Complex polyclonal resistance mechanisms to ivosidenib monotherapy in *IDH1*-mutant relapsed or refractory acute myeloid leukemia revealed by single-cell sequencing analyses

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Background

- Somatic mutations in *IDH1* (*IDH2*) occur in 6–10% (9–13%) of patients with AML, resulting in production of the oncometabolite 2-HG
- Ivosidenib, a mutant IDH1 (mIDH1) inhibitor, is approved in the US for m*IDH1* R/R AML, and newly diagnosed m*IDH1* AML in patients ≥75 years old or with comorbidities precluding intensive induction chemotherapy
- Durable remissions in m*IDH1* R/R AML were achieved with ivosidenib in a phase 1 study (NCT02074839)[1]
  - ORR 42%, CR 22%, and CR+CRh 30%
  - Median duration of CR+CRh: 8.2 months
- Initial case report identified two patients with m*IDH1* acquiring m*IDH2* at relapse following ivosidenib monotherapy[2]

2-HG, D-2-hydroxyglutarate; AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; IDH, isocitrate dehydrogenase; m, mutant; ORR, overall response rate; R/R, relapsed or refractory

1. DiNardo CD et al. *N Engl J Med* 2018;378:2386-98. **2.** Harding JJ et al. *Cancer Discov* 2018;8:1540-7.

Objectives

Use single-cell mutation profiling to explore the evolution of m*IDH2* clones under the selective pressure of ivosidenib monotherapy in a subset of patients

- Resolve clonal architecture
- Examine the genetic mechanism by which AML retains dependency on 2-HG

Analysis dataset and methods

Phase 1 study
m*IDH1* R/R AML, 500 mg QD ivosidenib
N = 174

↓

Baseline and any on-treatment time point
(targeted NGS profiling, sensitivity 2–5%)
n = 129

↓

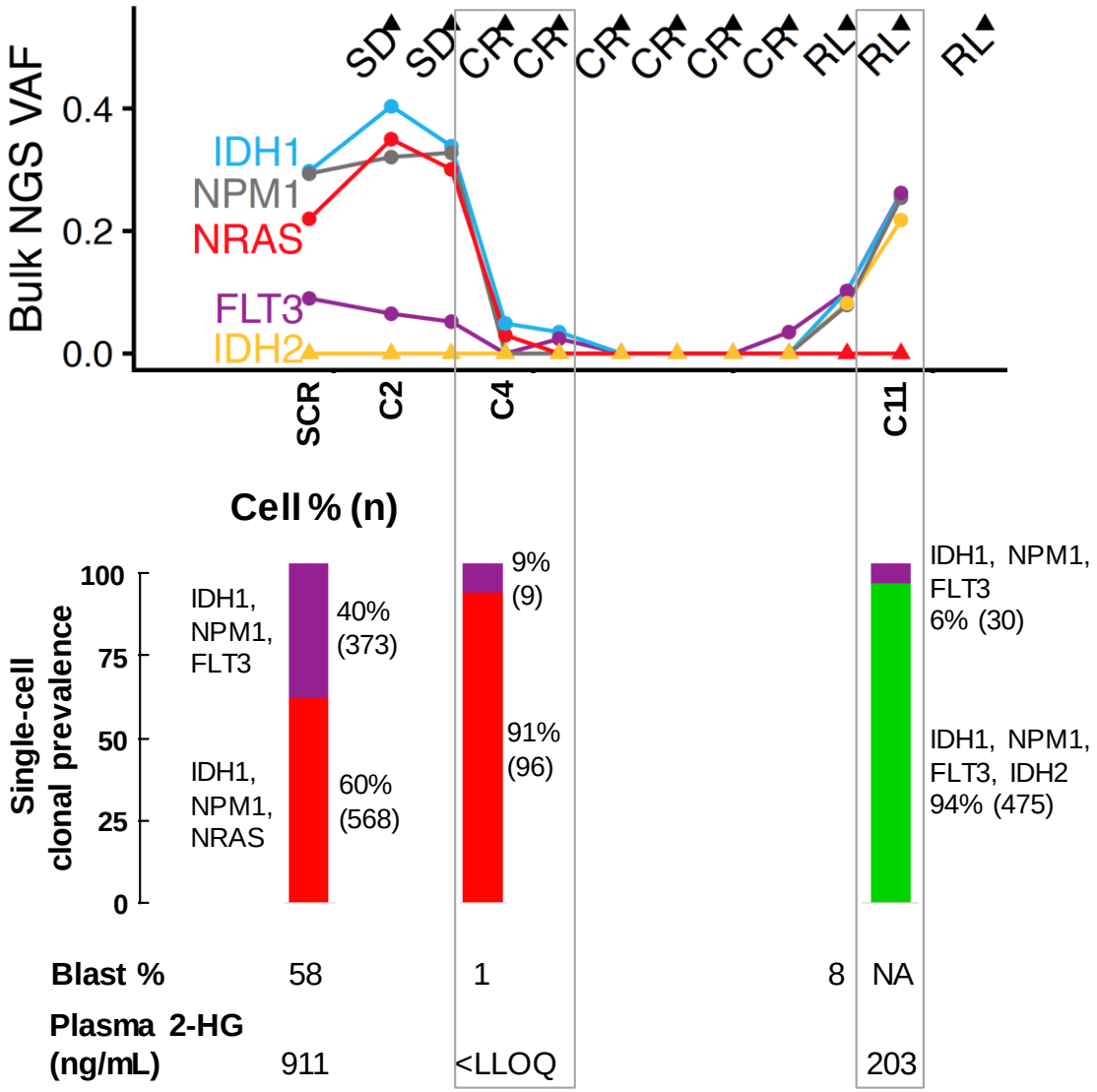
m*IDH2* detected on treatment
(targeted NGS profiling, sensitivity 2–5%)
n = 15

Available single-cell DNAseq data (PBMC)
(sensitivity 0.1%)
n = 9

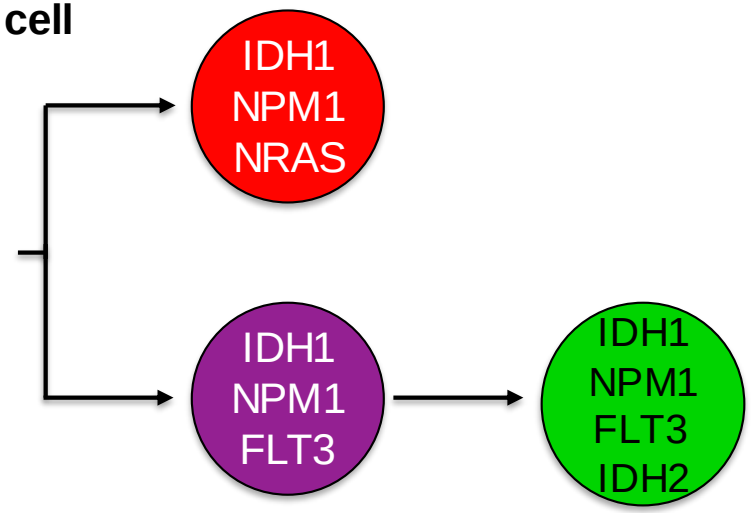
Tapestri® with a 19-gene AML panel		
ASXL1	*JAK2*	*RUNX1*
DNMT3A	*KIT*	*SF3B1*
EZH2	*KRAS*	*SRSF2*
FLT3	*NPM1*	*TP53*
GATA2	*NRAS*	*U2AF1*
IDH1	*PTPN11*	*WT1*
IDH2		

Clinical data cutoff: Nov 2, 2018
DNAseq, DNA sequencing; NGS, next-generation sequencing; PBMC, peripheral blood mononuclear cell; QD, once daily

Case 1:
62 y, M, de novo AML, prior IC, then R/R to azacitidine and decitabine (HMA)



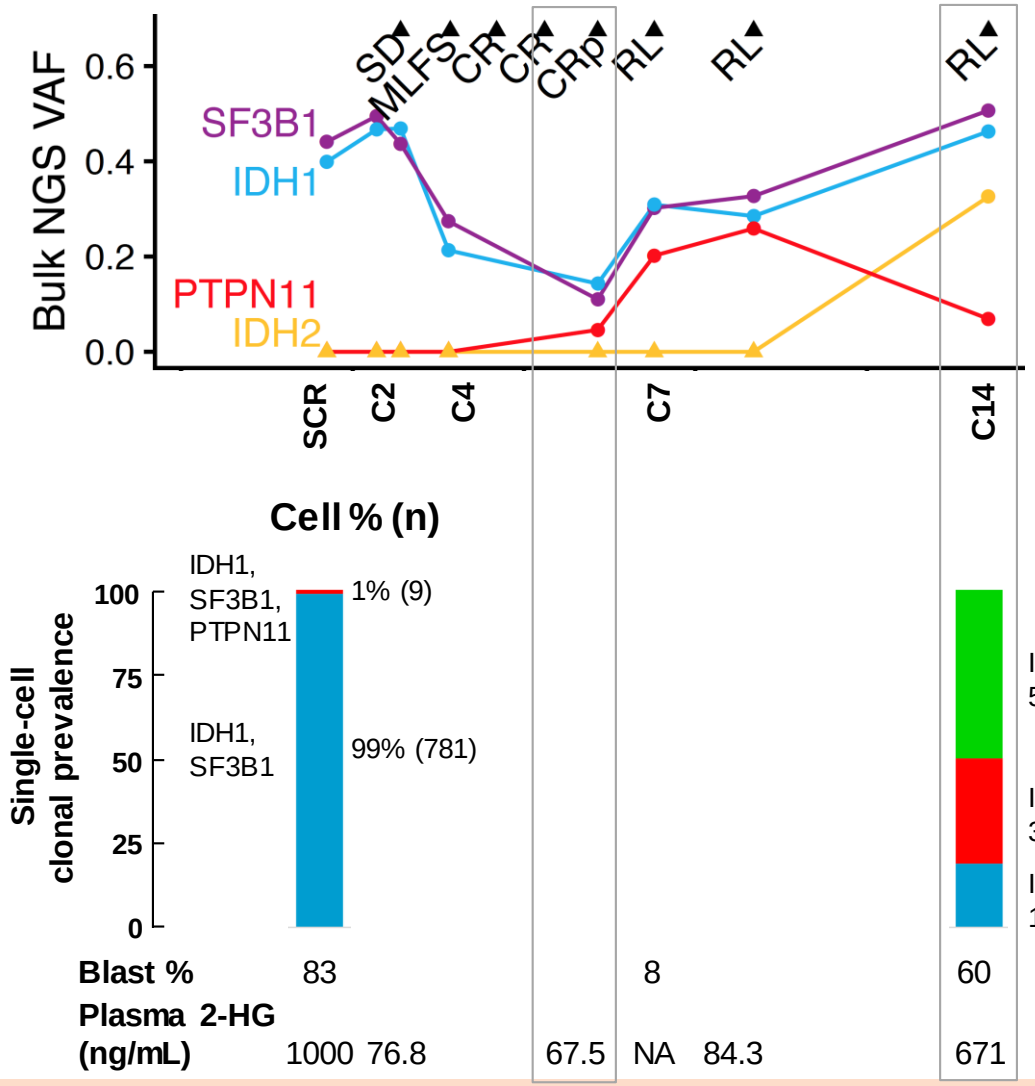
Clonal structure:
Single cell



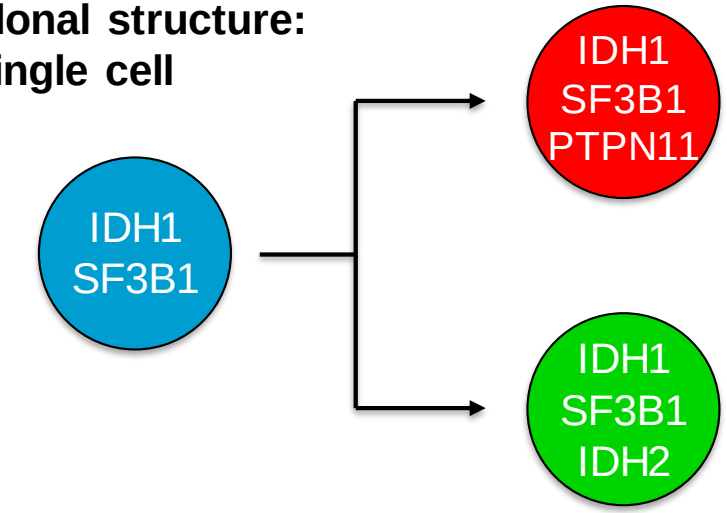
- Both m*IDH1/NPM1/NRAS* and m*IDH1/NPM1/FLT3*-TKD clones are sensitive to ivosidenib
- Resistance evolves through acquisition of m*IDH2* within m*IDH1* clone (2-HG–dependent mechanism)

C, cycle; IC, intensive chemotherapy; HMA, hypomethylating agent; M, male; NA, not available; y, years; LLOQ, lower limit of quantification; RL, relapse; SCR, screening; SD, stable disease; TKD, tyrosine kinase domain; VAF, variant allele frequency

Case 2:
85 y, F, sAML, prior therapy with azacitidine and lenalidomide, del 5q



Clonal structure: Single cell



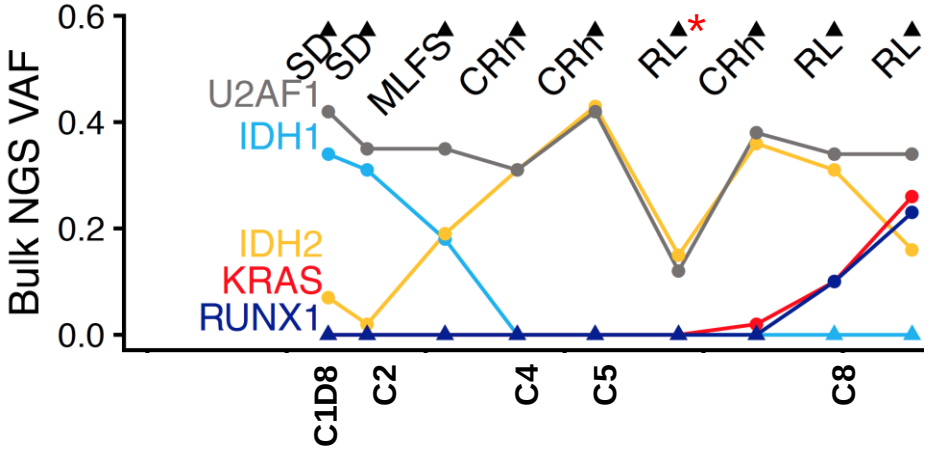
Kinetics of relapse

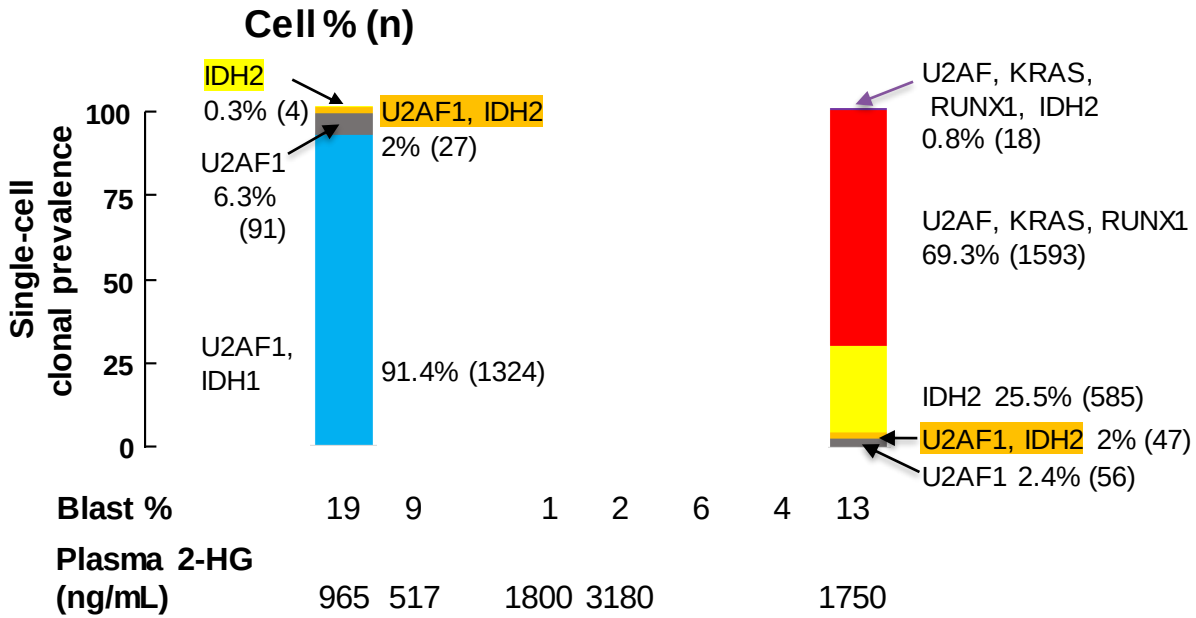
- Early: subclonal expansion of *PTPN11* (2-HG–independent)
- Late: acquisition of m*IDH2* within m*IDH1* clone (2-HG–dependent)

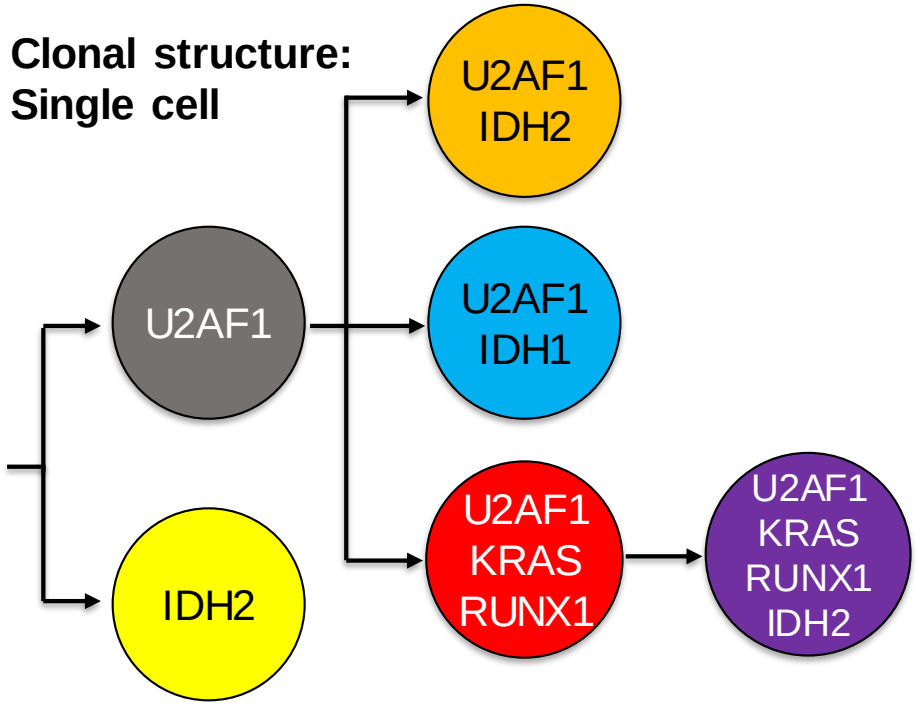
CRp, CR with incomplete platelet recovery; F, female; sAML, secondary AML; MLFS, morphologic leukemia-free state

Case 3:

67 y, M, de novo AML, prior decitabine and vosaroxin, refractory AML with +8 karyotype



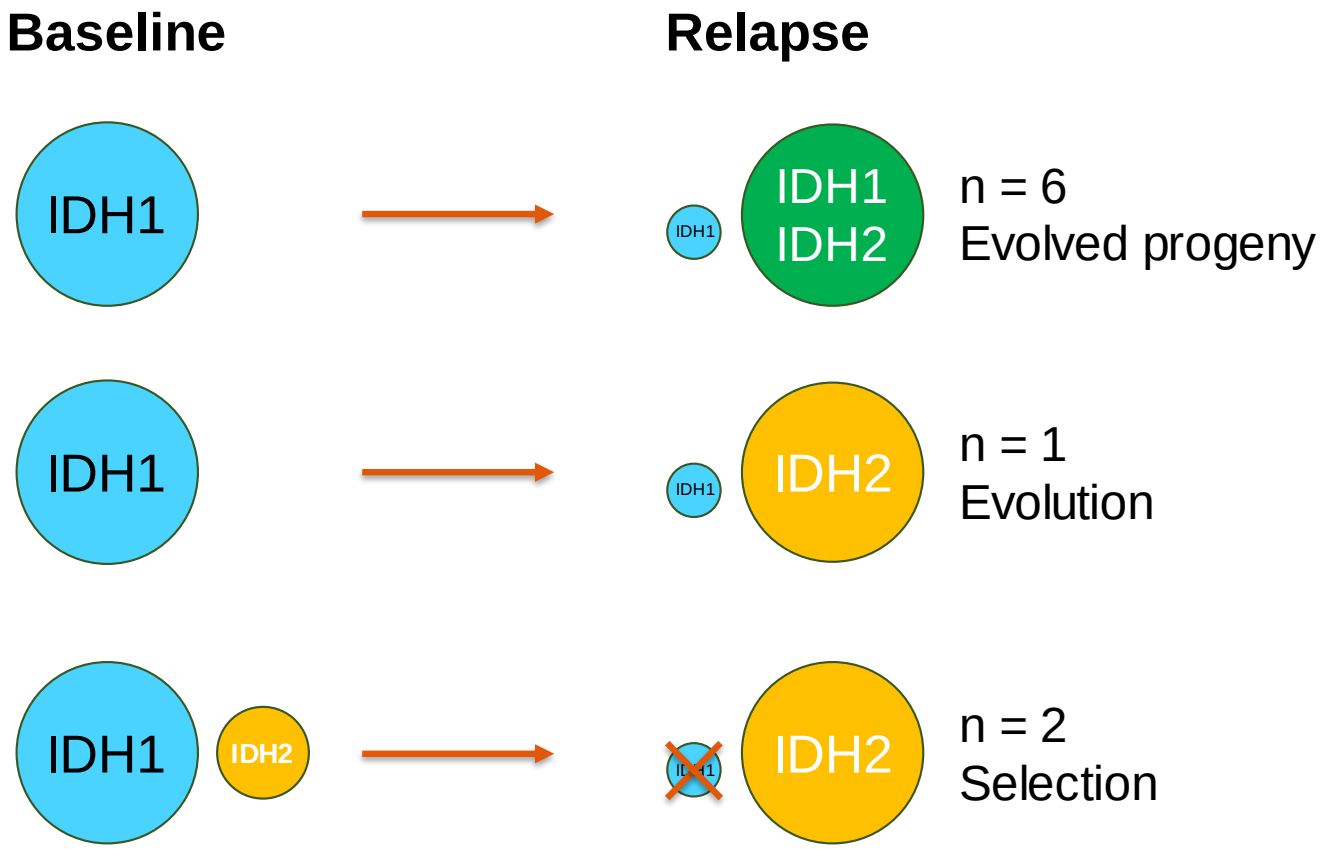




- Polyclonal disease with m*IDH1* clone being cleared with ivosidenib treatment
- Relapse due to:
  - Evolution of *IDH*-wild type clone
  - Expansion or evolution of multiple m*IDH2* clones

*RL: only 6% blasts

2-HG restoration via m*IDH2* in diverse clonal architecture



Conclusions

- Single-cell mutation profiling reveals multiple evolutionary mechanisms by which m*IDH2* contributes to relapse
- 2-HG restoration via m*IDH2* acquisition underscores the key role of 2-HG production in m*IDH* AML
- These results inform the design of combination or sequential treatment strategies with ivosidenib in m*IDH1* AML, for example, enasidenib treatment at relapse
- Frequency of relapse mechanisms via comprehensive genomic analysis will be presented shortly in this session (**Presentation 545, 8:00 AM**)

Acknowledgments

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