Longitudinal molecular profiling in patients with *IDH1*-mutant newly diagnosed acute myeloid leukemia treated with ivosidenib

Sung Choe, PhD[1], Hongfang Wang, PhD[1], Gail J Roboz, MD[2], Courtney D DiNardo, MD[3], Eytan M Stein, MD[4], Alice S Mims, MD[5], Gabrielle T Prince, MD[6], Justin M Watts, MD[7], Bin Fan, PhD[1], Parham Nejad, BSc[1], Vickie Zhang, PhD[1], Hua Liu, PhD[1], Eyal C Attar, MD[1], Bin Wu, PhD[1], Richard M Stone, MD[8]

[1]Agios Pharmaceuticals, Inc., Cambridge, MA, United States; [2]Weill Cornell Medicine and The New York Presbyterian Hospital, New York, NY, United States; [3]University of Texas MD Anderson Cancer Center, Houston, TX, United States; [4]Memorial Sloan Kettering Cancer Center, New York, NY, United States; [5]Ohio State University Wexner Medical Center, Columbus, OH, United States; [6]Johns Hopkins Hospital, Baltimore, MD, United States; [7]University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL, United States; [8]Dana-Farber Cancer Institute, Boston, MA, United States

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Ivosidenib monotherapy is FDA-approved for the treatment of m*IDH1* ND AML in adults ≥ 75 years of age or with comorbidities precluding intensive IC

Ivosidenib (IVO) induces deep durable remissions in patients with newly diagnosed *IDH1*-mutant AML[1]

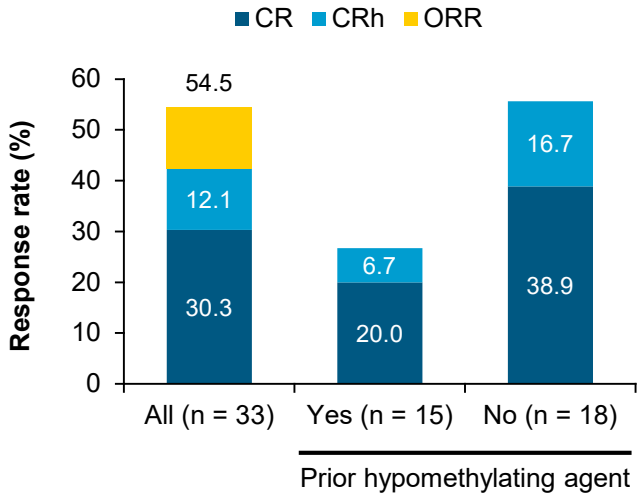
- *IDH1*-mutant newly diagnosed AML
- Ineligible for standard therapy
- N = 34

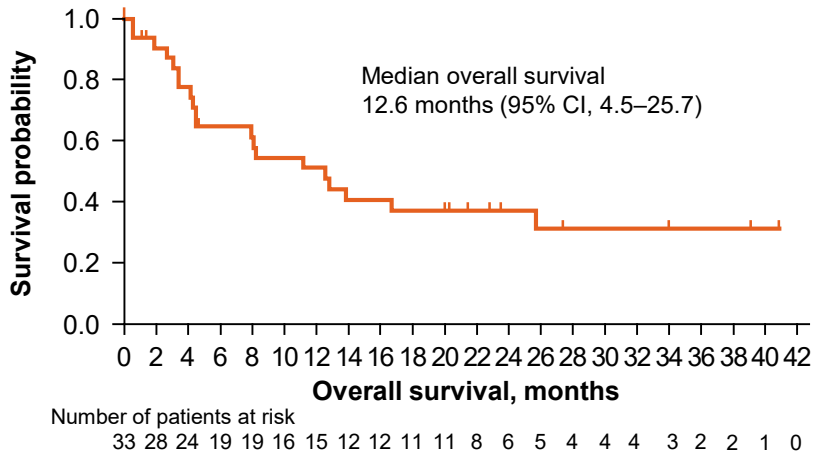
56% aged ≥ 75 years

47% prior exposure to HMA

76% secondary AML

Mutant *IDH1* inhibitor ivosidenib 500 mg once daily





Objectives

- To characterize the depth of molecular response for m*IDH1* and co-occurring mutations
- To determine relapse mechanisms via longitudinal bulk and single-cell DNAseq profiling

Clinical data cut: 02Nov2018

Of the patients who were transfusion-dependent at baseline, 43% became transfusion independent

1. Roboz GJ et al. *Blood* 2020;135(7):463–71.

AML = acute myeloid leukemia; CI = confidence interval; CR = complete response; CRh = complete response with partial hematologic recovery; DNAseq = deoxyribonucleic acid sequencing; FDA = Food and Drug Administration; HMA = hypomethylating agent; IC = induction chemotherapy; *IDH1* = isocitrate dehydrogenase 1; mo = months; ND = newly diagnosed; ORR = objective response rate.

Ivosidenib monotherapy induces deep *IDH1* mutation clearance in > 50% of ND AML patients achieving CR or CRh

Summary of *IDH1* mutation clearance in BMMC, PBMC, and neutrophils using BEAMing PCR (sensitivity 0.02–0.04%)[a]						
	BMMC		PBMC		Neutrophils	
Response	n	*IDH1* mutation clearance, n (%)	n	*IDH1* mutation clearance, n (%)	n	*IDH1* mutation clearance, n (%)
CR+CRh	**14**	**9 (64.3)**	**11**	**8 (72.7)**	**11**	**8 (72.7)**
CR	10	5 (50.0)	7	4 (57.1)	7	4 (57.1)
CRh	4	4 (100)	4	4 (100)	4	4 (100)
Others	**16**	**0 (0)**	**13**	**1 (7.7)**	**11**	**1 (9.1)**
Non-CR/CRh responders	4	0 (0)	3	1 (33.3)	3	1 (33.3)
Non-responders	12	0 (0)	10	0 (0)	8	0 (0)
P-value[b]		**< 0.001**		**0.002**		**0.008**

[a] Sysmex OncoBEAM™ (BEAMing digital PCR). *IDH1* mutation clearance was defined as a reduction in m*IDH1* variant allele frequency to below the limit of detection of 0.02–0.04% in at least one on-study time point.
[b] P-value is based on Fisher's exact test comparing IDH1 mutation clearance in patients with best overall response of CR+CRh to Others (non-CR+CRh responders and non-responders).

- 64% of ND AML patients achieving CR or CRh show *IDH1* mutation clearance in BMMCs by digital PCR, compared with 26% in R/R AML[1]
- *IDH1* mutation clearance was observed across multiple sample types (BMMC, PBMC, neutrophils)

1. Pollyea et al. Presented at the 23rd Congress of the European Hematology Association June 2018 (#S1560).

AML = acute myeloid leukemia; BMMC = bone marrow mononuclear cells; CR = complete response; CRh = complete response with partial hematologic recovery; *IDH1* = isocitrate dehydrogenase 1; ND = newly diagnosed; NGS = next generation sequencing; PBMC = peripheral blood mononuclear cells; PCR = polymerase chain reaction; R/R = relapsed/refractory.

Summary of co-mutation clearance by NGS[a]

	CR or CRh best response (n = 13 with data)		Non-CR or CRh (n = 14 with data)	
Gene	Patients with mutation at baseline (n)	Patients with mutation clearance (n)	Patients with mutation at baseline (n)	Patients with mutation clearance (n)
IDH1	13	11	13	2
NPM1	2	2	2	1
RUNX1	4	2	5	2
SRSF2	3	2	3	0
BRSK1	1	1	0	0
DNMT3A	5	1	6	0
ETV6	1	1	1	0
FLT3	1	1	1	0
KMT2A	1	1	0	0
KRAS	1	1	2	0
PHF6	1	1	2	1
SETBP1	1	1	1	0
TET2	2	1	4	0

- In 13 patients with a best response of CR/CRh and with available data, non-DTA (*DNMT3A*, *TET2*, *ASXL1*) gene mutation clearance by NGS[a] was observed for *IDH1*[b] (11/13), *RUNX1* (2/4), *SRSF2* (2/3), and *NPM1* (2/2)
- One patient had all co-occurring mutations (*IDH1*, *FLT3*, and *NPM1*) cleared by ivosidenib monotherapy

[a] Targeted NGS was conducted on BMMC samples collected at baseline and on-treatment (1–5% sensitivity). Detailed methods in Choe et al. *Blood Adv* 2020;4(9):1894–905.
[b] *IDH1:* p-value = 0.001 based on Fisher's exact test comparing IDH1 mutation clearance in patients with best overall response of CR+CRh to Others (non-CR+CRh responders and non-responders).

CR = complete response; CRh = CR with partial hematologic recovery; *IDH1* = isocitrate dehydrogenase 1; NGS = next generation sequencing.

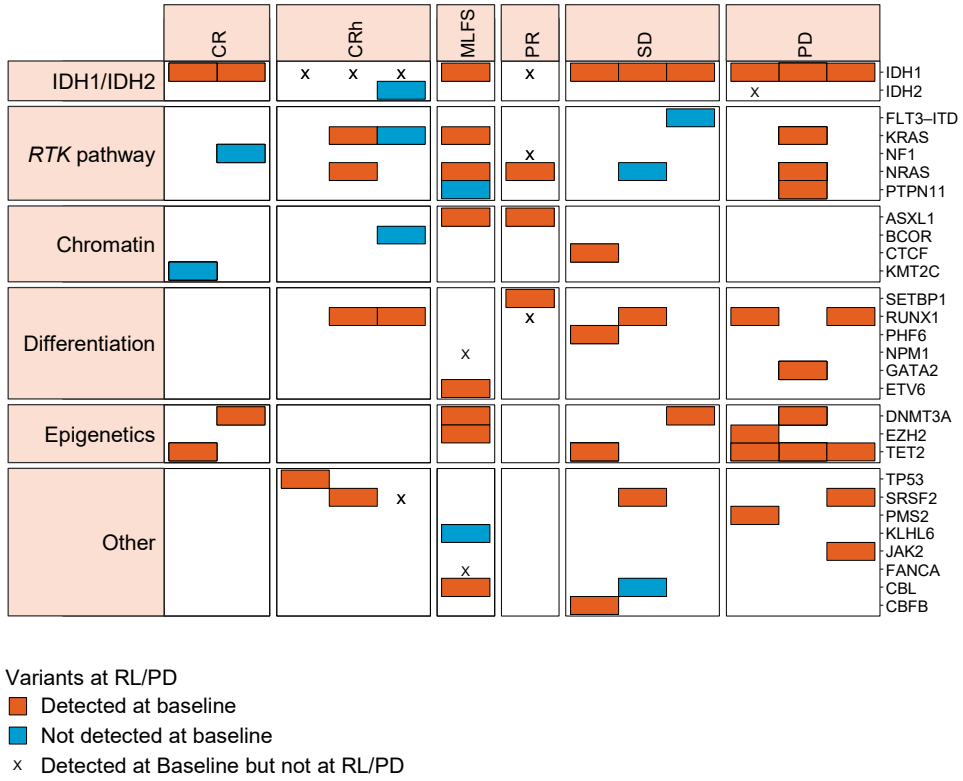
At relapse or disease progression, newly detected *RTK* pathway gene mutations are frequently observed

Frequency of emergence of mutations by pathway in patients with data at baseline and on study using NGS (sensitivity 1–5%)		
Pathway/Gene	**Patients with emerging mutations on study (n = 27 with data)**	**Patients with emerging mutations at relapse or disease progression (n = 13 with data)**
RTK pathway[a]	9 (33%)	5 (38%)
IDH1 2nd site mutation	0 (0)	0 (0)
IDH2	3 (11%)	1 (8%)
Chromatin[b]	3 (11%)	2 (15%)

[a] RTK pathway genes include *NRAS, KRAS, FLT3, PTPN11,* and *NF1*
[b] Chromatin genes include *BCOR, KMT2C, RAD21,* and *STAG2.*

At relapse or disease progression, IDH-related mutations (*IDH2* and second site *IDH1*) occur less frequently in newly diagnosed AML, compared with R/R AML[1]

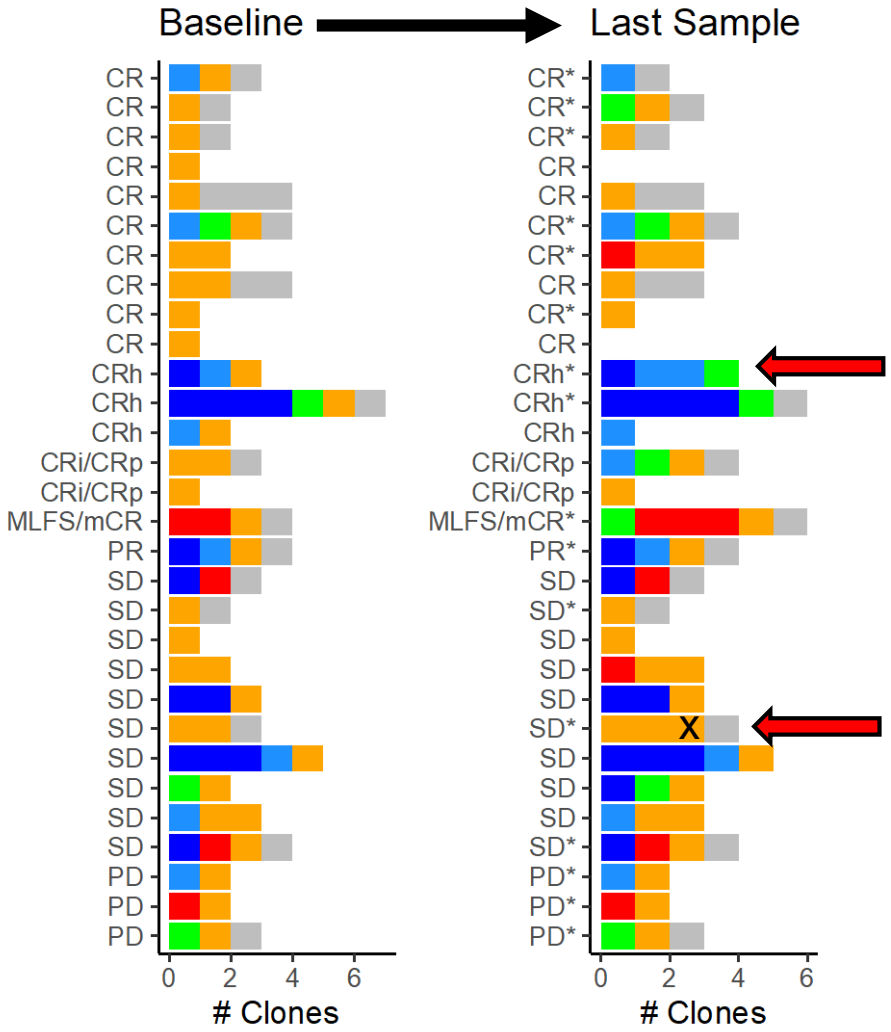
Variants detected at RL/PD (n = 13)

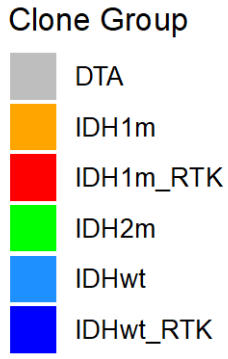


1. Choe et al. *Blood Adv* 2020;4(9):1894–905.

AML = acute myeloid leukemia; *IDH* = isocitrate dehydrogenase; NGS = next generation sequencing; RL/PD = relapse/progressive disease; R/R = relapsed/refractory; RTK = receptor tyrosine kinase.

Single-cell DNAseq dataset summary (N = 30)





- Baseline and longitudinal single-cell DNAseq profiling was performed on PBMC samples from 30 patients using MissionBio's Tapestri™ 20-gene AML panel
- As a result of the higher sensitivity of the single-cell DNAseq platform, *IDH2* mutations were detected more frequently upon treatment than with bulk sequencing (8 out of 30 patients). In this dataset, *IDH2* mutations did not co-occur with m*IDH1* in the same cell
- *RTK* pathway mutations were also frequently detected in *IDH1* wild type clones (8 out of 12 patients with mutations in *NRAS, KRAS,* or *PTPN11*)

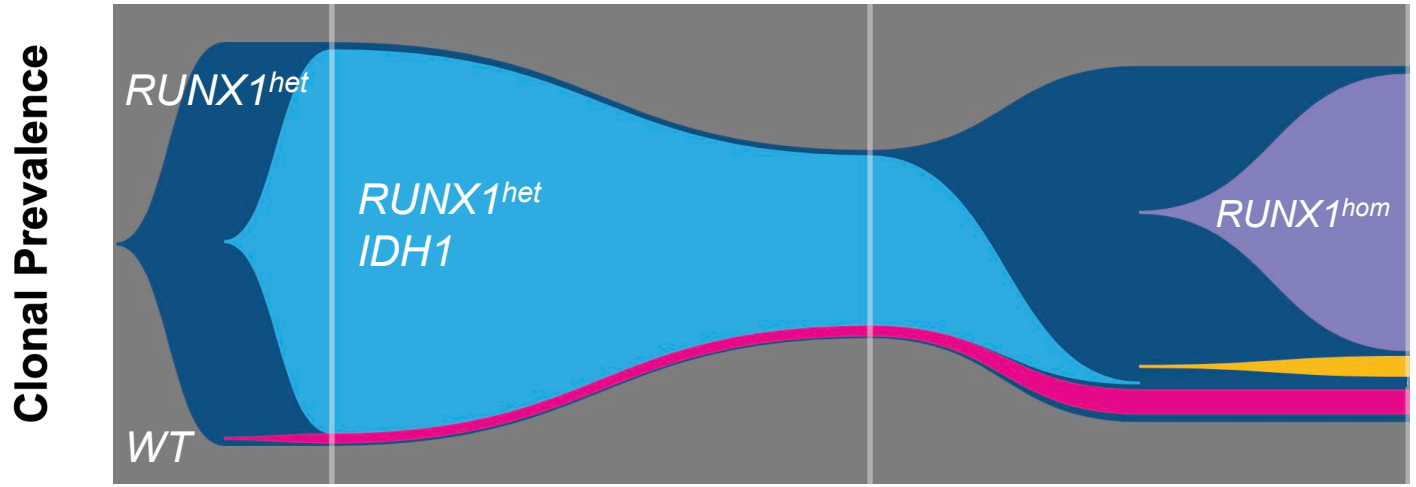
x IDH1 R119P acquired in *cis*

* Relapse or disease progression timepoint

Case Studies (following slides)

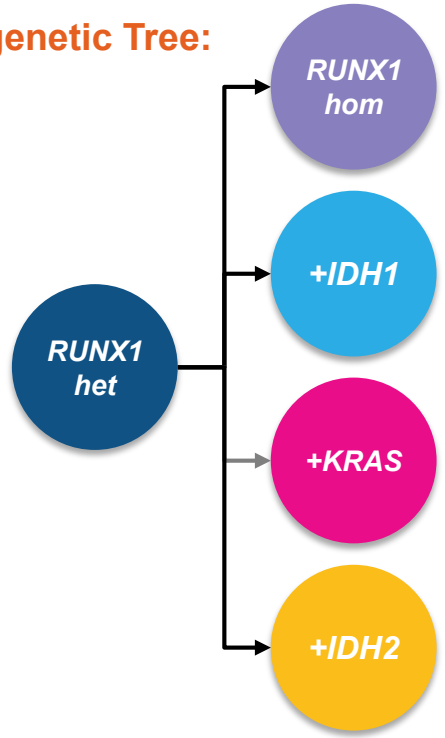
CR = complete response; CRh = complete response with partial hematologic recovery; DNAseq = deoxyribonucleic acid sequencing; *IDH* = isocitrate dehydrogenase; m = mutant; PD = progressive disease; SD = stable disease; wt = wild type; DTA = DNMT3A, TET2, and/or ASXL1

Case 1 (CRh)
84 y, M, *de novo* AML, trisomy 11 at baseline, no prior Tx



	SCR	C3: MLFS	(C12–C17: CRp)	C18: RL
Blast %	85	2		18
2-HG (ng/mL)	7630	97		272

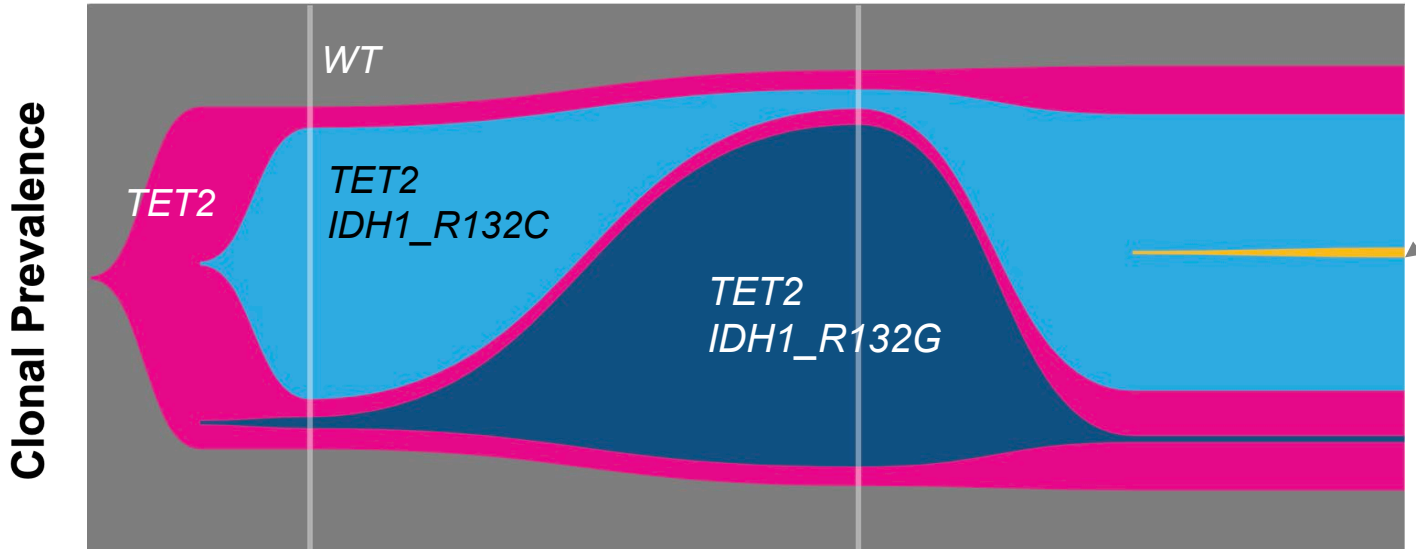
Phylogenetic Tree:

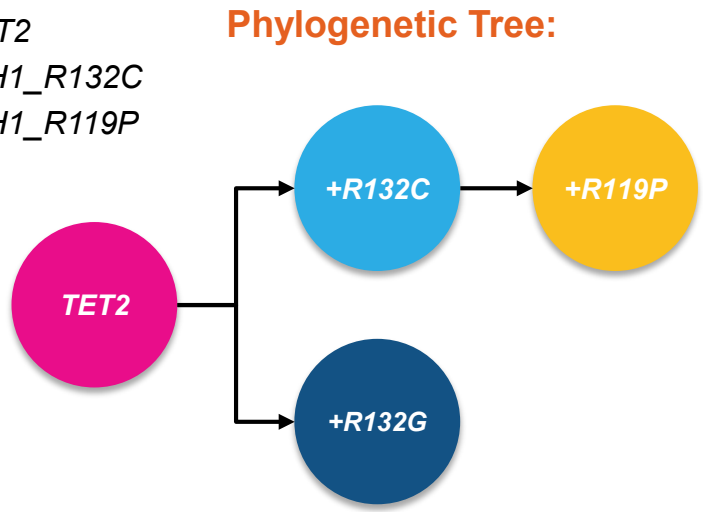


mIDH1 subclone is cleared at relapse, while resistance is likely the result of 3 independent wt*IDH1* clones containing m*IDH2*, m*KRAS*, and *RUNX1* LOH

2-HG = 2-hydroxyglutarate; AML = acute myeloid leukemia; CRh = complete response with partial hematologic recovery; CRp = CR with incomplete platelet recovery; DNAseq = deoxyribonucleic acid sequencing; *het* = heterogenous; *hom* = homogenous; *IDH* = isocitrate dehydrogenase; LOH = loss of heterozygosity; m = mutant; M = male; MLFS = morphological leukemia-free state; SCR = screen; RL = relapse; Tx = treatment; wt = wild-type; y = years of age.

Case 2 (SD), 70 y, F, prior MDS, normal karyotype at baseline, Tx with azacitidine, decitabine, and dexamethasone





	SCR	C4: SD	C10: PD
Blast %	77	7	75
2-HG (ng/mL)	348	48	62

- Two m*IDH1* subclones at baseline (*R132C, R132G*) show differential responses to ivosidenib
- A subset of *R132C* cells acquire *R119P* (in *cis*) at PD

2-HG = 2-hydroxyglutarate; CRh = complete response with partial hematologic recovery; F = female; *IDH1* = isocitrate dehydrogenase 1; MDS = myelodysplastic syndrome; PD = progressive disease; SCR = screen; SD = stable disease; Tx = treatment; y = years of age; wt = wild type.

Summary

- m*IDH1* clearance rate (64% in CR/CRh responders) was high in this newly diagnosed AML cohort relative to m*IDH1* R/R AML
- The pattern of co-mutation clearance (by NGS) and the clonal relationship to m*IDH1* warrant further investigation in a larger study
- Consistent with R/R AML dataset, *RTK* pathway mutations were observed to emerge at relapse or disease progression
- Single-cell DNAseq exploration showed that emerging m*IDH2* and *RTK* pathway mutations were frequently observed in wt*IDH1* clones, suggesting the potential benefit of ivosidenib in combination with either chemotherapy or other agents that target co-mutations
  - See **Poster #1943, Daigle et al.**, for molecular characterization of newly diagnosed AML patients treated with ivosidenib and azacitidine combination therapy

AML = acute myeloid leukemia; CR = complete response; CRh = complete response with partial hematologic recovery; DNAseq = deoxyribonucleic acid sequencing; *IDH* = isocitrate dehydrogenase; m = mutant; NGS = next generation sequencing; R/R = relapse/refractory; *RTK* = receptor tyrosine kinase; wt = wild-type.

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