Molecular characterization of clinical response and relapse in patients with *IDH1*-mutant newly diagnosed acute myeloid leukemia treated with ivosidenib and azacitidine

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This study was funded by Agios Pharmaceuticals, Inc.

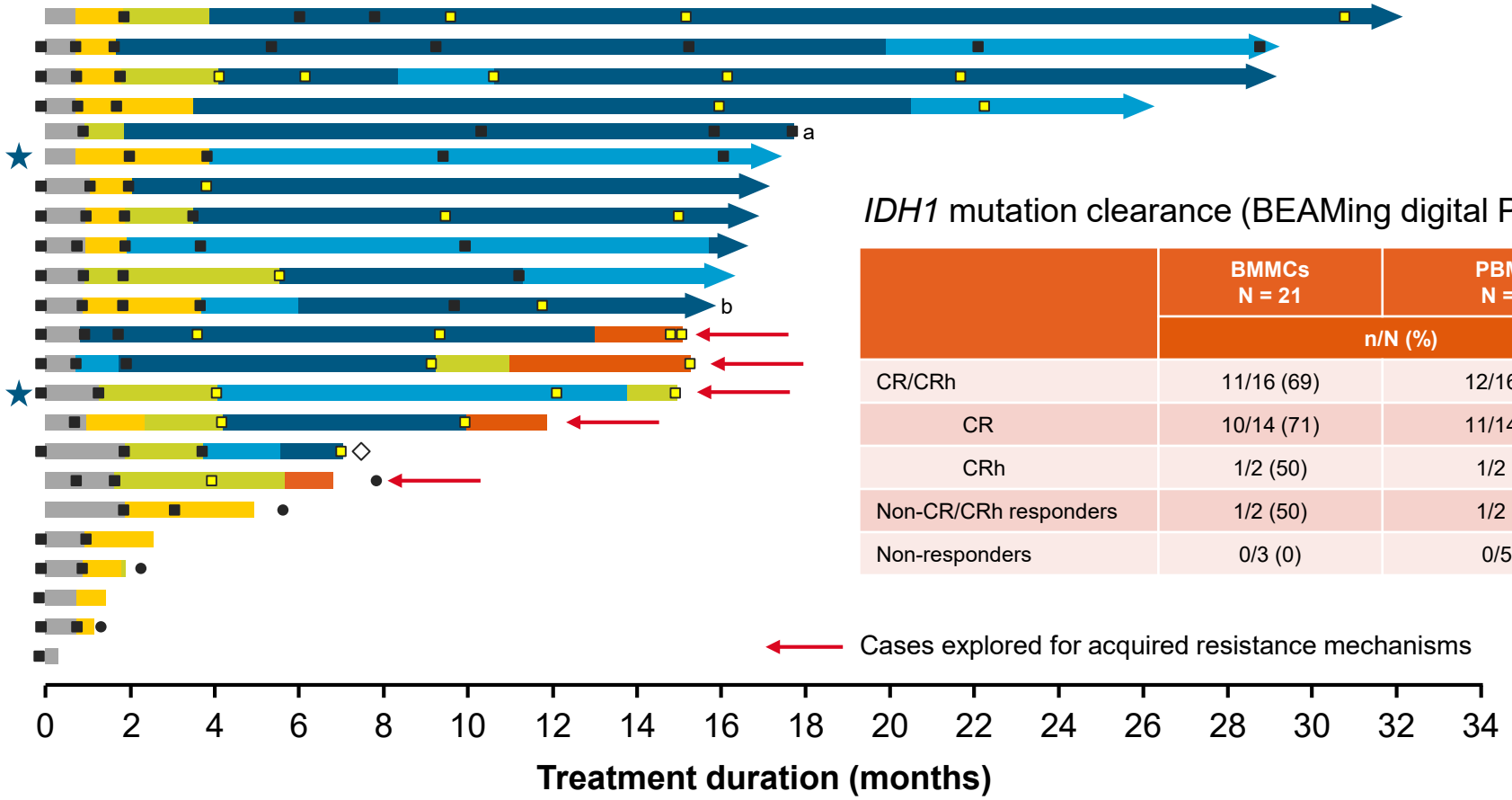
Background

- Somatic mutations in *IDH1* occur in 6–10% of patients with AML, resulting in the production of the oncometabolite 2-HG[1–5]
- Ivosidenib, a m*IDH1* inhibitor, is approved in the United States for m*IDH1* relapsed/refractory AML, and newly diagnosed m*IDH1* AML in patients ≥ 75 years old or with comorbidities precluding intensive induction chemotherapy
- Deep and durable remissions in m*IDH1* newly diagnosed AML patients treated with ivosidenib and azacitidine were observed in a phase 1b study (NCT02677922)[6]
  - ORR 78.3% (18/23), CR 60.9% (14/23), and CR + CRh 69.6% (16/23)
  - Median duration of response in months, not estimable (95% CI, [10.3, NE])
  - 82% 12-month overall survival rate (95% CI, [58.8–92.8])

2-HG = 2-hydroxyglutarate; AML = acute myeloid leukemia; CI = confidence interval; CR = complete remission; CRh = CR with partial hematologic recovery; *IDH1* = isocitrate dehydrogenase 1; m*IDH1* = mutant *IDH1*; NE = not estimable; ORR = overall response rate.

1. Mardis ER et al. *N Engl J Med* 2009;361:1058–66. 2. Ward PS et al. *Cancer Cell* 2010;17:225–34. 3. Patel KP et al. *Am J Clin Pathol* 2011;135:35–45. 4. DiNardo CD et al. *Am J Hematol* 2015;90:732–6. 5. Dang L et al. *Nature* 2009;462:739–44; 6. DiNardo CD et al. *J Clin Oncol*. 2020. DOI: 10.1200/JCO.20.01632.

Per patient treatment duration, response, and *IDH1* mutation clearance (N = 23)



IDH1 mutation clearance (BEAMing digital PCR)*

	BMMCs N = 21	PBMCs N = 23
	n/N (%)	
CR/CRh	11/16 (69)	12/16 (75)
CR	10/14 (71)	11/14 (79)
CRh	1/2 (50)	1/2 (50)
Non-CR/CRh responders	1/2 (50)	1/2 (50)
Non-responders	0/3 (0)	0/5 (0)

- *IDH1* mutation detected
- *No IDH1* mutation detected
- CR
- CRi/CRp
- MLFS/PR
- SD
- Relapse
- NA
- Death[c]
- Ongoing
- HSCT
- CRh criteria met

*m*IDH1* clearance assessed by BEAMing digital PCR (detection limit 0.02–0.04%); [a]Patient continued on commercially available ivosidenib; [b]Patient had m*IDH1* clearance in PBMCs only (BMMCs not available); all other patients had m*IDH1* clearance in both BMMCs and PBMCs; [c]Only deaths occurring within 60 days of last dose were included.

BMMCs = bone marrow mononuclear cells; CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete hematologic recovery; CRp = CR with incomplete platelet recovery; HSCT = hematopoietic stem cell transplant; MLFS = morphological leukemia-free state; NA = not assessed; PBMCs = peripheral blood mononuclear cells; PCR = polymerase chain reaction; PR = partial remission; SD = stable disease.

Objectives and methods

Objective

- Molecular characterization of clonal evolution and relapse in patients with m*IDH1* newly diagnosed AML treated with ivosidenib + azacitidine (IVO + AZA)

Analysis data set and methods

Phase 1b study
m*IDH1* ND AML, IVO + AZA
N = 23

Bulk DNAseq[a] (sensitivity 2%)
Baseline and any on-treatment timepoint[b]
N = 22 (BMMC and/or PBMC samples) including 5/5 cases of relapse or PD after CR/CRh

Single-cell DNAseq[c] (sensitivity 0.1%)
Baseline and any on-treatment timepoint[b]
N = 22 (PBMC samples) including 5/5 cases of relapse or PD after CR/CRh

20-gene AML panel single-cell panel[c]				
ASXL1	*GATA2*	*KIT*	*PTPN11*	*TET2*
DNMT3A	*IDH1*	*KRAS*	*RUNX1*	*TP53*
EZH2	*IDH2*	*NPM1*	*SF3B1*	*U2AF1*
FLT3	*JAK2*	*NRAS*	*SRSF2*	*WT1*

[a]1400 gene ACE Extended Cancer Panel, Personalis Inc; [b]Including the latest time point available as of 01March2020; [c]Mission Bio AML panel V2.
ACE = Accuracy and Content Enhanced; AML = acute myeloid leukemia; BMMC = bone marrow mononuclear cells; CR = complete remission; CRh = CR with partial hematologic recovery; DNAseq = deoxyribonucleic acid sequencing; *IDH1* = isocitrate dehydrogenase 1; PBMC = peripheral blood mononuclear cell; PD = progressive disease.

Frequency of emerging mutations by pathway in patients with bulk DNAseq data at baseline and on study

Pathway/Gene	Patients with emerging mutations during IVO + AZA therapy (n = 22)	Patients with emerging mutations at relapse/progression (n = 5)
IDH1/IDH2	3	2
IDH1 2nd site mutation	0	0
IDH2	3	2
RTK Pathway[a]	0	0
Differentiation[b]	4	1
Chromatin/epigenetic[c]	3	2
JAK/STAT[d]	1	0
Other[e]	1	1

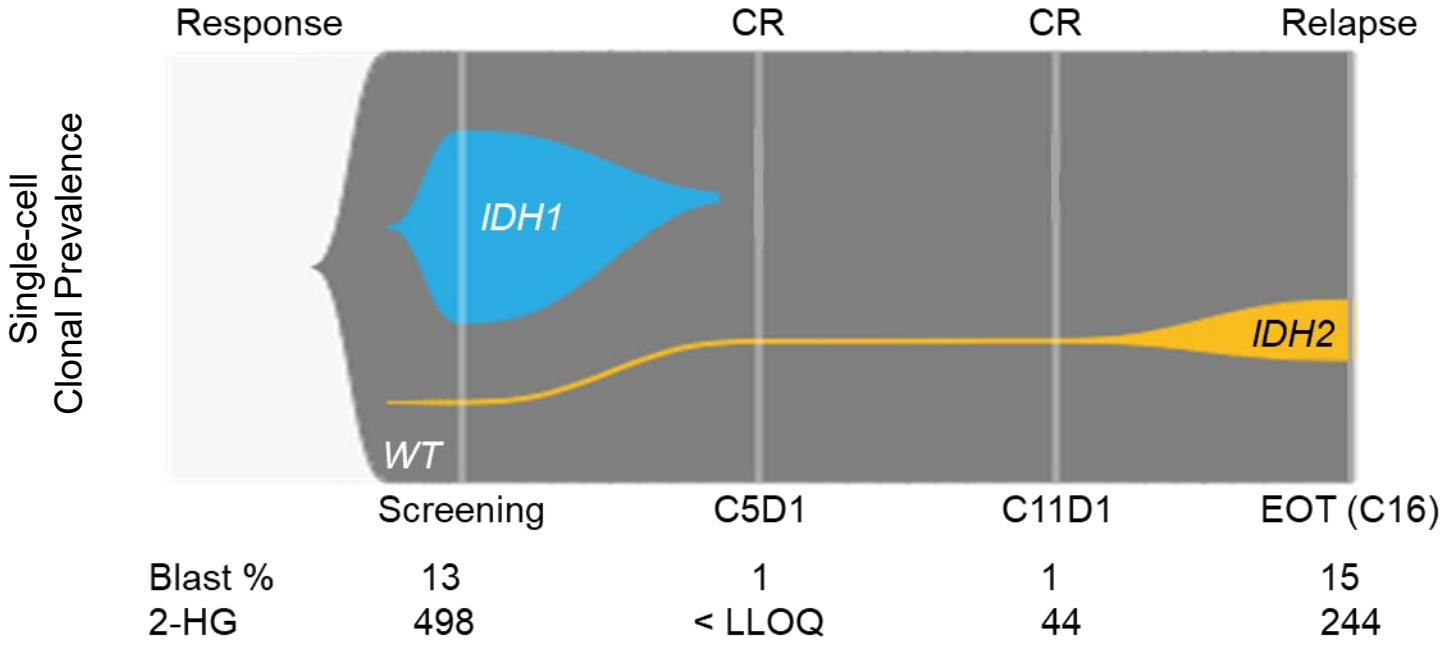
[a]*RTK* pathway genes examined include *FLT3*, *KRAS*, *NRAS*, and *PTPN11*
[b]Differentiation pathway genes include *CIC*, *CUX1*, *SETBP1*, and *RUNX1*
[c]Chromatin/epigenetic pathway genes include *DNM3TA*, *KMT2D*, *TET2*, and *WT1*
[d]JAK/STAT pathway gene is *JAK2*
[e]Other pathway gene is *SMC1A*

- Overall *IDH1* 2nd site and *RTK* pathway mutations occurred less frequently when compared with R/R AML patients treated with monotherapy IVO[1]
- Within the relapse/progression cases, emerging mutations were observed in 4/5 patients:
  - Patient 1: *IDH2, SMC1A*
  - Patient 2: *CUX1*, *IDH2*, *SETBP1*
  - Patient 3: *DNMT3A, TET2*
  - Patient 4: *WT-1*

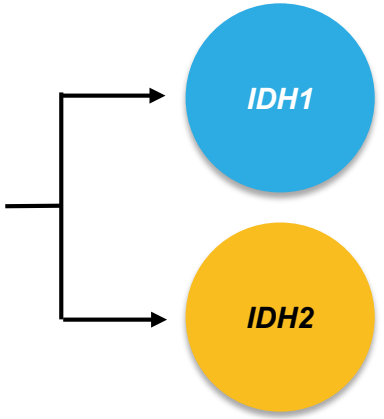
AML = acute myeloid leukemia; AZA = azacitidine; DNAseq = deoxyribonucleic acid sequencing; *IDH1* = isocitrate dehydrogenase 1; *IDH2* = isocitrate dehydrogenase 2; IVO = ivosidenib; JAK = Janus kinase; R/R = relapsed/refractory; *RTK* = receptor tyrosine kinase; STAT = signal transducer and activator of transcription proteins.

1. Choe et al. *Blood Adv* 2020;4:1894–1905.

Single-cell DNAseq relapse case 1: 76 y, M, *de novo* AML, normal karyotype



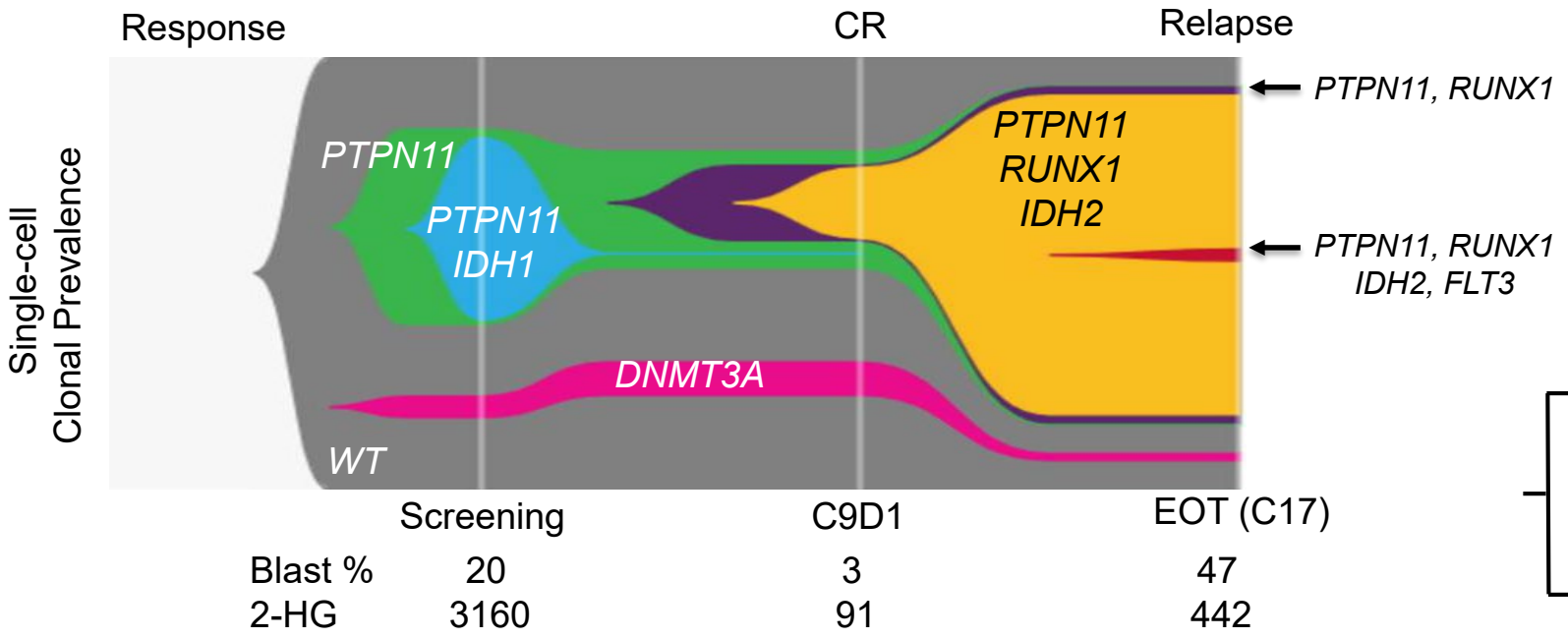
Clonal structure single-cell:



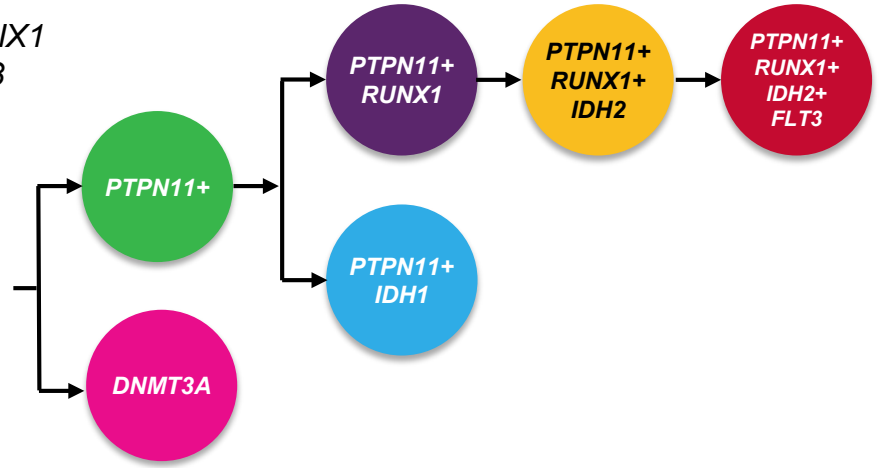
- Baseline *IDH1* clone cleared with IVO + AZA treatment
- At relapse a minor *IDH2* clone present at baseline expands independently of the *IDH1* clone with a concurrent rise in 2-HG

Subclones with > 1% of total cells in at least one time point shown; LLOQ < 30 ng/mL.
2-HG = 2-hydroxyglutarate; AML, acute myeloid leukemia; AZA = azacitidine; C = cycle; CR = complete remission; D = day; EOT = end of treatment; *IDH1* = isocitrate dehydrogenase 1; *IDH2* = isocitrate dehydrogenase 2; IVO = ivosidenib; LLOQ = lower limit of quantitation; M = male; y = year; WT = wild type.

Single-cell DNAseq relapse case 2: 68 y, M, *de novo* AML with del 12p



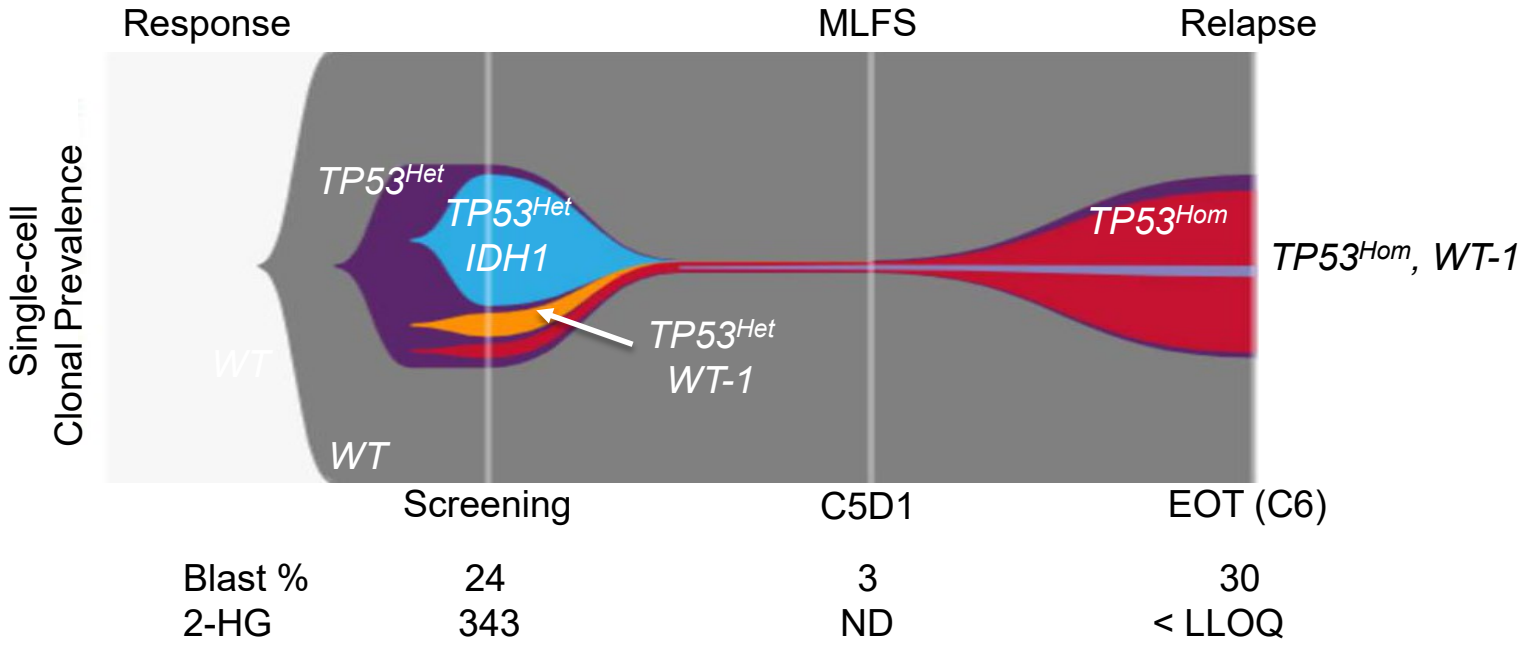
Clonal structure single-cell:



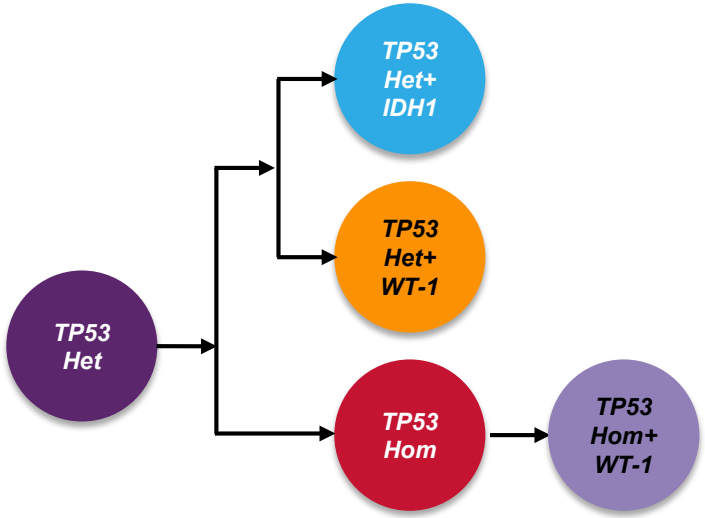
- Polyclonal disease with the *IDH1* containing clone cleared with IVO + AZA therapy
- A baseline *PTPN11* clone evolved to gain multiple pathway mutations, including an *IDH2* mutation with concurrent rise in 2-HG at relapse

Subclones with > 1% of total cells in at least one time point shown; LLOQ < 30 ng/mL.
2-HG = 2-hydroxyglutarate; AML, acute myeloid leukemia; AZA = azacitidine; C = cycle; CR = complete remission; D = day; EOT = end of treatment; *IDH1* = isocitrate dehydrogenase 1; *IDH2* = isocitrate dehydrogenase 2; IVO = ivosidenib; LLOQ = lower limit of quantitation; M = male; WT = wild type.

Single-cell DNAseq relapse case 3: 76 y, F, secondary AML



Clonal structure single-cell:



- Polyclonal disease with the *IDH1* containing clone cleared with IVO + AZA therapy
- Selection and expansion of a baseline *TP53*^{Hom} clone was observed at relapse and most likely cause of resistance

Subclones with > 1% of total cells in at least one time point shown; LLOQ < 30 ng/mL.
2-HG = 2-hydroxyglutarate; AML = acute myeloid leukemia; AZA = azacitidine; C = cycle; D = day; EOT = end of treatment; F = female; *Het* = heterozygous; *Hom* = homozygous; *IDH1* = isocitrate dehydrogenase 1; IVO = ivosidenib; LLOQ = lower limit of quantitation; MLFS = morphological leukemia-free state; ND = not determined; y = year; WT = wild type.

Summary

- IVO + AZA treatment leads to a high rate of durable molecular remissions in intensive chemotherapy-ineligible patients with newly diagnosed AML[1]
- 5/18 responding patients (CR/CRh/MLFS) relapsed or progressed, with the predominant mutation at relapse/progression involving *IDH2* (n = 2), *TP53* (n = 2), and *TET2* (n = 1)
  - In comparison to R/R AML pts treated with IVO monotherapy, no emerging *IDH1* 2nd site or *RTK* pathway mutations were observed (Bulk DNAseq)
  - Single-cell DNAseq demonstrated multiple mechanisms leading to relapse, with each mechanism evolving separate from the *IDH1* clone
- These results underline the importance of mutational testing, particularly at progression, to determine optimal salvage therapy
- See **Poster #2900, Choe et al.**, for longitudinal molecular profiling of newly diagnosed AML patients treated with monotherapy IVO, and **Poster #2814, Montesinos et al.**, for an update on the phase 3 AGILE study

1. DiNardo CD et al. *J Clin Oncol*. 2020. DOI: 10.1200/JCO.20.01632.

AML = acute myeloid leukemia; AZA = azacitidine; CR = complete remission; CRh = CR with partial hematologic recovery; DNAseq = deoxyribonucleic acid sequencing; *IDH1* = isocitrate dehydrogenase 1; *IDH2* = isocitrate dehydrogenase 2; IVO = ivosidenib; MLFS = morphological leukemia-free state.

Acknowledgments and disclosures

- We would like to thank the patients taking part in this study
- **Scott R Daigle** – Agios – employee and stockholder; **Sung Choe** – Agios – employee and stockholder; **Courtney D DiNardo** – AbbVie, Agios, Celgene – honoraria, consultant/advisor, and research funding; Novartis – consultant; Daiichi Sankyo – honoraria and research funding; Takeda – honoraria; ImmuneOnc, Jazz, MedImmune, Syros – honoraria; Notable Labs – board of directors/ advisory committee member; Calithera – research funding; **Anthony S Stein** – Amgen, Celgene, Stemline – speakers bureau member; Amgen – consultant; **Eytan M Stein** – Agios, Astellas, Amgen, Abbvie, Biotheryx, Seattle Genetics, Genentech, Novartis – consultant; Agios, Astellas, Bioline, Celgene, Daiichi Sankyo, Genentech, Novartis, PTC Therapeutics, Syros, Genentech – board of directors/advisory committee member; Daiichi Sankyo, Celgene – research funding and honoraria; Syndax – consultant and research funding; Bayer, Novartis – research funding; Auron Therapeutics – current equity folder in private company; **Amir T Fathi** – AbbVie, Agios, Amgen, Amphivena, Astellas, BMS, Blue Print Oncology, Boston Biomedical, Celgene, Daiichi Sankyo, Forty Seven, Jazz, Kite, Kura, NewLink Genetics, Novartis, Pfizer PTC Therapeutics, Seattle Genetics, Takeda, Trillium, TrovaGene – consultant; Amphivena, Jazz, Kite, NewLink Genetics – honoraria; Agios, Celgene, BMS, Seattle Genetics – research funding; **Olga Frankfurt** – no conflict of interest to disclose; **Andre C Schuh** – Agios, Novartis, Abbvie, Amgen, Celgene, Jazz, Pfizer. Teva Canada Innovation – honoraria; Novartis – research funding; Abbvie, Amgen, Celgene, Jazz, Pfizer. Teva Canada Innovation – board membership of advisory committee; **Hartmut Döhner** – AbbVie, Agios, Amgen, Astellas, Astex, Celgene, Janssen, Jazz, Novartis, Roche, Seattle Genetics – consultant; Amgen, Arog, Bristol-Myers Squibb, Celgene, Jazz, Novartis, Pfizer – research funding; AbbVie, Agios, Amgen, Astellas, Astex, Celgene, Janssen, Jazz, Novartis, Roche, Seattle Genetics – honoraria; Sunesis – other; **Giovanni Martinelli** – AbbVie, Amgen, Celgene, Daichii Sankyo, Janssen, Jazz, Incyte, Pfizer, Roche – consultant; Celgene, Novartis, Pfizer – speakers bureau member; Abbvie, Daichii Sankyo, Pfizer – research funding; **Prapti A Patel** – Celgene, Agios – consultant/advisor; Celgene – speakers bureau member; DAVA Pharmaceuticals, France Foundation – honoraria; **Emmanuel Raffoux** – no conflict of interest; **Peter Tan** – Agios, Janssen, NOHLA Therapeutics, Novartis – research funding; Novartis – travel expenses; AbbVie – investigator on an AbbVie funded clinical trial; **Amer M Zeidan** – Acceleron, AbbVie, ADC Therapeutics, Aprea, Astex, Boehringer Ingelheim, BMS, Celgene, Incyte, Medimmune/AstraZeneca, Otsuka, Pfizer, Takeda, Trovagene – research funding; AbbVie, Acceleron, Agios, Ariad, Astellas, BeyondSpring, BMS, Boehringer Ingelheim, Cardinal Health, Celgene, Daiichi Sankyo, Epizyme, Ionis, Incyte, Novartis, Otsuka, Pfizer, Seattle Genetics, Jazz, Takeda, Taiho, Cardiff Oncology, Trovagene – consultant and honoraria; Novartis – travel support and research funding; Cardiff Oncology, Leukemia and Lymphoma Society, CCITLA – other; **Stéphane de Botton** – AbbVie, Agios, Astellas, Bayer, Celgene, Daiichi Sankyo, Forma, Janssen, Novartis, Pfizer, Pierre Fabre, Servier, Syros – consultant; Agios, Forma – honoraria and research funding; Celgene – speakers bureau member and honoraria; Astellas, Daiichi Sankyo, Syros, AbbVie, Bayer, Seattle Genetics, Janssen – honoraria; **Richard M Stone** – AbbVie, Actinium, Agios, Amgen, Argenx, Arog, Astellas, AstraZeneca, Biolinerx, Celgene, Cornerstone Biopharma, Daiichi-Sankyo, Elevate, Fujifilm, Gemoab, Janssen, Macrogenics, Hoffman LaRoche, Stemline, Syndax, Syntrix, Syros, Jazz, Merck, Novartis, Ono, Orsenix, Otsuka, Pfizer, Sumitomo, Trovagene, Takeda – consultant; Argenx, Celgene, Takeda Oncology – data and safety monitoring board/ committee member; Astellas – board of directors or advisory committee; Abbvie, Agios, Arog, Novartis – research funding; **Mark Frattini** – BMS employment and equity ownership; **Aleksandra Franovic** – BMS employment and equity ownership; **Thomas Winkler** – Agios – employee and stockholder; **Bin Wu** – Agios – employee and stockholder; **Emily Xu** – Agios – employee and stockholder; **Paresh Vyas** – Celgene, Forty Seven, Novartis – research funding; AbbVie, Astellas, Celgene, Daiichi Sankyo, Novartis, Pfizer – speakers bureau member
- Editorial assistance was provided by Chloe Malloy, MSc, Onyx Medica, London, UK, and supported by Agios Pharmaceuticals, Inc.