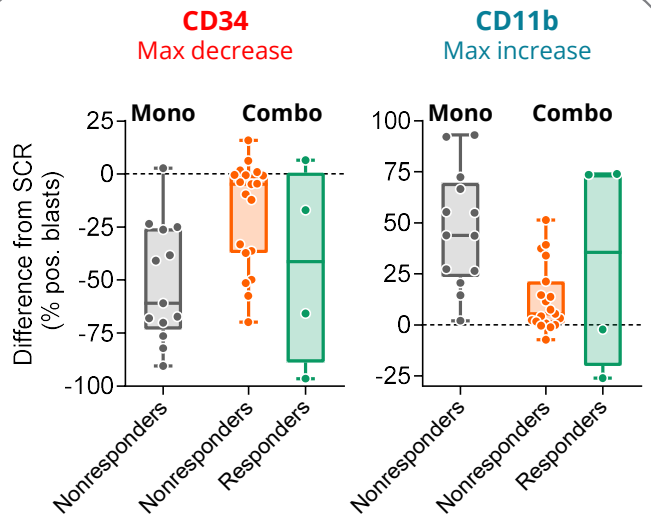


Correlation to FHD-286 exposure
Monotherapy and combination cohorts



Monotherapy; n = 23 samples
Combination; n = 44 samples

Correlation to clinical response

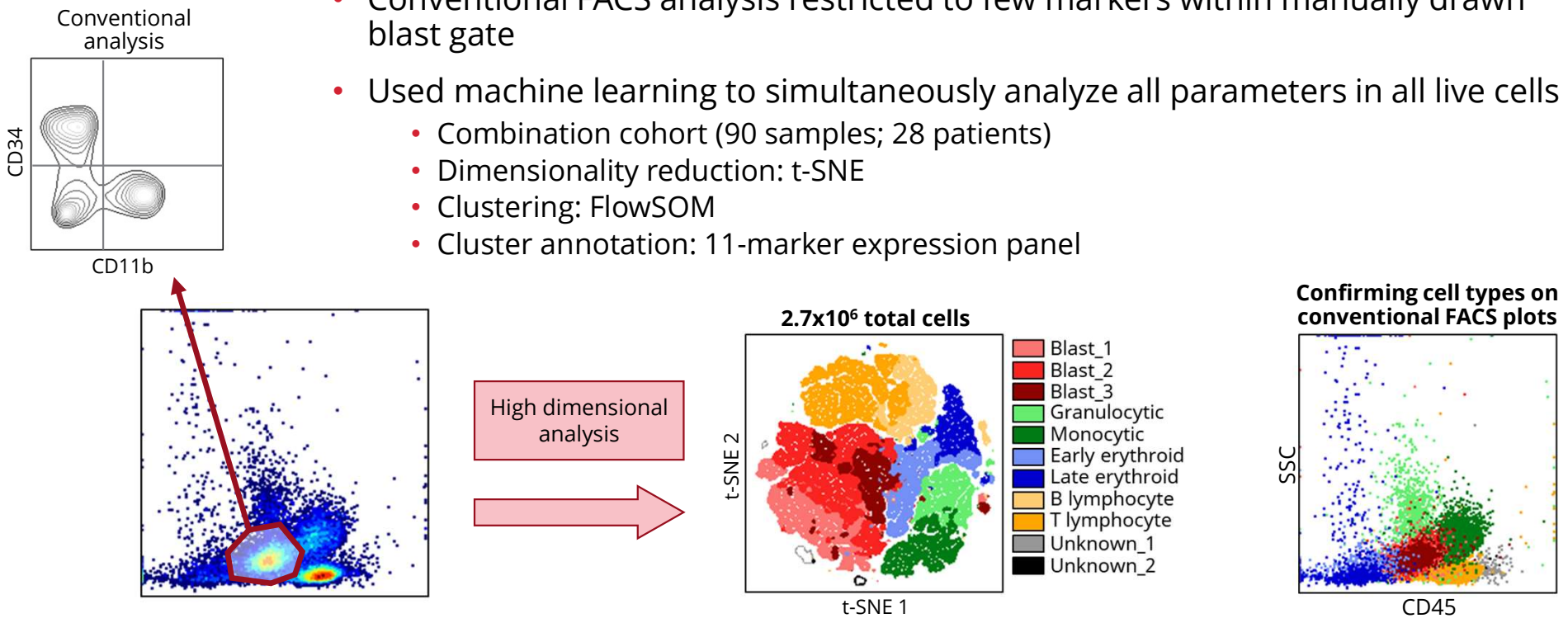


How do we explain this discrepancy – weaker differentiation but improved clinical activity – with the combination?

Combo, combination therapy; FACS, fluorescence-activated cell sorting; max, maximum; mono, monotherapy; pos, positive; SCR, screening.

Beyond the blast gate: High-dimensional FACS analysis of all major bone marrow mononuclear cell types

- Conventional FACS analysis restricted to few markers within manually drawn blast gate
- Used machine learning to simultaneously analyze all parameters in all live cells
  - Combination cohort (90 samples; 28 patients)
  - Dimensionality reduction: t-SNE
  - Clustering: FlowSOM
  - Cluster annotation: 11-marker expression panel

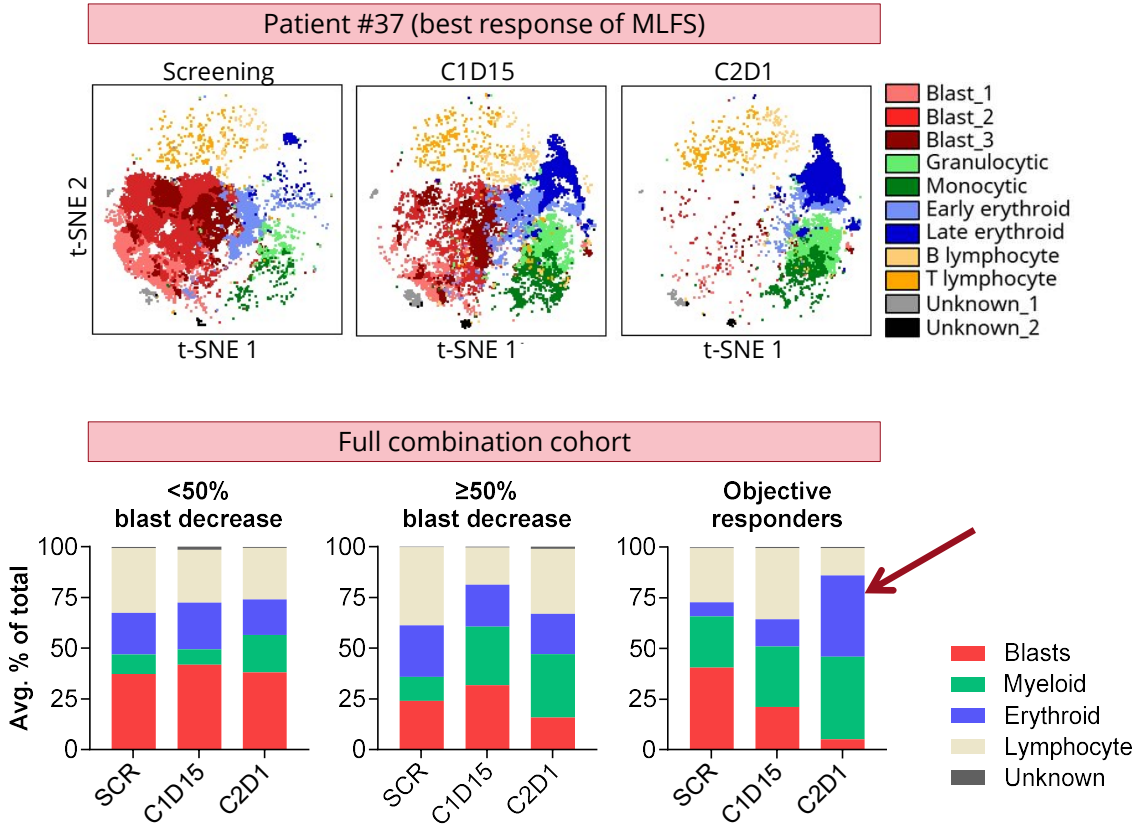


 FlowSom, flow self-organizing map; SSC, side scatter; t-SNE, t-stochastic neighbor embedding.

Objective responders in combination cohort exhibit marked expansion of erythroid compartment

Changes to cluster abundance in responders/non-responders

- **Blast decrease <50% (n=17):** Cell populations unchanged
- **Blast decrease ≥50% (n=4):** Increase in myeloid cell population; no change in erythroid cell population
- **Objective responders (n=5):** Modest increase in myeloid cell population; pronounced increase in erythroid cell population



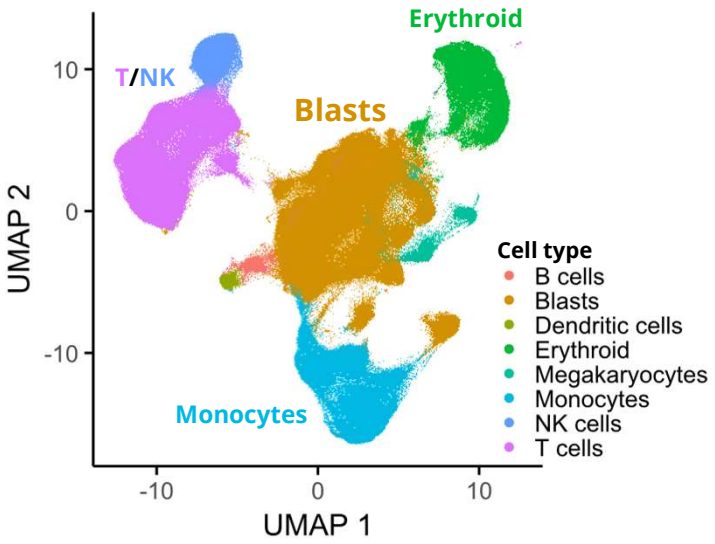
 Avg, average; MLFS, morphologic leukemia-free state.

Single cell genomic analysis for deeper interrogation of cell state changes

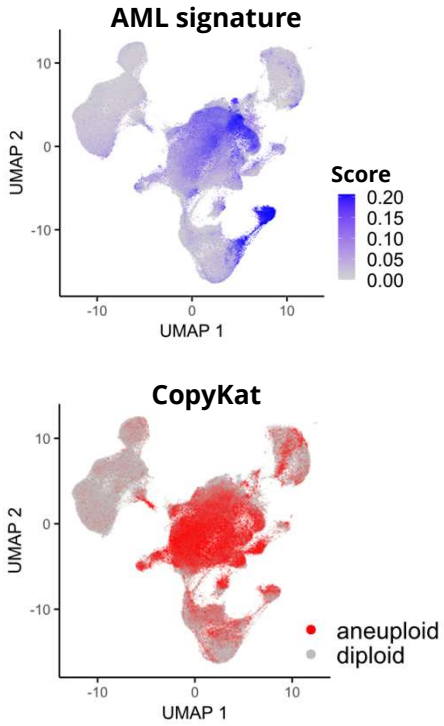
- scRNA-seq on 90 BMA samples from 40 patients
- Integration, dimensionality reduction, and clustering of monotherapy and combination cohorts
- **Cell type identification:** singleR, Azimuth, and BoneMarrowMap[1,2,3]
- **Blast compartment confirmation:** AML expression signature[4] and CopyKat[5] aneuploidy analysis

Cell type identification

- 5.7x10^5 total cells
- 2.9x10^5 blasts



Blast compartment confirmation

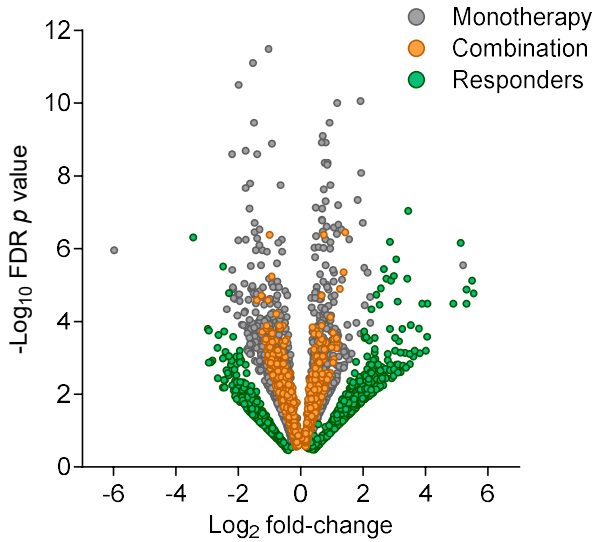


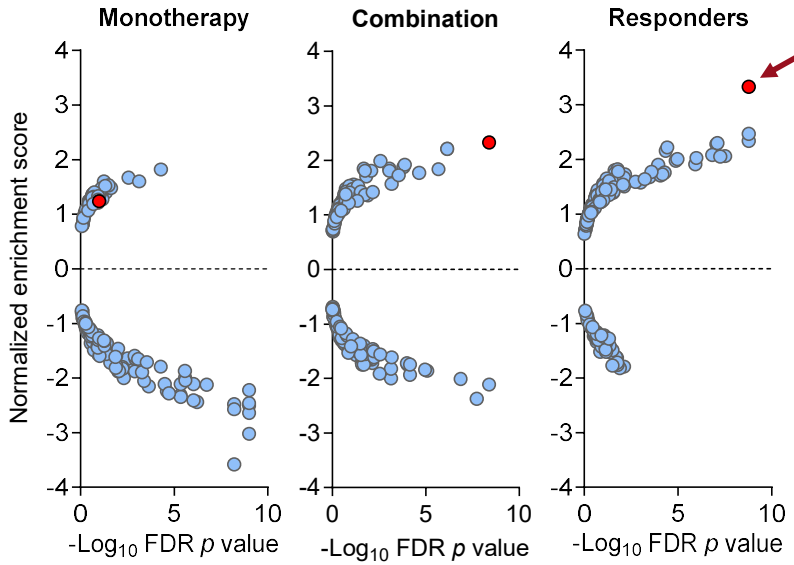
[1]Aran, D, et al. *Nat Immunol.* 2019. [2]Hao, Y, et al. *Cell.* 2021. [3]Zeng, AGX, et al. *Blood Cancer Discov.* 2025. [4]Mumme, H, et al. *Nat Commun.* 2023. [5]Gao, R, et al. *Nat Biotechnol.* 2021.
NK, natural killer; UMAP, uniform manifold approximation and projection.

Responders exhibit marked upregulation of erythroid maturation genes within blast compartment

Genes
Screening vs. on-treatment

Pathways
Screening vs. on-treatment





Heme Metabolism

Gene set collections analyzed:

- Hallmark[1] (50 gene sets)
- KEGG[2] (186 gene sets)

Heme Metabolism:

- #1 upregulated gene set in combination cohort

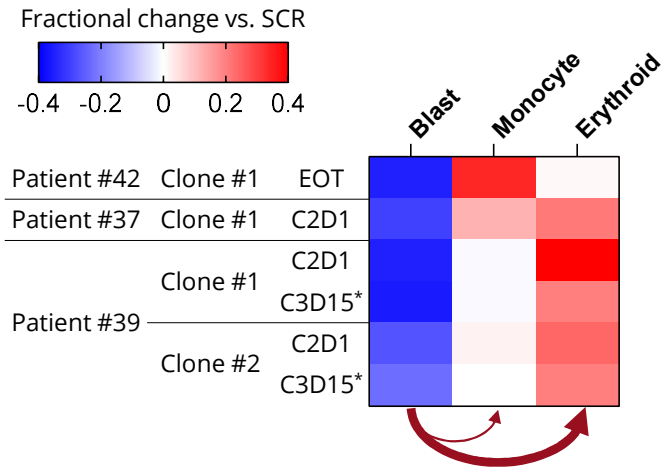
[1]Liberzon A, et al. *Cell Syst*. 2015. [2]Kanehisa M and Goto S. *Nucleic Acids Res*. 2000.
FDR, false discovery rate; KEGG, Kyoto encyclopedia of genes and genomes; vs, versus.

Numbat clonal analysis demonstrates that blasts shift into erythroid compartment

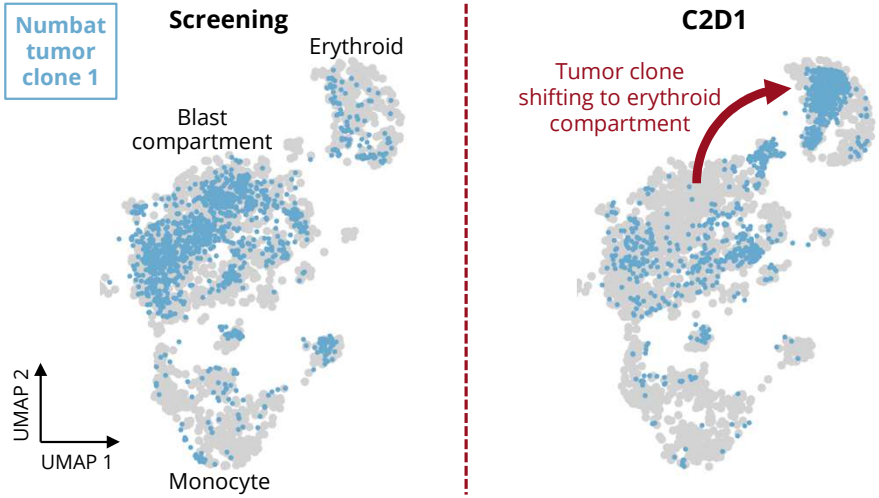
Numbat

- Computational tool for calling inferred copy number variants (CNVs) in scRNA-seq data[1]
- Identified CNVs had high concordance with cytogenetic lab testing
- CNV profiles enable identification and longitudinal tracking of tumor subclones

Heatmap of individual tumor clones in responders



Patient #39 (best response of MLFS)



[1]Gao, T, et al. *Nat Biotechnol.* 2022.
*Unscheduled.

Conclusions

- FHD-286 monotherapy promotes myelomonocytic differentiation in AML blasts
- FHD-286+decitabine combination
  - Dampens myelomonocytic differentiation
  - Promotes expansion of erythroid cell population
  - Improves clinical activity
- Objective responders have marked upregulation of erythroid maturation genes in blasts
- Numbat analysis tracks blast differentiation into monocyte and erythroid compartments
- Additional studies needed to understand the context in which FHD-286+decitabine leads to greater efficacy, and may support patient enrichment strategies

Acknowledgements

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